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Review

Aging and Rejuvenation of Neural Stem Cells and Their Niches

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Aging has a profound and devastating effect on the brain. Old age is accompanied by declining cognitive function and enhanced risk of brain diseases, including cancer and neurodegenerative disorders. A key question is whether cells with regenerative potential contribute to brain health and even brain "rejuvenation." This review discusses mechanisms that regulate neural stem cells (NSCs) during aging, focusing on the effect of metabolism, genetic regulation, and the surrounding niche. We also explore emerging rejuvenating strategies for old NSCs. Finally, we consider how new technologies may help harness NSCs' potential to restore healthy brain function during physiological and pathological aging.

Introduction

More than any other organ, the brain feels central to us for its ability to coordinate higher-order cognitive functions. But brain function deteriorates with age. In parallel, neurodegenerative disorders (e.g., Alzheimer's and Parkinson's diseases) and brain cancers (e.g., gliomas) surge in the elderly population. Although all cell types in the brain are affected during aging and could contribute to physiological decline and disease, resident neural stem cells (NSCs) in the adult brain have the potential to generate new neurons (neurogenesis) and regenerate aspects of brain function. Thus, maintaining a healthy stem cell pool in the brain throughout aging could be critical to improve overall brain health and reduce the incidence of neurodegenerative diseases and cancer.

The adult mammalian brain contains two primary reservoirs of regenerative NSCs (known as "neurogenic niches"): the subventricular zone (SVZ) of the lateral ventricles and the dentate gyrus (DG) of the hippocampus (Figure 1; Bond et al., 2015; Silva-Vargas et al., 2013). A third pool of NSCs has been reported more recently in the hypothalamus (Bolborea and Dale, 2013; Pellegrino et al., 2018). This review will primarily focus on the SVZ and hippocampal neurogenic niches but will also discuss specific results from NSCs in the hypothalamus. Neurogenic niches are specialized microenvironments comprising a variety of different cell types, including cells from the NSC lineage, but also endothelial cells (blood vessels) and microglia (Aimone et al., 2014). The head of the NSC lineage consists of quiescent NSCs (qNSCs), which are normally dormant but can be activated to generate proliferating NSCs. Activated NSCs (aNSCs), in turn, give rise to neural progenitor cells (NPCs), which have the potential to differentiate primarily into new neurons, and, in smaller proportions, into astrocytes and oligodendrocytes (Bond et al., 2015). The SVZ and hippocampal neurogenic niches have similarities in their overall cellular composition and neurogenic potential. However, these reservoirs also exhibit differences in their turnover dynamics (symmetric versus asymmetric divisions; Calzolari et al., 2015; Encinas et al., 2011; Obernier et al., 2018), their ability to give rise to glia (oligodendrocytes versus astrocytes; Bonaguidi et al., 2011; Ortega et al., 2013), and their contribution to brain function (Aimone et al., 2014; Corsini et al., 2009; Dupret et al., 2008; Gao et al., 2018; Gheusi et al., 2000).

In the SVZ, NSCs are located within "pinwheel" structures and contact the brain's vasculature and the cerebrospinal fluid (CSF) in the lateral ventricle (Mirzadeh et al., 2008; Shen et al., 2008; Tavazoie et al., 2008). SVZ NSCs produce neuroblasts that migrate along the rostral migratory stream and generate new neurons in the olfactory bulb in rodents (Doetsch et al., 1997; Mizrahi et al., 2006) or incorporate into the striatum in humans (Ernst et al., 2014). SVZ neurogenesis is important for various olfactory functions in rodents, such as odor discrimination and olfactory learning and memory (Bragado Alonso et al., 2019; Gheusi et al., 2000; Sakamoto et al., 2011). Interestingly, SVZ NSCs can also be activated upon injury (e.g., stroke) to generate newborn neurons and astrocytes that can help to repair brain injury in mice (Benner et al., 2013; Faiz et al., 2015; Li et al., 2010a).

In the hippocampal niche, NSCs are located at the border of the inner granule cell layer in the DG, and they generate neuroblasts, which migrate along the subgranular zone to produce granule neurons (Gage, 2002; Ming and Song, 2011; Sun et al., 2015). Hippocampal neurogenesis contributes to learning and memory formation (Corsini et al., 2009; Dupret et al., 2008; Gao et al., 2018; Guo et al., 2018) and stress resilience in mice (Anacker et al., 2018; Levone et al., 2014). In humans, the level and duration of hippocampal neurogenesis have been subject to debate, but neurogenic regions with regenerative potential are likely present in adulthood in humans (Boldrini et al., 2018; Moreno-Jiménez et al., 2019; Sorrells et al., 2018; Tobin et al., 2019).

During aging, the ability of NSCs to proliferate and give rise to new neurons decreases dramatically. *In vivo* labeling and microscopy revealed a decline in neurogenesis in SVZ and hippocampal neurogenic niches during aging (Ben Abdallah et al., 2010; Bondolfi et al., 2004; Enwere et al., 2004; Kuhn et al., 1996;

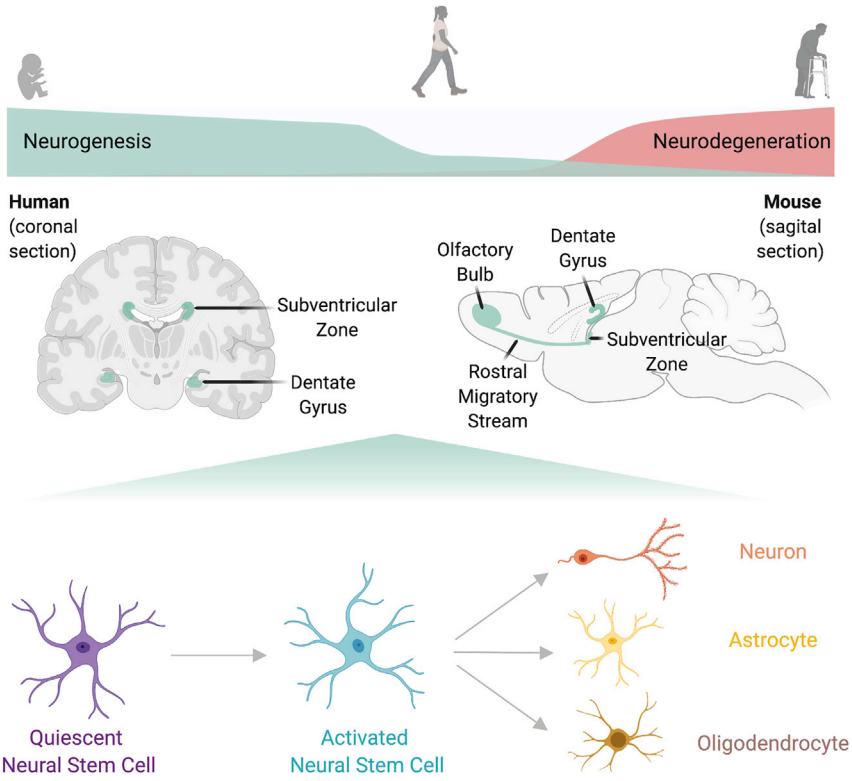

Figure 1. Neurogenesis during Aging

The ability of NSCs to proliferate and produce new neurons declines sharply after development and continues to decline during aging, whereas the incidence of neurodegeneration and age-related diseases increases (the diagram shows conceptual trajectories for neurogenesis and neurodegeneration). The adult mammalian brain contains two reservoirs of regenerative neural stem cells (NSCs): the DG of the hippocampus and the SVZ of the lateral ventricles (teal green). These niches contain qNSCs that can be activated to produce actively proliferating NSCs (aNSCs). aNSCs have the potential to differentiate into neurons, oligodendrocytes, or astrocytes.

Luo et al., 2006; Maslov et al., 2004). This decline likely involves a number of cellular processes, including increased NSC dormancy, decreased NSC self-renewal, a decline in neuronal fate commitment, and NSC death (Encinas et al., 2011; Obernier and Alvarez-Buylla, 2019; Urbán et al., 2016). The decrease in neurogenesis with age is accompanied by poorer performance on learning and memory tasks and reduced olfactory discrimination (Enwere et al., 2004; Gage and Temple, 2013; McAvoy et al., 2016), suggesting that age-related NSC defects may have broad functional consequences. In humans, the decline in neurogenesis in elderly individuals has been associated with cognitive impairment and neurodegenerative diseases (Moreno-Jiménez et al., 2019; Tobin et al., 2019). Thus, key questions emerging in this field include the following. How do regenerative regions containing NSCs change over a lifespan? Do the various regenerative niches differ, or do they rely on similar mechanisms? Are the cells that divide in the old brain the same cells that had already divided and produced neurons in the younger brain? How can the regenerative potential of NSCs be leveraged to promote brain homeostasis and repair?

In this review, we discuss recently discovered mechanisms leading to the age-related decline in neurogenesis in vertebrates, focusing on intrinsic factors (e.g., metabolism and genetic regulation) and extrinsic factors from the niche (e.g., systemic factors and other cell types). We also review the connection between NSCs and brain diseases as well as emerging strategies to rescue NSC decline during aging. In addition, we speculate regarding the evolutionary role of vertebrate neurogenesis with a focus on human neurogenesis. Finally, we present how new technological advances could shape our understanding of NSC aging at the molecular, niche, brain, and organismal levels and provide new avenues to slow or potentially even reverse the age-dependent decline in neurogenesis.

Nutrient-Sensing Pathways, Metabolism, and Protein Homeostasis during NSC Aging

Neurogenic niches are sensitive to changes in nutrient availability and signaling, including those occurring during aging. The various cell types in the niche have very different metabolic and protein homeostasis needs, depending on their state (e.g., qNSCs versus actively proliferating NSCs). In this section, we review recent evidence supporting the role of these processes in NSC aging and rejuvenation.

Nutrient-Sensing Pathways

Nutrient-sensing pathways, such as the insulin/insulin growth factor 1 (IGF1)-FOXO pathway, are key conserved regulators of aging (Chantranupong et al., 2015) and are also essential for NSC maintenance and function in the SVZ and DG. For example, early work revealed that loss of FOXO transcription factors (FOXOs), the downstream effectors of the insulin/IGF1 pathway, leads to premature exhaustion of the NSC pool (Paik et al., 2009; Renault et al., 2009; Yeo et al., 2013). Consistently, loss of the PTEN phosphatase (which is upstream of FOXO) also causes NSC depletion (Bonaguidi et al., 2011), even when PTEN loss initially triggers NSC proliferation (Gregorian et al., 2009). More recent work has shown that suppression of IGF1 signaling in young NSCs via IGF1 receptor (IGF1R) conditional knockout *in vivo* (which results in FOXO activation) improves neurogenesis in the SVZ, increases spine density in newborn neurons, and enhances olfactory learning (Chaker et al., 2015). Together, these results indicate that suppressing insulin/IGF1 signaling (and, subsequently, activating FOXO) is beneficial for long-term maintenance of the NSC pool. Suppression of signaling pathways downstream of the insulin/IGF1 pathway, such as the mTOR pathway, are also likely to enhance NSC maintenance (see below). However, it is important to note that increased IGF1 signaling can be beneficial for neuronal function by promoting neuronal differentiation and organization during neurogenesis in the hippocampus and the olfactory bulb (Hurtado-Chong

et al., 2009; Nieto-Estévez et al., 2016). Thus, alternating cycles of low and high insulin/IGF1 signaling might help maintain the stem cell pool while still allowing NSC proliferation and neuronal differentiation. Indeed, cycles of a fasting-mimicking diet with *ad libitum* feeding, which periodically change the levels of insulin and IGF1, increase hippocampal neurogenesis and cognitive performance in old mice (Brandhorst et al., 2015).

