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Opinions

Neural stem cell secretome: a secret key to unlocking the power of regeneration in the adult and aging brain

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ABSTRACT

Adult neurogenesis involves the activation of quiescent neural stem cells (qNSCs) to generate new neurons, which migrate and integrate into existing neural circuits. In addition to their role in neurogenesis, adult NSCs also secrete bioactive compounds collectively known as the secretome, which contribute to the regulation of this process. However, aging and neurodegenerative diseases impair neurogenesis by promoting a pro-inflammatory environment within the neurogenic niche. With age, NSCs become increasingly quiescent, leading to a decline in their secretory activity— a hallmark of aged NSCs. Enhancing the function of adult NSCs holds therapeutic potential for restoring brain function under these conditions. Specifically, reactivating quiescent NSCs and possibly eliminating senescent ones can boost neurogenesis and improve cognitive function in aging and neurodegenerative diseases. In this review, we explore the role of adult NSCs and their secretome in sustaining brain function throughout adulthood and aging. A comprehensive analysis of the literature sheds light onto how NSCs and their secretome influence neurogenesis, from activation and differentiation to integration into neural circuits. Targeting adult NSCs in aged and neurodegenerative models presents a promising strategy for brain function restoration.

Introduction

Adult neurogenesis is a process where qNSCs become active in response to external stimuli, giving rise to different lineages: on one hand new neurons that integrate into pre-existing neural circuits, and on the other hand astrocytes and oligodendrocytes, which are essential for neural support and myelination [1]. In adult mice, neurogenesis occurs mainly in two discrete regions and serves distinct functions. Olfactory neurogenesis takes place in the subventricular zone (SVZ)- rostral migratory stream (RMS)- olfactory bulb (OB) system and participates in olfactory perception and memory. In this system, active NSCs (aNSCs) residing in the SVZ will differentiate into neuroblasts (immature neurons), which migrate tangentially and rapidly within the RMS until they arrive to the OB, where they switch from tangential to radial migration to integrate into the olfactory circuitry and become gamma-aminobutyric acid (GABA)ergic interneurons [2–4]. On the other hand, hippocampal neurogenesis takes place locally in the subgranular zone (SGZ) of the dentate gyrus of the hippocampus. In this system, SGZ NSCs become neuroblasts which migrate radially into the granule cell layer to become glutamatergic granule cells [5]. These processes have been extensively reviewed previously and are not the focus of the current review.

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NSCs are regulated by a complex and dynamic network of signals originating from their adult neurogenic niches, which collectively maintain the delicate balance between quiescence and activation [6,7]. While many extrinsic factors have been extensively characterized [8,9], the role of the NSC secretome—comprising the range of molecules secreted by NSCs themselves—remains comparatively underexplored [10,11]. This review aims to shed light on this less studied aspect, emphasizing how NSC-derived secreted factors contribute to niche regulation and neurogenesis. NSCs, neuroblasts and newly generated neurons produce a diverse secretome capable of ensuring autocrine, paracrine, and bidirectional signaling and participating in regulation of neurogenesis, neuroplasticity, and immunomodulation [4,12,13].

Neurogenesis declines progressively with aging, primarily due to alterations in the neurogenic niche, which adopts a pro-inflammatory state in part due to the secretion of pro-inflammatory cytokines by activated microglia and senescent cells [12,12,14–16]. This shift leads to a disruption in NSC activity, with a subset of NSCs becoming unresponsive to mitotic stimuli, while others contribute to the exacerbation of inflammation within the neurogenic niche [17,18]. The decline in neurogenesis has been observed in several neurodegenerative diseases, such as Alzheimer disease [19] and depression [20], where impaired neurogenesis and glial cell production contribute to cognitive deficits. Restoring the neurogenic niche by enhancing the activity of adult NSCs holds significant therapeutic potential for rejuvenating brain function in neurodegenerative conditions.