Mitochondria

Mitochondria play a central role in maintaining NSC states during aging. Transcriptomic analysis of NSCs isolated from the SVZ or hippocampus revealed that qNSCs express genes involved in β-oxidation, which partly takes place in mitochondria, whereas aNSCs express genes involved in mitochondrial oxidative phosphorylation (Leeman et al., 2018; Shin et al., 2015). Indeed, mitochondria are morphologically different in qNSCs and aNSCs in the adult hippocampus; mitochondria are thin and elongated in qNSCs, whereas they have mixed globular and tubular shapes in aNSCs (Beckervordersandforth et al., 2017). During aging, mitochondria become more dispersed and less perinuclear in qNSCs of the SVZ niche (Capilla-Gonzalez et al., 2014). Furthermore, aging causes mitochondria to become more densely packed in hippocampal aNSCs, with decreased membrane potential and lower levels of ATP (Beckervordersandforth et al., 2017). Restoring mitochondrial function in old aNSCs with piracetam (a drug with suggested use for age-related cognitive decline) can improve hippocampal neurogenesis *in vivo* in old mice (Beckervordersandforth et al., 2017). Similarly, ectopic expression of proliferator-activated receptor gamma coactivator 1 alpha (PGC1a), a factor that increases cellular aerobic capacity by promoting mitochondrial biogenesis and metabolic gene transcription, also improves neurogenesis in the aged SVZ *in vivo* (Stoll et al., 2015). Because aNSCs and qNSCs rely on mitochondria to optimally control metabolism, restoring mitochondrial function in old individuals could improve cellular function across the NSC lineage, resulting in an overall boost in neurogenesis.

Lipid Metabolism

Lipid metabolism is emerging as an important component of NSC regulation, but its role during NSC aging remains unknown. Degradation of lipids via fatty acid oxidation (FAO) is important for maintenance of quiescence in young hippocampal qNSCs *in vivo*, and inhibition of FAO (via addition of malonyl-coenzyme A [CoA]) is sufficient to induce exit from quiescence and enhance NSC proliferation *in vitro* (Knobloch et al., 2017). FAO is also a major regulator of quiescence in hematopoietic (Ito et al., 2012), intestinal (Mihaylova et al., 2018), and muscle stem cells (Ryall et al., 2015). Whether FAO changes with age in NSCs has not yet been examined. However, this process decreases with age in intestinal stem cells (Mihaylova et al., 2018), suggesting that maintaining FAO could play an important role in protecting qNSCs during aging. In contrast, young aNSCs upregulate lipid production through fatty acid synthase (FASN)-dependent *de novo* lipogenesis in the hippocampus (Knobloch et al., 2013). Furthermore, inhibiting FASN *in vivo* abolishes the beneficial effects of running on hippocampal neurogenesis and cognitive function in mice (Chorna et al., 2013). Proper FASN function is also required for hippocampal NSC proliferation in mice and humans (Bowers et al., 2020). Thus, maintenance of lipogenesis in aNSCs could be essential to counter NSC decline during aging. Lipid accumulation in other cells in the niche may also indirectly contribute to NSC aging. For example, dietary supplementation with the mono-unsaturated fatty acid oleic acid leads to lipid droplet formation in ependymal cells, and this is associated with decreased neurogenesis in the SVZ (in the context of an Alzheimer's disease mouse model, 3xTg-AD) (Hamilton et al., 2015). Similarly, obesity induces build-up of senescent glial cells containing excessive fat deposits in the SVZ, and genetic ablation of these senescent glial cells can restore neurogenesis in the SVZ niche (Ogrodnik et al., 2019). Future studies will be needed to determine how specific lipids regulate NSC function during aging and whether lipids could have critical roles in processes beyond metabolism, including membrane homeostasis and signaling. Given the malleability of dietary interventions, modulating the composition of lipids in the diet could provide novel ways to "rejuvenate" old neurogenic niches.

Protein Homeostasis

Preservation of a pristine proteome is essential for the maintenance of cells such as NSCs that must continuously function over long periods of time. NSCs and their progeny use different strategies to maintain protein homeostasis (proteostasis); qNSCs and differentiated progeny rely mostly on the lysosome-autophagy pathway, whereas aNSCs turn to active proteasomes and chaperones (Kobayashi et al., 2019; Leeman et al., 2018; Schaffner et al., 2018; Vonk et al., 2020). During aging, impaired function of the lysosome-autophagy pathway in qNSCs from the SVZ contributes to their reduced ability to exit quiescence and start proliferating (Leeman et al., 2018). However, this decline is not inexorable. Overexpression of a key transcription factor that activates the lysosome-autophagy pathway (transcription factor EB, TFEB) in primary cultures of qNSCs from old SVZs improves the ability of these old qNSCs to exit quiescence (Leeman et al., 2018). The role of the lysosome-autophagy pathway in quiescence (and its decline with age) has also been reported in the hematopoietic stem cell pool (Ho et al., 2017) and in the nematode germline (Bohnert and Kenyon, 2017), suggesting that targeting this pathway in old qNSCs could improve dormant cell function and reactivation upon stimulation. Autophagy is also important in proliferative NSCs. The FOXO family member FOXO3 functionally regulates induction of autophagy genes in primary cultures of aNSCs isolated from the SVZ of young adult mice (Audesse et al., 2019). Finally, differentiated progeny (new neurons) rely mainly on the lysosome-autophagy pathway to maintain a healthy proteome (Schaffner et al., 2018). Induction of autophagy via FOXO transcription factors regulates the morphology and spine density of newborn hippocampal neurons in young adult mice (Schaffner et al., 2018). Thus, targeting the autophagy pathway in old individuals could have multiple beneficial effects by improving the function of qNSCs, helping aNSCs, and favoring newborn neurons.

The function of the proteasome deteriorates in aNSCs during aging, which may contribute to the reduced proliferative capacity of these cells. Expression of proteasomal components declines in SVZ aNSCs with age (Zhao et al., 2016). Enhancing the activity of the proteasome by overexpression of PSMB5 (a component of the 20S proteasome complex) or 18α-GA (a proteasome activator) leads to increased NSC proliferation in culture and *in vivo* in young mice (Zhao et al., 2016), but it remains to be determined whether increased proteasome activity also boosts NSCs from old individuals. Similarly, other proliferative

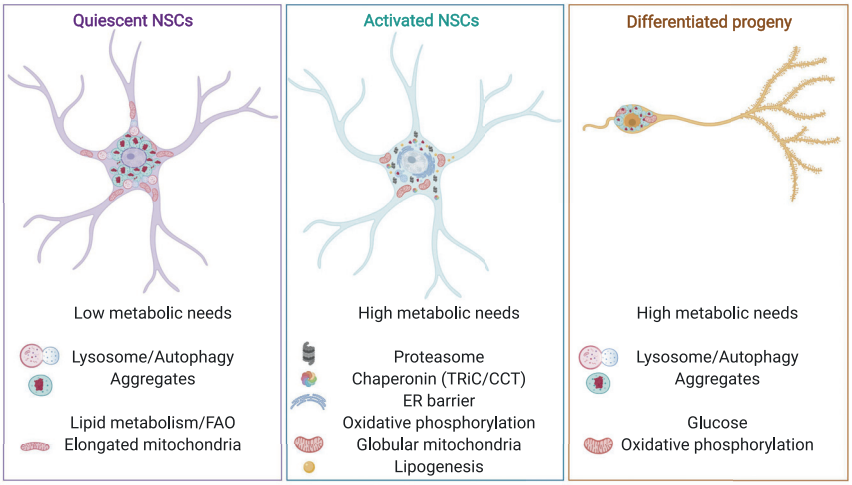

Figure 2. Cellular Pathways Involved in NSC Aging
Shown are cellular and metabolic pathways involved in maintaining NSC and differentiated progeny homeostasis that change during aging.

stem cell pools, including embryonic stem cells (Vilchez et al., 2012) and induced pluripotent stem cells (Buckley et al., 2012), exhibit high proteasome activity, which may be essential for their "immortal" features. Enhancing proteasome activity in old proliferating stem cell pools could help to ameliorate proteostatic stress and restore their regenerative potential.

The chaperone network also declines with aging, and this deficit affects aNSCs and their progeny. Chaperones are heavily remodeled during NSC differentiation (Vonk et al., 2020); proliferating NSCs express high levels of the chaperonin TRiC/CCT, whereas differentiated progeny express small heat shock proteins (Vonk et al., 2020). TRiC/CCT protein levels decline in hippocampal aNSCs during aging (Vonk et al., 2020). It will be interesting to determine the relative contributions of the chaperone network to NSC function and differentiation during aging and its interplay with the other branches of the proteostasis network.

Protein Aggregates

The decline in proteostasis during aging leads to accumulation of aggregated proteins. Interestingly, young adult qNSCs already contain protein aggregates, whereas young aNSCs have very few aggregates (Leeman et al., 2018). These observations suggest that quiescent stem cells may tolerate more protein aggregates or may require proteins with increased propensity to aggregate for their function, which may have deleterious consequences during aging. Old qNSCs freshly isolated from the SVZ have more aggregates than young ones (Leeman et al., 2018), consistent with a decline in lysosome-autophagy function in these cells. qNSCs isolated from the hippocampus also harbor protein aggregates (Morrow et al., 2020). Localization of proteasomes to these protein aggregates, mediated by the intermediate filament vimentin, is important for the transition from quiescence to proliferation (Morrow et al., 2020). The difference in aggregate content between aNSCs and qNSCs may be explained by differences in their protein synthesis rates and proteostasis strategies. Proteasomes in aNSCs may be more efficient at eliminating protein aggregates, and the combination of proteasome and autophagy induction in aNSCs may help to efficiently remove aggregates (Audesse et al., 2019). Furthermore, the high expression levels of the chaperonin TRiC/CCT in proliferative NSCs also contribute to maintenance of misfolded protein solubility (Vonk et al., 2020). Finally, by virtue of being proliferative stem cells, aNSCs may dilute or differentially segregate protein aggregates during cell division and differentiation. Indeed, when young aNSCs divide, the endoplasmic reticulum (ER) forms a physical barrier that segregates damaged proteins to the non-stem daughter cell, protecting aNSCs from proteostatic stress (Moore et al., 2015). This barrier weakens with age in primary cultures of aNSCs from the hippocampus of old mice, which leads to an equal distribution of damaged proteins between stem and non-stem daughter cells during cell division and an increase in proteostatic burden in aNSCs (Moore et al., 2015). This increase in proteostatic burden could lead to an age-dependent decline in NSC function by slowing the rate of NSC proliferation or by promoting a more quiescent state. The specific proteins in these aggregates could also participate in NSC defects, but the composition of the protein aggregates in young and old NSCs remains entirely unknown.