This review provides a comprehensive analysis of the current understanding of adult NSCs and their secretome across different stages, including youth, normal aging, and neurodegenerative conditions in animal models. Initially, we will characterize the secretome of adult NSCs, with a particular focus on the bioactive factors that modulate both neurogenic and non-neurogenic cells within the brain. Subsequently, we will assess the influence of the adult NSC secretome on neuroblast proliferation and migration, as well as its critical role in neuroblast maturation and integration into neural circuits. Furthermore, we will examine the feedback mechanisms governing interactions between adult NSCs and neuroblasts. Finally, we will discuss age-related alterations in adult NSCs and their secretome, along with potential strategies for rejuvenating aged NSCs and restoring their secretory functions to support brain health.

NSC secretome and extracellular vesicles

The secretome is a cellular concept that refers to the collection of bioactive factors released by the cells. In this section, we will particulary define the secretome of adult NSCs, its composition and mode of secretion.

The adult NSC secretome comprises a diverse array of bioactive compounds that NSCs release into the extracellular environment, facilitating autocrine and paracrine interactions with both neurogenic and non-neurogenic cells Table 1. Autocrine signaling refers to the process by which NSCs secrete molecules that act upon themselves, thereby modulating their own activity. In contrast, paracrine signaling involves the release of molecules from NSCs that influence neighboring and distant cells. The NSC secretome includes various bioactive factors, such as growth factors, pro-inflammatory cytokines, microRNAs (miRNAs), and metalloproteinases, which play a crucial role in regulating neurogenesis [44], modulating inflammation [45], and contributing to tissue repair following brain injury [46]. Consequently, the NSC secretome has been shown to regulate several fundamental cellular processes, including cell proliferation, differentiation and survival [32,47–49]. Furthermore, various techniques and therapeutic strategies have been employed to characterize the composition of the NSC secretome, particularly through proteomic [50] and transcriptomic analyses [51], as well as NSC transplantation studies [52]. Notably, the NSC secretome has emerged as a promising therapeutic approach, with increasing research efforts focusing on its potential application in regenerative medicine [53–55]. Utilizing the NSC secretome in treatments could offer advantages by avoiding immune system-related complications commonly associated with cell transplantation, as well as overcoming issues related to the limited long-term viability of NSC grafts [56].

The NSC secretome is predominantly released through extracellular vesicles (EVs), which are classified into two main categories:

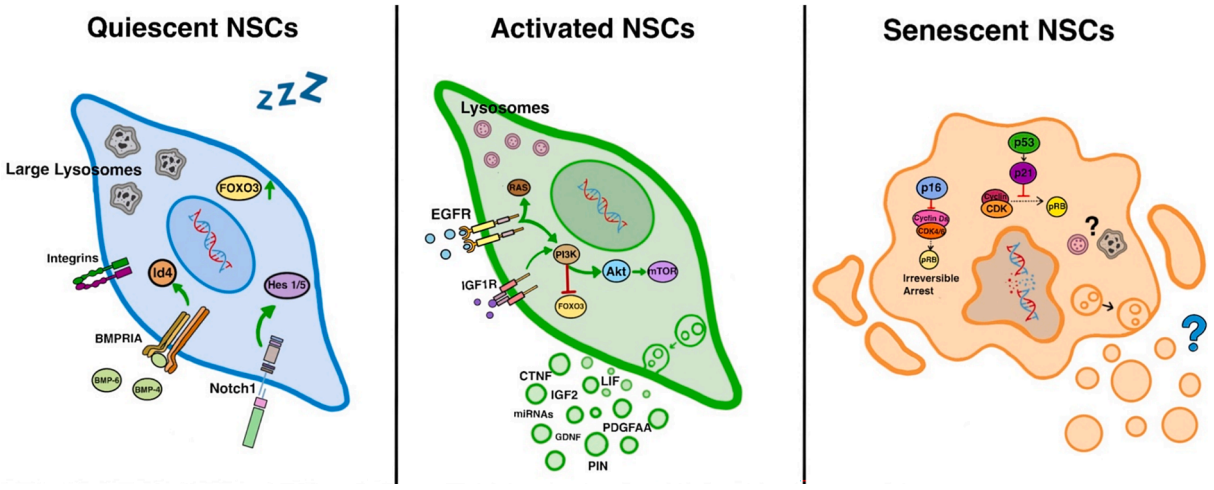

Fig. 1. Cell-cycle in quiescent, activated and senescent NSCs.

Table 1
Summary of adult NSC secretome and their neurogenesis function.