Integration of Nutrient-Sensing, Metabolism, and Proteostasis Pathways in NSCs

Overall, the different metabolic and proteostatic strategies used by qNSCs and aNSCs and their progeny are likely necessary to support the fundamental functional differences between these cell types (Figure 2; see reviews by Cavallucci et al., 2016; Knobloch and Jessberger, 2017). Dormant, non-dividing qNSCs have lower metabolic demands and employ mechanisms to produce energy long term, such as the lysosome-autophagy pathway and FAO. In contrast, actively dividing aNSCs have higher metabolic and protein synthesis rates (Baser et al., 2019), so they rely mostly on oxidative phosphorylation, an effective and fast energy production process, and they upregulate lipogenesis. Actively proliferating aNSCs also require chaperones and active proteasomes to remove short-lived proteins, such as cell cycle regulators, as well as damaged or unfolded proteins to prevent them from forming large aggregates that could compromise their function or be transferred to their progeny. Although metabolic and proteostatic processes ultimately decline with age, this decline can be counteracted. Inducing autophagy can facilitate not only removal of protein aggregates but also clearing of defective mitochondria (mitophagy) and degradation of lipids (lipophagy) to produce free fatty acids for oxidative phosphorylation (Singh and Cuervo, 2011). Similarly, reducing nutrient intake or blocking nutrient-sensing pathways (insulin/IGF1 and mTOR) can improve NSC function by triggering activation of transcription factors (FOXO and TFEB) that coordinate metabolism and proteostasis. Given how connected these pathways are, targeting one of these processes in old NSCs may also restore related pathways, resulting in a synergistic effect to improve old NSC function.

Nutrient-sensing, metabolism, and proteostasis pathways may also be regulated differentially with age, depending on the cell type or even the neurogenic niche. Interestingly, because many aspects of organismal metabolic regulation are non-cell autonomous, it is possible that age-dependent changes in one neurogenic niche could affect other regions. For example, NSCs in the hypothalamus, a region involved in systemic regulation of metabolism, may participate in regulation of organismal metabolism (Bolborea and Dale, 2013). Understanding the integration of different pathways and their specific actions within neurogenic niches or at a distance in the whole organism will be crucial for identifying strategies to counter NSC aging.

Transcriptional, Epigenomic, and Cell Cycle Changes in NSC Aging

The decline in neurogenic potential exhibited by aged NSCs is partly mediated by changes to the global transcriptional and epigenomic landscape that regulates stem cell function. Among these global changes, expression changes in key cell cycle regulators have emerged as critical for NSC activation, exhaustion, and senescence. Cell cycle regulators are particularly interesting because they could be readily modulated to improve old NSC function.

Transcriptomic Analyses of the Aging NSC Niche

Analysis of the NSC transcriptome provides a global snapshot of the cellular processes and pathways that are most affected by age. RNA sequencing (RNA-seq) of freshly isolated astrocytes, qNSCs, aNSCs, and NPCs from the SVZ of young and old mice revealed fundamental transcriptomic differences in aging qNSC and aNSC states (Leeman et al., 2018). During aging, quiescent cells (astrocytes and qNSCs) undergo more transcriptional changes than proliferative cells (aNSCs and NPCs), including changes in proteostasis pathways (lysosome and proteasome) (Leeman et al., 2018). Consistently, cultured aNSCs from the SVZ of young and old mice displayed few transcriptomic differences with age (Lupo et al., 2018). Because aNSCs arise from qNSCs, these results raise intriguing possibilities. The rapid proliferation and differentiation of the transient aNSC population could preclude accumulation of transcriptional changes. Alternatively, the very process of activation could functionally reset the aging hallmarks of qNSCs, leading to a more "youthful" transcriptional landscape.

One challenge in unravelling how aging affects complex tissues, such as neurogenic niches, is cellular heterogeneity. The rapid expansion of single-cell RNA-seq technologies has helped probe the heterogeneity of cell types and transcriptional profiles in young and old neurogenic niches in the SVZ and hippocampus (Artegiani et al., 2017; Basak et al., 2018; Dulken et al., 2017, 2019; Hochgerner et al., 2018; Kalamakis et al., 2019; Llorens-Bobadilla et al., 2015; Luo et al., 2015; Mizrak et al., 2019; Shi et al., 2018; Shin et al., 2015; Zywitza et al., 2018). By capturing the transcriptomes of individual cells along a continuous differentiation lineage, these analyses have identified intermediary cell states during activation and neuronal differentiation (Dulken et al., 2017; Llorens-Bobadilla et al., 2015; Shin et al., 2015) and key genes that change throughout NSC differentiation (Shin et al., 2015). Single-cell transcriptomic analyses of the whole SVZ niche have revealed that the majority of age-related transcriptional changes occur in specific cell populations (microglia, endothelial cells, oligodendrocytes, astrocytes, and qNSCs), all of which exhibit strong transcriptional upregulation of interferon signaling pathways with age (Artegiani et al., 2017; Dulken et al., 2019; Kalamakis et al., 2019). Single-cell RNA-seq analyses have also shown that qNSCs and aNSC population numbers are significantly smaller in SVZs from old mice (Dulken et al., 2019; Kalamakis et al., 2019), consistent with previous data by immunofluorescence staining and bromodeoxyuridine (BrdU) incorporation (Luo et al., 2006). Collectively, these single-cell transcriptomic studies have established a global cell atlas of the neurogenic niches and revealed changes in cell composition (with decreases in NSCs) and in the transcriptome of specific cell populations (e.g., microglia) with aging. It will be interesting to determine which of these age-dependent changes can be reversed by known "rejuvenation" interventions, such as dietary changes.

Chromatin Modifiers and Epigenomic Changes

Analysis of the epigenomic landscape and resulting chromatin states of NSCs during aging can provide key information about how age affects cell identity and function (Klemm et al., 2019). Because of the reversibility of epigenomic marks, identifying the enzymes that are responsible for the epigenomic changes observed during NSC aging is an attractive strategy for therapeutic intervention.

Historically, many studies have been dedicated to understanding the role of DNA methylation and its upstream modifiers, such as DNA methyltransferases, in embryonic and adult neurogenesis (extensively reviewed in Cui and Xu, 2018; Jobe and Zhao, 2017). More recently, studies have begun to characterize global DNA methylation changes throughout aging. Global levels of 5-hydroxymethylcytosine (5hmC) decrease with age in whole hippocampus samples and correlate with the age-related decline in neurogenesis (Gontier et al., 2018). In parallel, mRNA levels of TET2, the enzyme that catalyzes formation of 5hmC from 5-methyl cytosine (5mC) via oxidation, also decrease in the hippocampus with age. Reducing *in vivo* TET2 expression in young hippocampal NPCs alone (by injection of tamoxifen in *Tet2*$^{flox/flox}$; *NestinCre-ER*^{T2} mice) is sufficient to decrease neurogenesis and cognitive performance, suggesting a cell-autonomous effect (Gontier et al., 2018). Conversely, overexpression of TET2 in the DG of young adult mice via *in vivo* lentivirus administration increases the number of newborn neurons in the hippocampus and improves spatial learning and memory (Gontier et al., 2018). Thus, overexpressing or activating TET2 in middle-aged animals could be a strategy to enhance neurogenesis and cognitive performance in aging animals.

Global profiling of histone methylation marks (histone H3 lysine 4 trimethylation [H3K4me3] and histone H3 lysine 27 trimethylation [H3K27me3] chromatin immunoprecipitation sequencing [ChIP-seq]) and DNA methylation marks (5mc and 5hmC) have uncovered changes in aNSCs cultured from young and old SVZs (Lupo et al., 2018). Although there are relatively few epigenomic (and transcriptomic) differences, the regulatory marks associated with the *Dbx2* locus change with age (Lupo et al., 2018). The *Dbx2* locus encodes a transcription factor that was previously implicated in spinal cord development (Pierani et al., 1999). Overexpression of DBX2 in young aNSCs *in vitro* leads to reduced NSC proliferation and changes in the transcriptome that resemble those occurring in old aNSCs (Lupo et al., 2018).

Thus, decreasing DBX2 levels could have potential therapeutic advantages for improving neurogenesis in old individuals.

Several studies have also characterized the global epigenomic differences between qNSCs and aNSCs derived from embryonic stem cells (ESCs) or neonatal mice, although it is not yet known how these epigenomic marks could be affected during aging. Co-localization of histone H3 lysine 27 acetylation (H3K27ac) (a chromatin mark associated with enhancers) and p300 (a transcriptional co-activator that binds enhancers) has been used to identify quiescence- and activation-specific enhancers genome-wide in cultured murine ESC-derived NSCs (Martynoga et al., 2013). Enhancers in quiescent cells exhibit enrichment for the nuclear factor one (NFI) transcription factor family motif (Martynoga et al., 2013). The loss of the family member nuclear factor one X (NFIX) (in *Nfix*$^{-/-}$ mice) is sufficient to reduce the proportion of qNSCs in the hippocampus of postnatal mice, implicating NFIX as a key regulator of the quiescent state (Martynoga et al., 2013). Epigenomic assays that profile long-range binding interactions, such as chromatin interaction analysis with paired-end tag sequencing (ChIA-PET), have also uncovered how transcription factors bind to regulate NSC maintenance. ChIP-seq and ChIA-PET of murine neonatal forebrain-derived aNSCs identified SOX2 binding sites predominantly located in promoters and enhancers (Bertolini et al., 2019). SOX2 is an important transcription factor for NSC maintenance, and its loss causes self-renewal defects (Graham et al., 2003). SOX2 enhancer-promoter interactions are particularly important for regulation of the gene *Socs3*, a JAK/STAT signaling inhibitor, and SOCS3 overexpression can rescue the self-renewal defect observed in *Sox2*$^{-/-}$ NSCs (Bertolini et al., 2019). However, how NFIX and SOX2 and their target genes change with age and affect NSC aging has yet to be determined.

Global profiling of epigenomic changes within aging neurogenic niches has identified potential therapeutic targets, such as DBX2 and TET2. However, most of the studies so far have been conducted on whole-tissue samples or using cultured cells. There is a need for single-cell epigenomic assays (such as single-cell assay for transposase-accessible chromatin using sequencing [scATAC-seq]; Buenrostro et al., 2015) to identify heterogeneous epigenomic regulation within and between cell types. In addition, profiling a greater diversity of epigenomic marks on specific, isolated *in vivo* cell populations in the niche during aging will provide key insights into how to restore this landscape and rejuvenate the niche.