Factors	In vitro/in vivo	Animal model	Brain region (SVZ/SGZ)	Specific neurogenesis function	Reference
PDGF-AA	In vitro/in vivo	Rat & Mice	SVZ	Involved in neuroblast differentiation and proliferation in the RMS.	[21,22]
VEGF-A	In vitro/ invVivo	Mice	SVZ & SGZ	Promote neuroblast proliferation. Control the balance of quiescence and proliferation of NSCs.	[23]
BDNF	In vitro/in vivo	Mice	SVZ & SGZ	Stimulates NSC proliferation and differentiation into neuroblasts Enhances neuroblast proliferation, migration and survival.	[24,25]
CNTF	In vivo	Mice	SVZ	Acts as a chemoattractant to guide neuroblast migration.	[26,27]
Tenascin-C	In vitro/in vivo	Mice	SVZ	Participate in proliferation of NSCs Regulation of tangential migration of neuroblast.	[28,29]
Leukemia inhibitory factor	In vivo	Mice	SVZ	Promotes NSCs differentiation into astrocytes.	[30,31]
PTN	In vivo	Mice	SGZ	Participate in maturation of new granule neurons.	[32,33]
GDNF	In vitro/in vivo	Mice	SGZ	Stimulates axonal growth and survival of new neurons.	[34–36]
GABA	In Vivo	Mice	SVZ & SGZ	Inhibits NSCs proliferation and differentiation.	[37,38]
DBI	In vivo/in vitro	Mice	SVZ	Antagonist to GABA, induce NSCs and NPCs proliferation.	[39]
miRNAs	In Vivo	Mice	SVZ & SGZ	Participate in maturation of new granule neurons.	[40]
IGF-1	In vitro/in Vivo	Mice	SVZ & SGZ	Promotes NSCs differentiation and neuroblasts migration and positioning.	[41,42]
IGF-2	In vitro/in Vivo	Mice	SVZ & SGZ	Promotes NSCs proliferation and differentiation.	[43]

large EVs, known as microvesicles (100–1000 nm in diameter), and small EVs, referred to as exosomes (40–100 nm in diameter) [57]. The type of EVs secreted by NSCs is largely determined by the nature of the bioactive molecules they contain. Soluble proteins, growth factors, and cytokines are typically packaged into microvesicles and released through exocytosis. In contrast, microRNAs (miRNAs) are first processed within endosomes, which subsequently fuse with the plasma membrane, leading to their release into the extracellular space as exosomes [57]. Notably, EVs derived from NSCs can modulate the surrounding microenvironment and possess the unique ability to cross the blood–brain barrier. This property has been demonstrated to mitigate cognitive deficits associated with normal aging [54], as well as in models of AD [58] and corticosterone-induced depression [59].

Impact of NSC secretome on proliferation, differentiation and migration of neuroblasts

In this section, we will discuss the influence of the NSC secretome on neuroblast proliferation and migration—two essential processes that ensure the generation of a sufficient number of neuroblasts and their effective migration to target regions.

Proliferation/Differentiation

NSCs support neuroblast proliferation through the secretion of various growth factors, including Platelet-Derived Growth Factor AA (PDGF-AA) [21,60], Brain-Derived Neurotrophic Factor (BDNF) [24,61], and Vascular endothelial growth factor-A (VEGF-A) [47] which exert paracrine effects. In mice, NSCs secrete PDGF-AA to promote neuroblast proliferation during both developmental and adult stages by interacting with the PDGFRα receptor [21,62]. This interaction activates the receptor's tyrosine kinase activity and the PKB/c-Akt signaling pathway, thereby supporting cell proliferation and survival [21].

Notably, the deletion of PDGFRα is lethal, as it leads to increased apoptosis, underscoring the essential role of the PDGF-AA/PDGFRα signaling axis in cell survival [63]. However, paradoxically, systemic infusion of PDGF-AA has been shown to reduce the number of neuroblasts in the SVZ of treated mice compared to controls, indicating a complex and context-dependent role for PDGF-AA in neurogenesis [22]. Despite these findings, the regulation of PDGF-AA expression during aging remains unclear.

BDNF, another key growth factor secreted by NSCs, plays a crucial role in promoting both neuroblast proliferation and survival within the SGZ by interacting with truncated tropomyosin receptor kinase B (TrkB) [25]. Upon binding to TrkB, BDNF activates the PI3K/Akt and ERK signaling pathways, which not only stimulate neuroblast proliferation but also inhibit apoptosis. [25,64,65]. Similarly, VEGF-A has been shown −in both mice and rat DG- to promote neuroblast proliferation through its interaction with VEGF receptor 2 (VEGFR-2) [66,67].

Together, these NSC-derived growth factors contribute to the formation of a supportive microenvironment that fosters neuroblast expansion. Through the secretion of these bioactive molecules, the NSC secretome ensures the availability of a sufficient pool of neuroblasts for subsequent differentiation into mature neurons.

As NSCs age, their secretome undergoes significant alterations, resulting in a reduced secretion of key growth factors. Notably, levels of VEGF and BDNF decline significantly in the hippocampus of several animal models, contributing to the cognitive decline associated with aging [23]. This reduction in growth factors negatively impacts paracrine signaling, which supports the neuroblast pool. In addition, emerging evidence suggests that these factors also act in an autocrine manner to promote NSC self-renewal but their

effects on NSCs have not been addressed. Additionally, the decline in growth factor availability is partly due to a decrease in the number of NSCs, as well as their transition into a state of deep quiescence, in which they stop to actively secrete these factors [68]. Ultimately, the diminished NSC secretome leads to a reduction in mitotic signaling, which results in a decrease in neurogenesis in the aging brain.

Migration

Several NSC-secreted factors are recognized to play a critical role in neuroblast migration. One such factor is Insulin-like Growth Factor 1 (IGF-1), which has been shown to significantly influence neuroblast differentiation, migration and organization [49,41,42]. IGF-1 is highly expressed in both SVZ and SGZ of mice from birth through adulthood [69]. Within the RMS, IGF-1 promotes neuroblast migration by increasing the phosphorylation of Disabled-1 (Dab1), which subsequently activates the PI3K/Akt signaling pathway [49]. This pathway regulates cytoskeletal rearrangement and motility during neuroblast migration [49]. Moreover, studies using IGF-1 knockout mice have demonstrated reduced phosphorylation of Dab1, which correlates with impaired neuroblast migration from the SVZ to the OB compared to normal mice [49]. These findings suggest that IGF-1 facilitates neuroblast migration and ensures the accurate positioning of neurons in their target regions. Aging is associated with reduced levels of IGF-1 in the SGZ and SVZ, which contribute to a decline in neuroblast migration [70]. While the number of migrating neuroblasts decreases with age, evidence suggests that impaired neurogenesis during aging is primarily driven by a reduction in the NSC pool rather than a direct effect on migration. Understanding how fluctuating IGF-1 signaling impacts NSC maintenance, proliferation, differentiation, and neuroblast migration may provide valuable insights into sustaining neurogenesis throughout aging.

Ciliary neurotrophic factor (CNTF), a neurotrophic cytokine belonging to the interleukin-6 (IL-6) family, was originally described as promoting the survival of neurons in the chick ciliary ganglion [71,72]. However, CNTF is now being investigated for its role in cell migration and adult neurogenesis [48,26,73,74]. Studies have shown that both NSCs and astrocytes from the SVZ and DG secrete CNTF to guide neuroblast migration and facilitate the myelination of oligodendrocyte progenitors in response to injury [26,27]. CNTF exerts its chemostatic effect through JAK/STAT signaling pathway [75]. Additionally, other cytokines, such as IL-10, have been reported to be secreted by adult NSCs to ensure immunomodulation; however, their specific role in neurogenesis remains to be established [76].