Regulation of the Cell Cycle and Senescence

The ability of NSCs to efficiently enter the cell cycle declines with age. Genes involved in regulating the cell cycle, including tumor suppressors, play a key role in the maintenance of NSC quiescence and activation. These same cell cycle regulators are involved in initiation of cellular senescence, which could diminish the functionality of the stem cell pool during aging. We next discuss how regulation of gene expression programs that control the balance between quiescence and proliferation is critical to guarantee lifelong neurogenesis and avoid premature stem cell exhaustion and senescence.

p16^{INK4a} is a negative cell cycle regulator and a prominent biomarker for cellular senescence, a cell state characterized by irreversible cell cycle arrest and distinct morphological and transcriptional changes (reviewed in Hernandez-Segura et al., 2018). Expression of *p16*^{INK4a} is strongly induced with age in the SVZ and may contribute to the accompanying decline in neurogenesis through cell cycle suppression of aNSCs and NPCs (Molofsky et al., 2006). In middle-aged mice, *p16*^{INK4a} suppresses hippocampal NSC proliferation in response to exercise (Micheli et al., 2019). This suppression could be mediated by the ability of *p16*^{INK4a} to induce senescence. Indeed, *p16*^{INK4a} upregulation (driven by removal of the monocytic leukemia zinc-finger protein [MOZ]) leads to replicative senescence in ESC-derived NSCs (Perez-Campo et al., 2014). In cultured NSCs derived from the hypothalamus, expression of an upstream repressor of the *p16*^{INK4a} locus, the non-coding RNA *Hnscr*, declines with age (Xiao et al., 2020). Knocking down *Hnscr in vivo* in hypothalamic NSCs increases cellular senescence and results in decreased cognitive performance (i.e., novel object recognition) (Xiao et al., 2020). Consistently, the senescence phenotype of primary NSCs cultured from the SVZ of an accelerated senescence mouse model (SAMP8 mice) could be prevented by decreasing the mRNA levels of *p19*^{ARF}, another tumor suppressor encoded within the same locus as *p16*^{INK4a}, through epigenomic regulation of the locus by histone acetyltransferases (Soriano-Cantón et al., 2015). Collectively, these studies suggest that increased expression of negative cell cycle regulators, such as *p16*^{INK4a} and *p19*^{ARF}, drives senescent phenotypes in NSCs and seems to be at least partially responsible for the decrease in neurogenic potential observed in NSCs during aging.

Conversely, expression of positive cell cycle regulators, such as the Polycomb family member BMI-1 (PCGF4) and cyclin-dependent kinases (CDKs), can promote NSC expansion and lead to cognitive improvement. BMI-1 is a known transcriptional repressor of cell cycle inhibitors, including *p19*^{ARF}*/Mdm2/p53* (Gu et al., 2014), and upregulation of BMI-1 increases self-renewal in hippocampal NSCs (Zelentsova-Levytskyi et al., 2017). Furthermore, simultaneous overexpression of CDK4 and cyclin D1 in hippocampal NSCs in older mice (16 months old) by lentiviral delivery of a transgene *in vivo* increased hippocampal neurogenesis and rescued aspects of age-related cognitive impairment (Berdugo-Vega et al., 2020).

Surprisingly, however, low-level overexpression of negative regulators of the cell cycle (*p16*^{INK4a}*/p19*^{ARF}*/p53)* in mice increases NSC numbers in the SVZ and DG of old individuals and improves cognitive performance (Carrasco-Garcia et al., 2015). The beneficial effects of low-level overexpression of negative cell cycle regulators might be due to their ability to prevent premature exhaustion of the stem cell pool. Thus, the timing and levels of cell cycle regulator expression are key to maintaining NSC fitness throughout life.

Overall, the critical nature of cell cycle regulators such as p16^{INK4a}, p19^{ARF}, p53, and BMI-1 in regulating NSC viability and neurogenesis has positioned them as potential therapeutic targets to rejuvenate aged NSCs. However, these pathways are delicately regulated. Future work remains to be done to determine the correct dosage and timing of manipulation that will improve NSC health without inadvertently causing premature stem cell exhaustion or senescence.

The Role of the Niche and Inflammation in NSC Aging

NSCs reside in complex and specialized microenvironments within the brain that contain different cell types and are

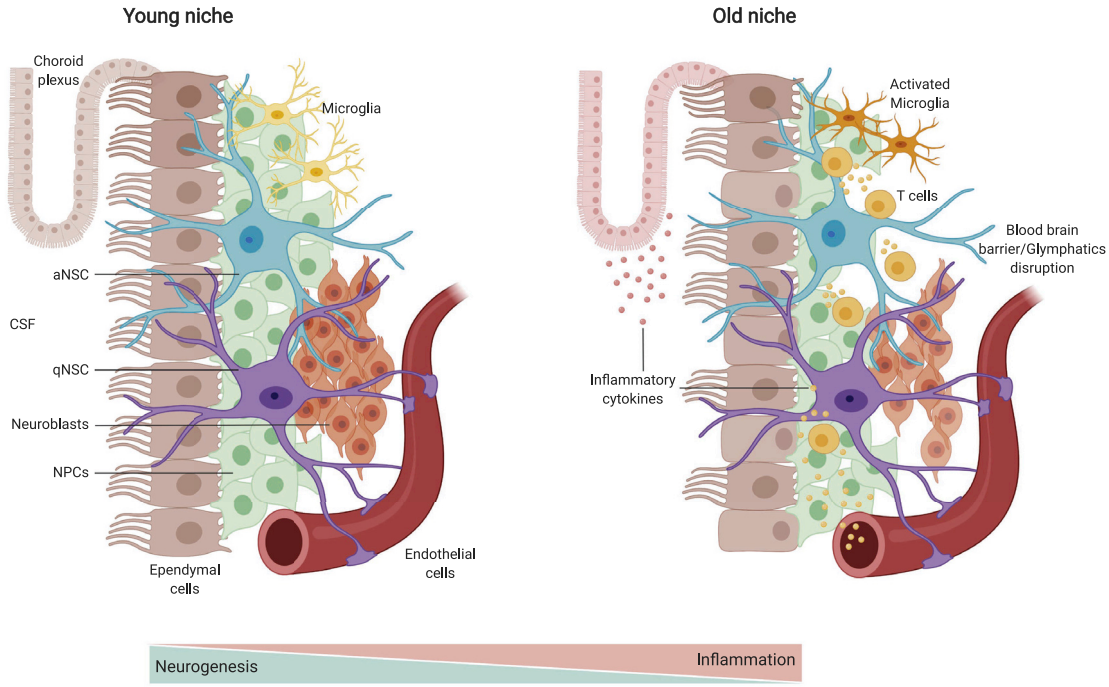

Figure 3. The Role of the Niche and Inflammation in NSC Aging
Shown are changes that occur in the NSC niche (the SVZ is depicted) during aging (left, young; right, old). Inflammation increases in the niche, highlighted by the increase in inflammatory cytokines, activated microglia, and T cell infiltration.

influenced by a variety of local and systemic factors. NSCs can integrate signals from the niche to couple their activation state and fate decisions to the tissue demands. The cellular composition of NSC niches, their response to local or systemic cues, and even their physical properties, such as stiffness (Segel et al., 2019), change during aging. This section examines recent advances in our understanding of how age-related changes in the niche (e.g., systemic or local extracellular cues or other cell types) can influence and contribute to the decrease in neurogenesis during aging (summarized in Figure 3). Although many of the mechanisms that underlie the NSC response to these extrinsic cues are not yet known, they are likely to impinge on the intrinsic pathways described above to affect NSC function. In the future, it will be interesting to better understand the interplay between extrinsic and intrinsic regulators of NSC aging.

Systemic Blood Factors and Local Factors

Systemic factors in the blood play an important role in NSC aging. Heterochronic parabiosis studies, in which the circulatory system of a young and an old mouse are joined, have revealed positive and negative effects of young and old blood on neurogenesis in the DG (Rebo et al., 2016; Villeda et al., 2011) and SVZ neurogenic niches (Katsimpardi et al., 2014). A variety of systemic factors and signaling pathways mediating these effects have been identified, many of which are immune related. CCL11/Eotaxin (Villeda et al., 2011), an inflammatory cytokine, and β_2-microglobulin (Rebo et al., 2016; Smith et al., 2015a), a component of major histocompatibility (MHC) class I, are elevated in old blood and have negative effects on neurogenesis and cognition in young animals. In contrast, GDF11, a circulating transforming growth factor, appears to be present at higher levels in young blood and to have positive effects on old SVZ NSCs (Katsimpardi et al., 2014), but the extent of GDF11 rejuvenating properties remain unclear (Egerman et al., 2015; Smith et al., 2015b). TIMP2, a metalloproteinase inhibitor found in human umbilical cord plasma, improves synaptic plasticity and cognition when injected systemically into old mice (Castellano et al., 2017). However, the number of newborn neurons in the hippocampus is unchanged upon TIMP2 injection, suggesting that this factor acts independent of neurogenesis, perhaps by changing the properties of the extracellular matrix (Castellano et al., 2017). It also remains to be determined whether these factors mediate their effects on neurogenesis by acting directly on niche cells or indirectly by shifting the niche milieu toward a less inflammatory state. In addition to systemic factors, local morphogens, including Notch, Wnt, sonic hedgehog, and bone morphogenic proteins (BMPs), are critical during embryonic development, and they also regulate NSCs throughout life (reviewed in Bond et al., 2015; Ming and Song, 2011). Upregulating Wnt signaling in the hippocampus can counteract the age-related decrease in neurogenesis and its associated cognitive decline (Seib et al., 2013). Notch signaling also plays an important role in maintaining NSC quiescence and activation in SVZ and hippocampal niches (Basak et al., 2012; Blomfield et al., 2019; Engler et al., 2018; Zhang et al., 2019) and could be critical during aging.

The Choroid Plexus and CSF

The choroid plexus is a monolayer of epithelial cells in the brain ventricles that produces CSF (Johanson et al., 2011) and constitutes the blood-CSF barrier, integrating signals from both systems. Analysis of the effects of the lateral ventricle choroid plexus secretome on the growth of freshly purified NSCs

in vitro revealed that aNSCs from the SVZ are very sensitive to age-related changes in secreted factors from the choroid plexus (Silva-Vargas et al., 2016). Specifically, factors that can induce NSC proliferation, such BMP5 and IGF1, are depleted from the choroid plexus secretome of old mice (Silva-Vargas et al., 2016). The aged choroid plexus also exhibits an expression profile corresponding to a type I interferon (IFN-I) response (i.e., IFNα and IFNβ) (Baruch et al., 2014). Notably, blocking IFN-I signaling by delivery of antibodies against the IFNα receptor into the CSF improves hippocampal neurogenesis and cognitive function in old mice (Baruch et al., 2014). Hypothalamic NSCs can secrete exosomes into the CSF at the third ventricle (Zhang et al., 2017). Thus, NSCs in the hypothalamic niche may not only be influenced by the CSF but may also contribute to systemic changes that affect the aging process (Zhang et al., 2017). The choroid plexus and CSF play a crucial role, relaying changes in the brain environment, including inflammatory signals during aging, to the NSC niche.