NSCs not only secrete factors that enhance and guide neuroblast migration but also produce extracellular matrix (ECM) components that help to create scaffolds for the migrating neuroblasts. Several studies have shown that SVZ NSCs secrete Tenascin-C (TnC), a glycoprotein that is a key component of the ECM in the SVZ during both development and the postnatal stage [77,78]. TnC is found surrounding migrating neuroblasts in the SVZ, where it contributes to the regulation of tangential migration [78,28]. While the precise signaling pathways through which TnC regulates the RMS remains unclear, it has been shown that TnC influences cell migration in cancer cells by activating c-Jun N-terminal kinase (JNK) [79]. This, in turn, modulates the expression and activity of matrix metalloproteinase 9 (MMP-9), a zinc-dependent proteolytic enzyme that cleaves the ECM to maintain homeostasis. Additionally, migrating neuroblasts secrete MMP-9, which promotes their differentiation and migration while maintaining ECM homeostasis [80]. Taken together, these studies suggest a potential role for TnC in guiding neuroblast migration through its interaction with MMP-9, which could represent a novel regulatory axis in neuroblast migration.

Several studies have suggested that a significant proportion of NSCs, during their migration to target areas, differentiate into astrocytes [81–84]. This process is partly driven by the secretion of leukemia inhibitory factor (LIF) by NSCs, a cytokine that activates the Jak-STAT pathway, promoting the differentiation of NSCs into astrocytes [30,31]. Along the RMS, astrocytes facilitate neuroblast migration by producing guidance molecules, such as Slit Guidance Ligand 2 (Slit2) [85,86]. Slit2 interacts with Robo receptors to regulate axon guidance and tangential migration [87,88]. Moreover, astrocytes secrete IL-1β and IL-6 at physiological concentrations, which promote neuronal differentiation of NSCs and support neuroblast migration [89]. These findings underscore the complex mechanisms that govern neuroblast migration in the adult brain, particularly along the processes of astrocytes.

The aging brain is characterized by a reduction in the number of NSCs and their progeny, including neuroblasts, as extensively reviewed in the literature [13,13,90–93]. However, the impact of aging on neuroblast migration appears to be less pronounced than its effect on the NSC pool within neurogenic niches. In fact, once reactivated, aged NSCs display functionality comparable to that of NSCs in young brains, giving rise to neuroblasts [17]. It was also reported that aging does not significantly affect the ability of neuroblasts to exit the SVZ or their migration rate through the RMS [94]. Interestingly, neuroblasts retain their capacity to migrate from the SVZ to the olfactory bulb (OB) by continuing to secrete Slit Guidance Ligand 1 (Slit1), which exerts an autocrine effect by activating the Slit-Robo signaling pathway [95]. However, the reduced number of neuroblasts produced by the aging neurogenic pool is insufficient to fully support their functions in target areas. Therefore, identifying strategies to boost neurogenesis in neurogenic niches could have a significant impact on mitigating the effects of aging.

Similarly to the NSC secretome, with aging the astrocyte secretome shifts to a pro-inflammatory state, and the number of senescent astrocytes increases with aging [96,97]. These changes have been particularly observed in the context of normal aging and Alzheimer's disease, as seen in post-mortem brain tissues of elderly individuals and in the brains of aged mice [98]. Senescent astrocytes are reported to secrete elevated levels of interleukin-6 (IL-6), interleukin-1 alpha (IL-1α), interleukin-8 (IL-8), matrix metalloproteinases 3 and 10 (MMP-3, MMP-10), and tissue inhibitors of metalloproteinases 2 (TIMP-2) [97]. Similar shifts have also been observed in microglia [99,100]. These findings suggest that senescence becomes a cellular predominant state during aging. However, the specific contribution of the senescence-associated secretory phenotype (SASP) of senescent astrocytes and microglia to the age-related decline in neurogenesis remains poorly understood and is still an area of ongoing research.

Impact of NSC secretome on maturation of neuroblasts and their integration

In the hippocampus, NSCs play a crucial role in regulating the maturation of new granule neurons through the secretion of pleiotrophin (PTN), a cytokine that acts as a growth factor [32]. PTN interacts with the anaplastic lymphoma receptor tyrosine kinase (ALK) to activate the AKT signaling pathway, which promotes the maturation of new neurons [32,101]. Since the number of NSCs declines with aging, this leads to a decrease in PTN expression over time. This decline negatively impacts the dendritic morphogenesis of new granule neurons in the hippocampus, contributing to age-related cognitive decline [32].