Endothelial Cells and Pericytes

The brain's vasculature (endothelial cells and surrounding pericytes) forms a tightly regulated interface between the circulatory system and the brain parenchyma, known as the blood-brain barrier. Recent studies have shown that the transcriptome of endothelial cells in the neurogenic niche changes dramatically with age, shifting toward an inflammatory transcriptomic profile (Dulken et al., 2019; Kalamakis et al., 2019; Leeman et al., 2018; Yousef et al., 2019). Endothelial cells and pericytes can secrete factors, such as placental growth factor 2 (PlGF-2), that promote proliferation of NSCs isolated from the SVZ of young mice (Crouch et al., 2015). However, in middle-aged mice, endothelial cells start producing increased levels of transforming growth factor-β (TGF-β), an inflammatory cytokine that triggers NSC apoptosis via TGF-β and SMAD3 signaling (Pineda et al., 2013). Consistently, genetic or pharmacological attenuation of the TGF-β pathway can rescue neurogenesis in old mice (Yousef et al., 2015). Endothelial cells also display focal upregulation of the vascular cell adhesion molecule (VCAM1) in old brains (Yousef et al., 2019). Decreasing VCAM1 levels in endothelial cells, genetically or via systemic anti-VCAM1 antibodies, reverses the negative effects of old plasma in the young brain and increases the number of NSCs in the hippocampus of old mice (Yousef et al., 2019). Although VCAM1 is normally known for facilitating vascular-immune cell interactions (Osborn et al., 1989; Schlesinger and Bendas, 2015), during aging, VCAM1 may allow tethering of blood cells to endothelial cells but not their transport, and this may induce chronic inflammation of endothelial cells (Yousef et al., 2019). The inflamed state of endothelial cells could, in turn, lead to microglia activation (see below), inhibition of NSC proliferation, and cognitive impairment (Yousef et al., 2019). Thus, restoring endothelial cell function in old brains may help to reduce inflammation, ameliorate NSC decline, and improve brain function.

Microglia

Microglia are the resident immune cells of the brain. These cells patrol the brain parenchyma, maintaining homeostasis through engulfment and degradation of extracellular materials via phagocytosis. The phagocytic activity of microglia helps to maintain homeostasis in the adult hippocampal neurogenic niche by removing newborn NPCs that undergo apoptosis before becoming neuroblasts (Sierra et al., 2010). Furthermore, the secretome of phagocytic microglia limits production of new neurons in hippocampal NSC cultures and when injected directly into the hippocampus of young adult mice (Diaz-Aparicio et al., 2020). However, during aging, microglial phagocytosis is impaired (Marschallinger et al., 2020; Pluvinage et al., 2019) which may contribute to accumulation of debris and aggregates in the niche and may perturb NSC niche homeostasis. Microglia also normally support neurogenesis in the hippocampus and SVZ through production of growth factors and cytokines in young animals (Shigemoto-Mogami et al., 2014; Ziv and Schwartz, 2008). Sustained inflammation during aging leads to increased microglial activation (i.e., proliferative microglia secreting inflammatory cytokines) and subsequent reduction in NSC proliferation in the SVZ and hippocampus (Bachstetter et al., 2011; Monje et al., 2003; Solano Fonseca et al., 2016). Therefore, improving microglial function in old brains might not only boost the function of other cells (e.g., NSCs) in the niche but also actively promote clearance and reduce infiltration of immune cells in the niche.

Infiltration of T Cells

The brain has long been regarded as an immune-privileged organ, especially under physiological conditions. Interestingly, however, immune cells, such as T cells, infiltrate the brain of old individuals in mice and humans (Dulken et al., 2019; Mrdjen et al., 2018; Ritzel et al., 2016). Single-cell RNA-seq of the entire SVZ niche revealed infiltration of CD8+ T cells in the old SVZ, which was confirmed by immunocytochemistry in aged mice and elderly humans (Dulken et al., 2019). T cell receptor sequencing showed that brain T cells are clonally expanded (Dulken et al., 2019), suggesting that they may recognize specific antigens in the brain rather than passively diffuse through a disrupted aged blood-brain barrier (Montagne et al., 2015). These T cells may be attracted to the old neurogenic niche by a combination of brain-specific antigens and chemokines. An exciting possibility is that they may recognize neo-antigens derived from aggregated proteins in old NSCs (Leeman et al., 2018). This is the case in Parkinson's disease and multiple sclerosis, where T cells recognize α-synuclein (Sulzer et al., 2017) and β-synuclein (Lodygin et al., 2019), respectively.

Infiltrating T cells are the main cellular source of IFNγ in the SVZ niche (Dulken et al., 2019). IFNγ is known to act as an anti-proliferative agent in the adult neurogenic niche, suggesting that accumulation of T cells might contribute to age-related neurogenic decline (Li et al., 2010b; Pereira et al., 2015). Indeed, the IFN response is associated with a decline in NSC proliferation in the SVZ (Dulken et al., 2019). Interestingly, inhibition of IFN signaling (using IFNα and IFNγ receptor knockout mice) results in higher proliferating NSC numbers in the SVZ of old animals (Kalamakis et al., 2019). Similarly, inhibition of the chemokine CXCL10, which is released in response to IFNγ, decreases the number of qNSCs and increases production of neuroblasts in old SVZ neurogenic niches, providing a causal link between inflammation and the inability of NSCs to activate in the old brain (Kalamakis et al., 2019). Thus, although infiltrating T cells may have beneficial effects during development (hippocampal neurogenesis and spatial learning abilities are significantly decreased in T cell-deficient mice in early adulthood; Wolf et al., 2009; Ziv et al., 2006), they may have a

detrimental effect on NSCs during aging, in part by secreting inflammatory cytokines.

It will be interesting to determine the relationship between infiltrating T cells and NSCs during development and aging and the potential shift from a protective role during development to a detrimental, possibly cytotoxic effect of T cells in the inflamed old brain. It will also be important to explore how the different neurogenic niches respond to immune cell infiltration and inflammatory signals. For example, the proinflammatory pathway involving IκB kinase (IKKβ) and the downstream nuclear factor κB (NF-κB) impairs survival, proliferation, and differentiation of adult NSCs in the hypothalamic neurogenic niche and results in obesity and pre-diabetes in mice (Li et al., 2012). Thus, blocking T cells or reducing inflammation levels in old neurogenic niches could be an effective strategy to restore old brain function.

Meningeal Lymphatic Vessels and the Glymphatic System

The brain contains dorsal and basal lymphatic vessels in the meninges that assist with drainage of CSF components and meningeal immune cells into the cervical lymph nodes (Ahn et al., 2019; Da Mesquita et al., 2018; Louveau et al., 2015). In addition, the "glymphatic" system, a glia-associated lymphatic system (Aspelund et al., 2015), is likely connected to lymphatic vessels (Louveau et al., 2017) and has been shown to be involved in β-amyloid clearance (Xie et al., 2013). Meningeal lymphatic vessels and the glymphatic system provide a new potential link between the CNS and the peripheral immune system. Interestingly, the meningeal lymphatic system also declines functionally during aging (Ahn et al., 2019; Da Mesquita et al., 2018), and disrupting meningeal lymphatic vessels with a photodynamic drug (Visudyne) results in cognitive impairments in young mice (Da Mesquita et al., 2018). Although enhancing meningeal lymphatics improves aspects of learning and memory in old mice, it does not increase the number of dividing NSCs in the hippocampus of these mice (Da Mesquita et al., 2018). Nonetheless, it will be exciting to determine how meningeal lymphatic vessels and the glymphatic system interact and integrate with the neurogenic niche to influence the function of NSCs and other niche cells during aging.

Ependymal Cells

Ependymal cells form a layer of epithelial multiciliated cells that line the brain's ventricular walls. The coordinated beating of ependymal cilia contributes to CSF dynamics, which is crucial for exposure of NSCs to trophic factors and metabolites and for clearance of waste and toxins from the brain (Spassky and Meunier, 2017). Although qNSCs and ependymal cells derive from a common radial glial cell progenitor during development (Ortiz-Alvarez et al., 2019; Spassky et al., 2005) and share phenotypic markers (SOX2, SOX9, NESTIN, and CD133), these two cell types have different morphologies and functions in the adult brain. Ependymal cells isolated by fluorescence-activated cell sorting (FACS) using α-smooth muscle actin (SMA) as a marker are transcriptionally different from NSCs and do not proliferate *in vitro* or *in vivo* under pro-growth conditions that normally induce NSCs proliferation (Shah et al., 2018). Single-cell RNA-seq confirmed that ependymal cells do not have NSC function (Shah et al., 2018). However, modulation of CSF dynamics by ependymal cell cilia can affect NSC function and neurogenesis, and this could be critical during aging. For example, beating of ependymal cilia is required for directional migration of neuroblasts toward the olfactory bulb in mice (Sawamoto et al., 2006). During aging, ependymal cells accumulate intermediate filaments, dense bodies, and lipid droplets and exhibit fewer cilia (Capilla-Gonzalez et al., 2014). Furthermore, ependymal cell cilium tufts are more tangled in old mice, resulting in extended ventricular areas completely devoid of cilia (Capilla-Gonzalez et al., 2014). These age-related changes in ependymal cells could contribute to neurogenic decline and negatively affect neuroblast migration, although this has not been tested directly. Thus, uncovering exactly how ependymal cells relay signals from the ventricle and choroid plexus to the SVZ niche and the changes they undergo during aging may help identify strategies to counteract NSC and brain function decline.

Neuronal Inputs

The neurogenic niche is embedded in and interacts with neural networks in the brain. In the hippocampus, NSC quiescence is maintained by tonic GABAergic innervations from parvalbumin-positive interneurons (Song et al., 2012), which are themselves regulated by long-range projections from the medial septum (Bao et al., 2017). Hippocampal mossy cells, which are glutamatergic neurons innervating mature granule cells and local interneurons (Scharfman, 1995), also contribute to this circuitry by promoting NSC quiescence via local interneurons and NSC activation through direct glutamatergic innervation of NSCs (Yeh et al., 2018). Likewise, the anterior ventral SVZ is innervated by proopiomelanocortin (POMC) neurons from the hypothalamus that promote NSC proliferation and deep granule neuron generation (Paul et al., 2017). Interestingly, hunger and satiety states could affect NSC proliferation in a POMC neuron-dependent manner (Paul et al., 2017). Although all of these studies were carried out in young animals, they suggest that modulating the neural circuitry of the old NSC niche by electrical stimuli or indirect input from feeding via the hypothalamus may rescue NSC function and neurogenesis.

The newborn neurons generated from the SVZ and hippocampal niches have to functionally integrate into the existing neural circuitry to survive. In the olfactory bulb, new neurons integrate into the granule cell and glomerular layers, where they function as interneurons (Whitman and Greer, 2007). Long-term *in vivo* imaging showed that newborn neurons do not compete for integration in the olfactory bulb but are added non-selectively (Platel et al., 2019). In the hippocampus, immature newborn neurons migrate to the granule cell layer of the DG and differentiate into dentate granule cells. Freshly integrated neurons provide new substrates for learning and might facilitate formation of new memories. Excitingly, favoring adult-born dentate granule cell integration by transient overexpression of Kruppel-like factor 9 (KLF9), a negative transcriptional regulator of dendritic spines in mature granule cells, can rejuvenate the DG with new neurons and improve cognitive function in old mice (McAvoy et al., 2016). However, it remains to be determined whether newborn neurons replace older, less functional neurons in the brain or whether they replace other neurons, especially in the DG (Murray et al., 2020). In addition, as new cells integrate, pre-existing circuits could also be altered, which could make established memories harder to access at later time points (Frankland et al., 2013; Gao et al.,

2018). Thus, ensuring that newborn neurons integrate into the correct circuits will be equally essential to rejuvenate old brain function.