Interestingly, exogenous infusion of PTN has been shown to rescue dendritic morphogenesis and improve cognitive function in aged individuals, highlighting the therapeutic potential of the NSC secretome [32,102]. Additionally, PTN has been found to be secreted by NSCs in the SVZ [33], although it remains unclear whether PTN influences the development of new neurons in the olfactory bulb. Furthermore, both in vitro and in vivo studies have shown that NSCs secrete GDNF, which stimulates axonal growth and enhances neuronal survival [34,35,103]. Overexpression of GDNF by NSCs has been demonstrated to provide neuroprotection in a mouse model of Parkinson's disease [34]. These findings suggest that NSC-derived GDNF offers promising neuroprotective benefits, particularly in models of neurodegenerative diseases.

MicroRNAs (miRNAs) are a large family of non-coding RNAs, typically 20–22 nucleotides in length, that regulate gene expression at the post-transcriptional level by targeting mRNA [104]. miRNAs are known to play a critical role in a variety of cellular processes, including stem cell self-renewal, neuronal maturation, and functional integration [105]. A high expression of several miRNAs, including miR-9 [40], miR-137 [106] and miR-124 [107], has been identified in NSCs. miR-9 has been shown to target multiple genes involved in neurogenesis, including REST [108], Foxg1 [109], Foxp2 [110], Hes1 [111], Pax6 [112], Lin28a [113], and Map1b [111]. Notably, miR-9 promotes axonal branching by decreasing the expression levels of Map1b [111]. In addition, NSCs have been reported to secrete miR-137, which regulates the translation of the ubiquitin ligase Mind Bomb-1 (Mib1), thereby influencing dendritic morphogenesis [106]. The ablation of NSCs leads to impaired development of newborn neurons, underscoring the importance of the aNSC secretome in supporting neuronal maturation and maintaining healthy brain function [32].

Feedback between NSCs and neuroblasts

NSCs and their secretome are tightly regulated through feedback mechanisms involving neuroblasts. These interactions modulate NSC quiescence, proliferation, and differentiation, ensuring that neurogenesis aligns with the brain's demands.

Neuroblasts in the SVZ and SGZ release the neurotransmitter gamma-aminobutyric acid (GABA), which binds to GABA_A receptors on NSCs. This interaction inhibits NSC proliferation and differentiation [37,38], via the PI3K signaling pathway and H2AX phosphorylation [114], acting as a negative feedback mechanism to control the number of proliferating NSCs. In response, NSCs secrete diazepam binding inhibitor (DBI), which antagonizes GABA signaling. DBI is released into the extracellular space, promoting the proliferation of both NSCs and neural progenitor cells (NPCs), thereby counteracting the inhibitory effects of GABA and stimulating neurogenesis [39]. Additionally, neuroblasts and active NSCs in close proximity to quiescent NSCs express the Notch ligands Delta-like 1 (Dll1) and JAGGED 1 (JAG1) on their surfaces. Through direct cell–cell interactions, Dll1 and JAG1 activate the Notch signaling pathway, helping to maintain a reservoir of quiescent NSCs [34,115]. This regulatory feedback ensures a balance between quiescent and activated NSCs, preventing niche depletion. Aging disrupts these key feedback mechanisms between neuroblasts and NSCs in the SVZ and SGZ, including increased GABAergic inhibition and impaired DBI counter-regulation, leading to reduced NSC proliferation. Additionally, age-related decline in Notch signaling weakens the maintenance of quiescent NSCs, contributing to the overall reduction in neurogenesis. Together, these feedback loops between NSCs and neuroblasts contribute to a well-coordinated environment that sustains neurogenesis.

Shift of NSC secretome during aging

With aging, the microenvironment of neurogenic niches becomes increasingly pro-inflammatory [116]. This shift is partially attributed to elevated levels of pro-inflammatory cytokines, increased activation of microglia, and the infiltration of T cells [116,117]. These changes disrupt the neurogenic niche, significantly affecting NSC function and likely altering their secretome.

Numerous systemic factors have been identified as pro-aging due to their capacity to induce cellular aging phenotypes. This concept of "pro-aging" extends to aged NSCs, whose cellular profile and secretome undergo changes that contribute to age-related brain decline. Several studies have emphasized the heterogeneity of aged NSCs in aging models, raising new questions about their possible transition into a state of deep quiescence and cellular senescence.