Similarities and Differences between Neurogenic Niches

Although many molecular mechanisms governing the regulation of NSC populations are shared between the SVZ and the hippocampus niches, some signaling pathways have antagonistic effects on NSC regulation, depending on the neurogenic region. For example, IFN signaling early in life seems to be important to maintain neurogenesis in the hippocampus (Baruch et al., 2014), whereas over-activation of this pathway during aging negatively affects the neurogenic niche in the SVZ (Dulken et al., 2019). Similarly, reducing p38 mitogen-activated protein kinase (MAPK) signaling (an important signaling pathway that coordinates inflammation, proliferation, and apoptosis) attenuates the age-dependent decline in neurogenesis in the hippocampus (Cortez et al., 2017), whereas inhibiting p38 signaling in cultured NSCs isolated from the SVZ of old mice increases their neurogenic potential (Moreno-Cugnon et al., 2020). Furthermore, NSCs from the hippocampus and SVZ differ in their long-term turnover dynamics. Hippocampal NSCs largely undergo asymmetric division, resulting in generation of neurons and decline in NSCs (Encinas et al., 2011), whereas NSCs in the SVZ undergo symmetric self-renewing and consuming divisions, allowing simultaneous self-renewal and neuronal production later in life (Calzolari et al., 2015; Obernier et al., 2018). A more complete understanding of the similarities and differences between SVZ and hippocampal niches and their age-dependent regulatory mechanisms would provide new insights into generalized versus specific strategies to improve regeneration in old brains.

NSCs and Diseases: Link with Aging and Translational Potential

Because of their regenerative abilities, therapeutic interventions involving NSCs have the potential to improve pathological brain phenotypes. Consequently, how NSCs are affected by disease states and how they might be harnessed to improve pathological states is an exciting current field of study.

Neurodegenerative Diseases

Aging is accompanied by a decline in neurogenesis and an increased risk of neurodegenerative diseases, including Alzheimer's and Parkinson's diseases. A recent study showed that Alzheimer's disease progression in humans is accompanied by a decline in the number and maturation level of newborn neurons in the hippocampus, which is more precipitous than the decline during non-pathological aging (Moreno-Jiménez et al., 2019). This is consistent with the notion that reduced neurogenesis may partially underlie aspects of Alzheimer's disease pathology. Thus, the capacity of NSCs to generate functional newborn neurons has sparked interest in transplanting NSCs or activating pre-existing NSCs in diseased brains for therapeutic purposes. Transplantation of human NSCs near the hippocampus in the amyloid precursor protein (APP)/presenilin1 (PS1) Alzheimer's mouse model can reduce amyloid plaque load and improve hippocampus-dependent cognition (McGinley et al., 2018). In an Alzheimer's mouse model, transplantation of fetal murine NSCs improves cognition, reduces amyloid processing, increases anti-inflammatory cytokine secretion, and restores synaptic impairment (Kim et al., 2015). However, this transplantation therapy is only effective when administered prior to advanced disease progression, indicating that the timing of stem cell transplants is essential for delivering therapeutic benefits (Kim et al., 2015). Similar proof-of-concept transplantation studies have been performed for other neurodegenerative diseases, such as Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), and multiple sclerosis (MS) (reviewed in Reekmans et al., 2012; Tang et al., 2017). A potentially more efficient strategy could be to identify ways to stimulate resident NSCs to improve neurodegenerative pathologies. Simultaneously increasing levels of hippocampal neurogenesis and elevating brain-derived neurotropic factor (BDNF) levels in an Alzheimer's disease mouse model is sufficient to improve cognition, although increasing neurogenesis alone does not confer cognitive benefits (Choi et al., 2018). It is also important to note that NSC-derived newborn neurons are functionally different from those that die during disease progression. Thus, further research is needed to assess whether the observed beneficial effects of NSC transplantation or stimulation are a consequence of the integration of newborn neurons into the neuronal circuits damaged by disease (e.g., dopaminergic neurons in PD) or whether they result from remodeling of the existing circuitry (i.e., by production of specific factors).

Stroke

The regenerative potential of NSCs is activated during stroke, when regions of the brain are deprived of oxygen (ischemia) because of arterial occlusion or rupture. Following ischemic injury, a common stroke model, resident NSCs receive cues to activate and differentiate into glial cells, which form a "glial scar" (Adams and Gallo, 2018), and neurons, which migrate to the site of injury and can improve neuropathology in rodents (Kernie and Parent, 2010) and humans (Jin et al., 2006). However, the regenerative potential of NSCs declines drastically with age, limiting their ability to repair injury following stroke. Transplantation of exogenous NSCs has the potential to improve recovery from ischemic injury in elderly stroke patients. Injection of human NSCs (derived from fetal brain tissue or induced pluripotent stem cells [iPSCs]) into the ipsilesional hippocampus of a mouse model of stroke results in infarct volume reduction, decreased expression of pro-inflammatory factors, and improvement of stroke-induced behavioral deficits (Eckert et al., 2015; Huang et al., 2014). Co-administration of human NSCs (derived from fetal brain tissue) with a small-molecule neuroprotectant (3K3A-activated protein C) in mice with ischemia following arterial occlusion results in increased neuronal production, promotion of synaptic circuit repair, and functional improvement of post-ischemic recovery (Wang et al., 2016). Significant interest is also being given to stimulating endogenous NSCs instead of transplanting them following ischemic injury. For example, treating rats post-stroke with cerebrolysin, a mixture of neurotrophic peptides, increases SVZ neurogenesis and oligodendrogenesis and improves neurological function (Zhang et al., 2013). Similarly, injections of GDF11 after stroke increase NPC numbers in the SVZ and improve neuronal regeneration in mice (Lu et al., 2018). However, sustained activation of NSCs after injury can also lead to stem cell exhaustion, depleting the brain's lifelong regenerative reservoir. Thus, finding a balance

between NSC activation and exhaustion will be essential. There is additionally concern that transplantation of exogenous NSCs could have deleterious effects because of improper functional integration of newborn neurons. Indeed, post-stroke hippocampal neurogenesis can be detrimental to contextual and spatial memory performance, and newborn neurons can improperly integrate into the pre-existing hippocampal circuitry (Cuartero et al., 2019). In this context, inhibiting hippocampal neurogenesis (using temozolomide or with a genetic model [*Nestin-Cre ERT2/NSE-DTA*]) actually improves memory retention (Cuartero et al., 2019). These results highlight the need to better understand neuronal circuit integration and synaptic remodeling to harness the regenerative potential of NSCs for stroke patients.

Cancer

The high proliferative capacity of NSCs increases their risk for mutagenesis and makes NSCs more prone to become precursors to certain brain cancers, such as gliomas and glioblastomas. Indeed, glioblastoma-initiating cells are remarkably similar to non-pathological NSCs (covered comprehensively in other reviews, such as Goffart et al., 2013). For example, acyl-CoA-binding protein (ACBP), a proliferative factor expressed exclusively in astrocytes, NSCs, and NPCs, is highly expressed in glioblastoma cells and drives tumorigenesis (Duman et al., 2019). Furthermore, deep sequencing of human glioblastoma samples showed that NSCs in the SVZ contained low-level driver mutations that matched the mutational landscape of the corresponding primary glioblastoma, suggesting that NSCs could be the cell of origin of human glioblastoma (Lee et al., 2018). Thus, understanding the processes underlying NSC activation and proliferation could help uncover the molecular triggers of tumorigenesis and provide new treatments for brain cancers. Furthermore, it will help ensure the safety of translational NSC therapies, such as transplantation and endogenous activation, by preventing potential glioblastoma formation.

Interventions to Rejuvenate Old Neurogenic Niches

Although NSC levels and neurogenic potential decline during aging, with detrimental functional consequences, this decline is not inexorable. As described above, targeting specific molecular pathways and metabolic organelles in NSCs, such as TFEB and lysosomes (Leeman et al., 2018), transcription factors (Carrasco-Garcia et al., 2015), and mitochondria (Beckervordersandforth et al., 2017), can improve NSC function in the elderly. Despite the promise of such molecular manipulation, an interesting parallel avenue of research involves using lifestyle interventions to improve NSC and brain function. So far, three interventions have shown the greatest potential for rejuvenating old neurogenic niches: diet, exercise, and systemic blood factors (Figure 4).

Dietary Interventions

Dietary interventions, such as dietary restriction and intermittent fasting, are arguably the most well-established longevity interventions to date and have been shown to confer multiple health benefits and extend the lifespan in mice (Mitchell et al., 2019). Studies have begun to investigate whether dietary interventions can protect against age-dependent neurogenic decline or even have a rejuvenating effect on neurogenesis. For example, a 40% reduction in caloric intake in mice from young adulthood (4 months old) onward protects the SVZ from age-dependent decline in neurogenesis and increases olfactory memory performance (Apple et al., 2019). Under basal conditions, 3 months of intermittent fasting can increase proliferation and survival of newborn neurons in the DG and SVZ of middle-aged mice (Manzanero et al., 2014). Intermittent fasting also limits the extent of cell death associated with ischemic injury and results in physiological improvements such as diminished sensorimotor deficits (Manzanero et al., 2014). However, intermittent fasting fails to boost generation of newborn neurons in the context of ischemic injury, suggesting that the observed neuroprotective effects are a result of reduced neuronal cell death rather than increased neurogenesis (Manzanero et al., 2014). Other intermittent fasting regimes, such as alternate-day feeding, are accompanied by a thicker pyramidal cell layer in the DG and result in cognitive improvements, such as improved learning and memory (Li et al., 2013), suggesting a possible link between fasting and neurogenesis. Because long-term dietary restriction is difficult to adhere to, other dietary interventions, such as the fasting-mimicking diet (FMD), have been developed to recapitulate the health benefits of caloric restriction while improving regimen adherence and compliance (Brandhorst et al., 2015). Four days on an FMD diet twice per month from 16 months onward increases the mean lifespan of mice by 11.3% and ameliorates performance on cognitive tests evaluating short-term memory, long-term memory, and learning (Brandhorst et al., 2015). This was also accompanied by an increase in hippocampal neurogenesis (as measured by BrdU incorporation and doublecortin (DCX) staining in 23-month-old animals) (Brandhorst et al., 2015). Thus, dietary interventions have the potential to improve neurogenesis and confer neuroprotective effects upon insult or injury as well as provide overall health and longevity for the organism.

The molecular mechanisms underlying the benefits of dietary interventions on NSCs remain to be determined, but nutrient-sensing pathways, including mTOR and insulin-IGF signaling, likely play a key role, given their importance in regulating cellular metabolism and maintaining NSC homeostasis. It will be crucial to determine whether the benefits of these interventions are due to the fasting period, when processes such as autophagy are activated, or whether they are due to an overall reduction in the intake of specific "damaging" nutrients, such as glucose or free oleic acid. Specific nutrients may also play an important role in preserving or rejuvenating NSCs. For example, dietary restriction (DR) and *ad libitum* low-protein, high-carbohydrate (LPHC) diets positively affect hippocampal biology and cognition in old mice (Wahl et al., 2018). Similarly, a ketogenic diet can recapitulate the systemic longevity and healthspan benefits of DR regimes and even improve memory in aged animals (but the specific effects on the neurogenic niches were not investigated in these studies; Newman et al., 2017; Roberts et al., 2017). Thus, modulating the levels of certain nutrients in the diet may be as effective as drastic removal of food in improving NSC function and overall brain health.

Exercise

Exercise is beneficial to combat age-dependent cognitive decline, as measured by scores in short- and long-term memory as well as executive function (reviewed by Hötting and Röder, 2013). Voluntary aerobic exercise increases adult hippocampal neurogenesis

	Dietary Interventions			Exercise		Systemic Factors	
	CR	IF	FMD	Moderate	Strenuous	Blood	Plasma
Effect on neurogenesis	↑ in SVZ ↑ in DG	↑ in SVZ ↑ in DG	Not Tested in SVZ ↑ in DG	↑ in SVZ ? ↑ in DG	Not Tested in SVZ ↑ in DG	↑ in SVZ ↑ in DG	No Effect
Functional improvement	↑ olfaction ↑ learning/ memory	Not Tested in SVZ ↑ learning/ memory	Not Tested in SVZ ↑ learning/ memory	Not Tested in SVZ ↑ spatial discrimination	Not Tested in SVZ No Effect	↑ olfaction ↑ learning/ memory	Not Tested in SVZ ↑ learning/ memory
Neuro-protective	AD PD - MS Stroke TBI	AD PD HD MS Stroke TBI	- PD - MS - -	AD PD HD ? MS Stroke TBI	- - - - - -	AD ? - HD MS Stroke -	AD ? - - MS Stroke -
Translational potential	High	High	Very High	High	Medium/High	Very Low	Low
Molecular mechanism	Nutrient Sensing Pathways: IGF-1/mTOR/AMPK			Reduced Inflammation Activated Platelets		Reduced Inflammation	

Figure 4. Interventions to Rejuvenate Old Neurogenic Niches

Shown is a comparison of three promising interventions to rejuvenate old neurogenic niches (the sub-ventricular zone [SVZ] and hippocampus dentate gyrus [DG]). Dietary interventions are divided into three sub-categories (caloric restriction [CR], intermittent fasting [IF], and fasting-mimicking diet [FMD]). Exercise is divided into moderate and strenuous groupings. Systemic factors are divided into those in blood or plasma. The neuroprotective effects of these interventions were assessed in various diseases and injuries: Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis (MS), stroke, and traumatic brain injury (TBI). A question mark signifies conflicting or insufficient evidence to support the claim.

in mice (van Praag et al., 1999, 2005) and rats (Nokia et al., 2016) and promotes development and integration of newborn granule cell neurons in the aging hippocampus (Trinchero et al., 2017). However, not all forms of exercise have an equal effect on improving brain health. The benefits of exercise for adult hippocampal neurogenesis in rats appear to be greater when the animals perform voluntary endurance training compared with resistance training (Nokia et al., 2016). Furthermore, although moderate and fatiguing exercise increase neuronal differentiation and migration in the hippocampus of young adult mice (2 months old), only moderate exercise improves cell proliferation and survival (So et al., 2017). Moderate exercise also results in a greater increase in hippocampal neurogenesis compared with fatiguing exercise, accompanied by improved cognitive benefits, such as enhanced spatial discrimination, that were absent in the fatigued group (So et al., 2017). Thus, moderate aerobic exercise may have the most rejuvenating effects in neurogenic niches compared with other forms of exercise.

Excitingly, exercise can also be a neuroprotective intervention in the context of certain neurodegenerative diseases, such as PD (Alvarez-Saavedra et al., 2016) and Alzheimer's disease (Choi et al., 2018). In transgenic mice with an ataxic phenotype to model PD, voluntary running improves lifespan and ameliorates motor dysfunction. These physiological improvements were accompanied by an increase in cerebellar oligodendrogenesis and subsequent *de novo* myelination mediated by VGF secretion (Alvarez-Saavedra et al., 2016). In an Alzheimer's mouse model, exercise increases hippocampal neurogenesis, improves cognition, and reduces β-amyloid load (Choi et al., 2018). These beneficial effects of exercise can be recapitulated when neurogenesis and BDNF levels are boosted together, suggesting that exercise increases the levels of both systemic factors (such as BDNF) and neurogenesis to ameliorate neurodegenerative disease pathology (Choi et al., 2018).

Although the molecular mechanisms underlying exercise-induced benefits remain largely unknown, particularly in old animals, recent evidence suggests that hippocampal neurogenesis and spatial memory improvements induced by running are dependent on secretion of Cathepsin B, a proteolytic enzyme known to be expressed in humans and monkeys upon exercise (Moon et al., 2016). Systemic factors, such as activated platelets, have also been implicated as mediators of the neurogenic benefits of exercise (Kratz et al., 2006; Leiter et al., 2019). Exercise-induced activated platelets promote NSC proliferation in the hippocampus

of young adult mice (8–10 weeks old) and increase subsequent neurogenesis *in vivo*. This NSC boost is likely mediated by platelet factor 4, which is sufficient to increase levels of DCX+ immature neurons in the DG (Leiter et al., 2019). It will be interesting to determine how platelet factor 4 affects old animals. Although acute exercise leads to increased inflammation in response to muscle damage, regular aerobic exercise exerts its beneficial effects at least in part by reducing systemic inflammation, as reflected by lower levels of inflammatory cytokines such as tumor necrosis factor alpha (TNF-α) and IFNγ (Woods et al., 2012). The beneficial neurogenic effects of running in the hippocampus of young (8 weeks old) and middle-aged (8 months old) mice are inversely correlated with the density of microglia, cells that normally contribute to age-related neuroinflammation (Gebara et al., 2013). Given the inflamed state of the old neurogenic niche, it is tantalizing to speculate that the positive effects of exercise on neurogenesis in old individuals may also result from a decrease in the inflammatory state of the cells and milieu in the old niche.

Blood Factors

Another promising regenerative strategy involves administering young blood, or the factors therein, to an aged animal to improve declining neurogenesis and cognitive performance. As described above, impaired neurogenesis and cognitive function in the aged hippocampus and SVZ can be improved by young blood during heterochronic parabiosis (Katsimpardi et al., 2014; Villeda et al., 2014). Dilution of factors in old blood and the presence of factors in young blood may underlie the beneficial effects of heterochronic parabiosis. In fact, injection of young blood plasma is sufficient to improve cognitive performance in contextual fear conditioning as well as spatial learning and memory (Villeda et al., 2014), although it is not clear whether these are due to improved neurogenesis or neuronal function per se. Despite promising results from small human clinical trials to assess the safety and feasibility of routine blood injections (Sha et al., 2019), the clinical challenges (and potential ethical concerns) of routinely administering young blood to elderly individuals has prompted ongoing work to identify the specific factors in young blood that are capable of independently conferring health benefits and increasing neurogenesis. More needs to be done to identify specific factors from young blood that could rejuvenate the old neurogenic niche and to determine the effector cells.

Given the neurogenic benefits of these different interventions, one intriguing hypothesis is that combinatorial application of two or more of these strategies could have additive or even synergistic beneficial effects (Fabel et al., 2009; Hutton et al., 2015). Additional "rejuvenating" strategies, such as *in vivo* partial reprogramming (Han et al., 2020; Ocampo et al., 2016) or microbiome transfer (Bárcena et al., 2019; Smith et al., 2017) could also be exploited to rejuvenate old NSCs and improve age-related sensorimotor decline. Although further studies will be required to determine the specific mechanisms of action of each strategy, the potential synergistic benefits of dietary interventions, exercise, and blood factors hold promise as a strategy to rejuvenate the brain for physiological and pathological aging.

Neurogenesis in the Vertebrate World

Evolution of Vertebrate Neurogenesis

Adult neurogenesis has been observed in all vertebrate species studied, but there is a wide range of neurogenic capacities in different species. For example, amphibians and teleosts have many neurogenic regions in their brains and display a remarkable capacity for neurogenesis and brain regeneration (reviewed in Alunni and Bally-Cuif, 2016). In contrast, mammals, including humans, display a relatively low degree of neurogenic potential among vertebrates, with limited regenerative potential and fewer neurogenic niches, even though they are still capable of producing newborn neurons throughout their entire lifespans (reviewed in Alunni and Bally-Cuif, 2016). Although generation of newborn neurons is necessary during embryonic and juvenile development, it is not immediately obvious why evolutionary pressures would have selected for ongoing generation of newborn neurons in the adult brain, especially given the associated increased risk of cancer formation. In fact, it was long assumed that adult neurogenesis is an evolutionary relic without functional benefits (reviewed in Kempermann, 2015). However, it seems increasingly likely that adult neurogenesis is under evolutionary positive selection, not only for its regenerative benefits in the event of brain injury but also to increase brain plasticity and improve an organism's ability to integrate novel information throughout life (reviewed in Konefal et al., 2013). This is perhaps best exemplified by the songbird brain, an important and historic model for study of adult neurogenesis (Goldman and Nottebohm, 1983; Nottebohm, 1985). Adult male starlings, among other species, exhibit dramatic seasonal plasticity in their ability to learn new songs, a mating behavior integral to the species' sexual selection (De Groof et al., 2009). Adult neurogenesis may also play an important role in rodent mating behaviors because generation of olfactory bulb neurons from SVZ NSCs might contribute to mate selection via olfactory cues. In fact, disrupting olfactory bulb neurogenesis in female mice using focal irradiation of the SVZ results in abnormal social interactions with males but not females, perhaps because of a reduction in the ability to detect male-specific odors, resulting in impaired mate selection (Feierstein et al., 2010).

Human Neurogenesis: Controversy, Challenges, and the Way Forward

Although the human brain was long regarded as an entirely postmitotic organ, over two decades ago, a seminal study showed dividing cells in the brains of cancer patients (Eriksson et al., 1998). Since then, many studies have tried to address this question, typically relying on carbon dating (Spalding et al., 2013) and immunostaining techniques (Knoth et al., 2010) in postmortem human brains. NSCs and neuroblasts have been observed lining the walls of the lateral ventricle in humans. However, although new neurons born from the SVZ are added to the olfactory bulb in mice and other mammals (Lois and Alvarez-Buylla, 1994), generation of new neurons in the olfactory bulb is practically negligible in humans (Bergmann et al., 2012; Sanai et al., 2011; Wang et al., 2011). Instead, new neurons born from the human SVZ integrate in the adult human striatum, adjacent to the lateral ventricle wall (Ernst et al., 2014). Whether these newborn neurons derive from *bona fide* NSCs in the SVZ and whether they have a functional role has not been tested directly. Thus, more work will be needed to better understand the importance of neurogenesis in the adult SVZ in humans and how it is affected by aging.

A key question that has been subject to much debate over the years is whether neurogenesis takes place in the human DG of

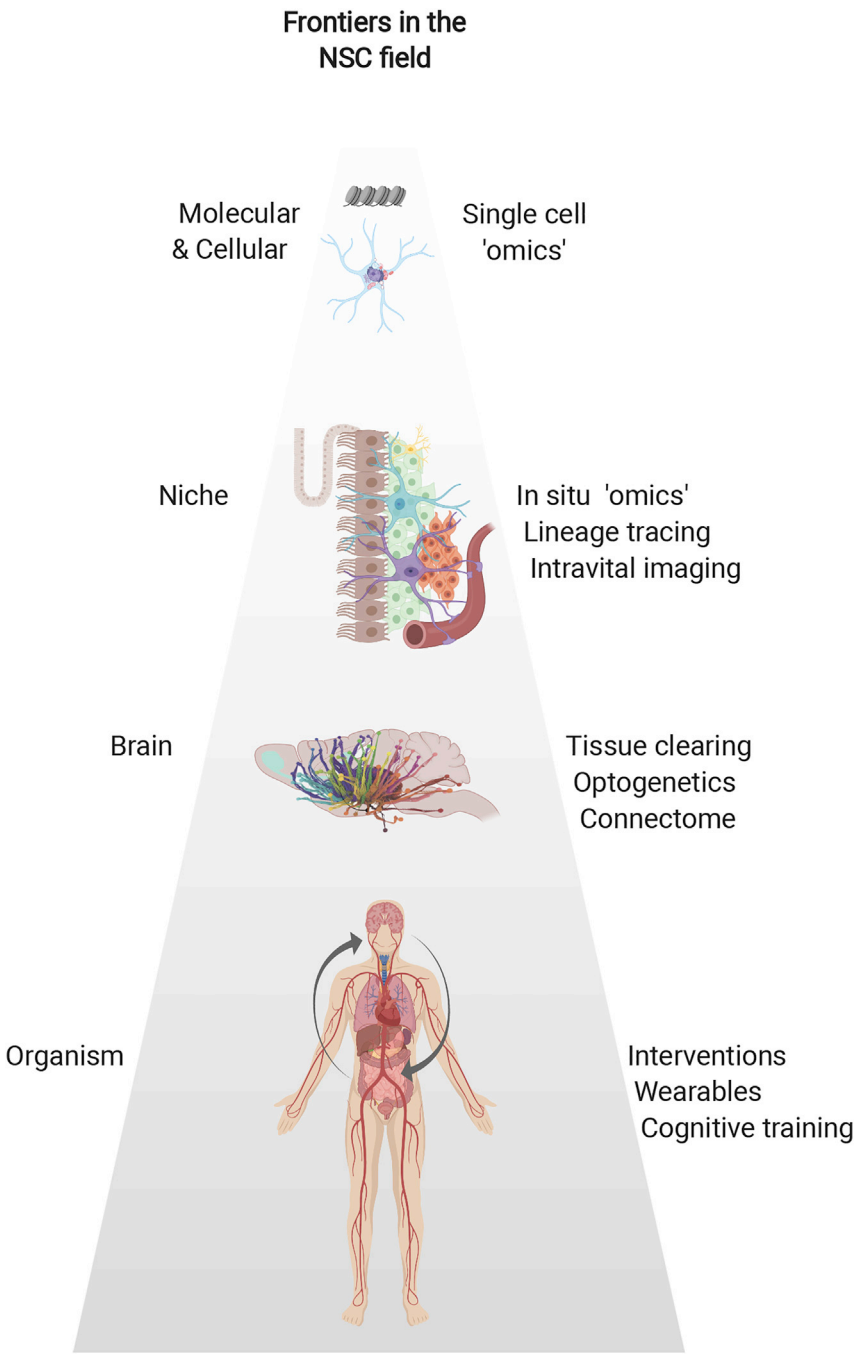

Figure 5. Frontiers in the Aging NSC Field
The advent and refinement of new technologies (right) should further improve our understanding of how aging influences NSCs and their niche and how NSCs interact with brain circuity and systemic and organismal signals.

the hippocampus, a region known to be important for learning and memory (reviewed by Ernst and Frisén, 2015; Kempermann et al., 2018; Paredes et al., 2018; Tartt et al., 2018)). Although some studies have reported a lack of evidence of neurogenesis in humans after adolescence (Cipriani et al., 2018; Sorrells et al., 2018), others have found the opposite: persistent human neurogenesis in adulthood with a small decline during aging (Boldrini et al., 2018; Moreno-Jiménez et al., 2019; Tobin et al., 2019). The number of neuroblasts also correlated with cognitive status, with higher numbers present in individuals with better cognitive performance (Tobin et al., 2019). Although correlative, these results suggest that neurogenesis may be linked to cognitive function in humans.

Additional work will be needed to reconcile opposing outcomes from different studies (Flor-García et al., 2020). For example, comparing staining protocols, preservation of samples from human donors, and post-mortem collection times will help address these discrepancies. Importantly, advances in single-cell RNA-seq technologies should help move the field forward by providing more specific cell markers for immunological identification of NSCs as well as transcriptomic signatures that could be compared across species. Indeed, a recent single-cell RNA-seq dataset from adult human olfactory neuroepithelium revealed cells with characteristics of NSCs and neural progenitors (Durante et al., 2020). It will be interesting to assess neurogenesis between basal conditions (as done in most of these studies) and conditions where neurogenesis should be elevated (e.g., after exercise or even brain injury in humans). Analyses in humans could help provide novel avenues to specifically boost neurogenesis and improve old brain function in humans.

Conclusion and Frontiers in the Aging NSC Field

NSCs have the potential to rejuvenate old brains and ameliorate age-related neurodegenerative diseases. In the past few years, intrinsic and extrinsic changes that occur in NSCs and their niches during aging have been uncovered. In parallel, interventions that improve health and/or lifespan (e.g., DR, exercise, blood factors, etc.) have been shown to improve neurogenesis in old individuals. Combining the knowledge gained from these two areas should accelerate development of specific and targeted interventions to recover brain function in aged individuals. The advent and refinement of new technologies (e.g., single-cell analyses, multi-omics, genome-wide screens, and innovative imaging) should further improve our understanding of how aging influences NSCs and their niche and how NSCs interact with brain circuity as well as with systemic and organismal signals (Figure 5).

Multiplexing of next-generation sequencing techniques at the single-cell level, such as single-cell RNA-seq, single-cell

ATAC-seq, or single-cell proteomics (Stuart and Satija, 2019), will capture a snapshot of the genomic, epigenomic, proteomic, and metabolomic landscapes of individual cells in a single assay. The resolution of these techniques should help refine our understanding of intermediate stages in NSC activation and differentiation *in vivo*. A next frontier will be to integrate all of this molecular and cellular information *in situ* to provide spatial and "omics" resolution of the niche using technologies such as STARmap (Wang et al., 2018) or Slide-seq (Rodriques et al., 2019).

Visualizing NSC activation and differentiation *in situ* will provide valuable insights into the dynamics of neurogenic niches during aging. Intravital imaging can be performed to visualize the fate of NSCs *in situ*, including their symmetric versus asymmetric divisions and integration of newborn neurons into pre-existing circuits (Breton-Provencher et al., 2016; Pilz et al., 2018; Wang et al., 2019). Lineage tracing is another powerful tool that can be leveraged to understand the cell fate decisions of NSCs; notably, the extent of self-renewal versus differentiation (Encinas et al., 2011; Obernier et al., 2018). Advanced lineage tracing tools with CRISPR-Cas9 or Cre recombination (Hwang et al., 2019; Marx, 2018; Spanjaard et al., 2018) will help reveal how the fate of cells in the NSC lineage changes over time during normal aging and disease and in response to interventions that boost neurogenesis. These advances in lineage tracing and imaging will help address outstanding questions in the field, such as to what degree individual NSCs persist and continue to produce newborn neurons and the extent and functional importance of neuronal turnover in the aging brain.

High-throughput functional genetic screening using different versions of the CRISPR technology could uncover new molecular mechanisms of NSC aging. In addition, mechanistic studies of NSCs during aging could be enhanced by the ability to directly reprogram fibroblasts from old healthy or diseased individuals into NSCs (Ring et al., 2012). Finally, adapting the human brain organoid system (Lancaster et al., 2013) to study brain aging and related diseases could allow deeper investigation of the neurogenic niche and how it becomes altered with time.

Many mechanisms of aging in the neurogenic niche remain mysterious. For example, the interaction between the neurogenic niche and the surrounding neural networks in the brain, and especially how this is affected with age, is still largely unknown. Tissue optical clearing techniques (Wan et al., 2018) paired with super-resolution imaging could help uncover neuronal inputs and outputs from the NSC niche. Optogenetics or related methods (Rajasethupathy et al., 2016) could also be exploited to modulate neuronal activity and determine the effect on the niche. Initiatives such as the mapping of the human connectome may help to uncover the interactions between the neural circuitry and the NSC niche and how they are perturbed with age and disease. Finally, it will be crucial to further investigate the crosstalk between neurogenic niches and organism-wide systemic aging. For example, understanding the systemic effects of circadian rhythms (Malik et al., 2015), sleep (Kumar et al., 2020), reproductive endocrine status (Oboti et al., 2015), or microbiome composition (Ogbonnaya et al., 2015) on neurogenic function during aging could be critical to understand long-range cues that could indirectly affect NSC regeneration over time.

At the population level, inter-individual variability is emerging as a defining aspect of old age that could reflect differences in aging trajectories and brain function (Li et al., 2017). Individuals are exposed to different environments and behavioral activities that continually alter the brain throughout life (Kempermann, 2019). Interestingly, differences in spatial memory function between individual old rats are positively correlated with newborn neuron numbers in the hippocampus (Drapeau et al., 2003). Likewise, inbred mice living together in one large enriched environment develop increasing individual differences in exploratory behavior that correlate with differences in hippocampal neurogenesis (Freund et al., 2013, 2015; Körholz et al., 2018). Understanding the sources and consequences of these differences between individuals could provide new strategies to rejuvenate the old neurogenic niche and lead to personalized and precision medical therapies.

Together, these technological and conceptual advances provide an unprecedented opportunity to develop a better understanding of the molecular mechanisms regulating NSC aging with the ultimate goal of developing novel regenerative therapeutic agents. As the global demographic shifts toward becoming increasingly geriatric, longevity strategies that promote healthy brain function rather than just extend the lifespan will become crucial to combat the devasting consequences of brain aging.

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AUTHOR CONTRIBUTIONS

P.N.N. wrote the introduction and the "Nutrient-Sensing Pathways, Metabolism, and Protein Homeostasis during NSC Aging" and "The Role of the Niche and Inflammation in NSC Aging" sections and generated Figures 1, 2, 3, and 5. R.W.Y. wrote the "Transcriptional, Epigenomics, and Cell Cycle Changes in NSC Aging," "NSCs and Diseases: Link with Aging and Translational Potential," and "Interventions to Rejuvenate Old Neurogenic Niches" sections and generated Figure 4. A.B. helped with writing and overall structure of the review. All authors contributed to writing the rest of the manuscript.

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