Deeply quiescent NSCs

In aged models, NSCs increasingly enter a deeper state of quiescence, making their reactivation and subsequent neurogenesis progression more difficult [17]. These aged or deeply quiescent NSCs (deep qNSCs) become arrested in the non-cycling G0/G1 phase, a state partly driven by the age-related decline in mitogenic factors, such as IGF-1 [70], IGF-2 [118], and VEGF [23], within the neurogenic niche.

This reduction contributes to the relative increase of deep qNSCs at the expense of active NSCs. Aged/deep quiescent NSCs exhibit elevated levels of bone morphogenetic protein (BMP) signaling, including BMP-4 [119] and BMP-6 [120], which contribute to the maintenance of their quiescent state. Furthermore, aged/deep qNSCs display lysosomal dysfunction, leading to the accumulation of

protein aggregates and lysosomal enlargement [121]. Such an impairment in cellular clearance mechanisms may further contribute to the reduced neurogenic potential of aged NSCs. Impairment in clearing waste also promotes the degradation of the epidermal growth factor (EGF) receptor, further exacerbating the decline in mitogenic signaling required for NSC activation [122]. Additionally, aged/deep quiescent NSCs exhibit increased intracellular expression of FoxO transcription factors, a consequence of reduced insulin/IGF-1 signaling, which further reinforces their quiescent state [123]. Interestingly, the ablation of IGF-1 receptors (IGF-1R) in adult NSCs has been shown to sustain neurogenesis in the aging brain, suggesting that IGF-1 signaling plays a crucial role in regulating the balance between quiescence and activation [124]. Despite these insights, it is still unclear whether quiescent NSCs secrete factors that contribute to maintaining their own quiescent state or influence other cells within the neurogenic niche. The concept of a "dormant secretome" remains an open question, requiring further investigation to identify the molecular factors that characterize this state.

Senescent NSCs

Cellular senescence is a state in which cell proliferation is irreversibly arrested, accompanied by distinct morphological and functional alterations [125]. It is primarily characterized by the activation of cyclin-dependent kinase inhibitors, such as $p21^{WAF1/Cip1}$ and $p16^{INK4a}$, which prevent cell cycle progression at the G0/G1 phase. Several biomarkers are commonly used to identify senescent cells in the aging brain, including the loss of Lamin B1, increased accumulation of lipofuscin, and elevated β-galactosidase activity [96,126,127]. However, caution needs to be used when aiming to distinguish between quiescent and senescent states. Furthermore, senescent cells contribute to a pro-inflammatory environment within tissues by secreting the senescence-associated secretory phenotype (SASP), which can impact surrounding cells and disrupt tissue homeostasis.

In the aging brain, several cell types including microglia [128], astrocytes [97], NSCs and NPCs [18], have been reported to transition into a senescent state. This cellular senescence has been proposed as a contributing factor to age-related cognitive decline. The hypothesis that NSCs and their progenitors undergo senescence has only recently begun to be explored. In vitro studies have shown that aged NSCs exhibit significantly higher levels of senescence-associated β-galactosidase (SA-β-gal) activity compared to adult and embryonic NSCs, suggesting that SA-β-gal could serve as a marker for senescent NSCs in aging models [129]. Furthermore, various in vitro models of NSC senescence have been established to investigate the underlying mechanisms and identify specific senescence markers. For instance, acute exposure to 10 Gy X-ray irradiation has been shown to induce senescence in NSCs [130], while treatment with 8 mM hydroxyurea for 12 h similarly leads to NSC senescence [131], providing valuable insights into this process. In both protocols, senescent NSCs were characterized by increased SA-β-gal activity, resistance to apoptosis, and upregulation of $p16^{INK4a}$, $p21^{WAF1/Cip1}$, and p53 expression. In primary culture of SVZ NSCs from senescence-accelerated SAMP8 mice, senescence appears to be triggered by p19-p53 [132]. Additionally, primary cultures of NSCs from aged C57BL/6 mice exhibited increased levels of p19, but not p16 [129], in contrast to the referenced study on the p16-mutant mice model published by Molofsky et al. [133]. Moreover, it is important to consider that depending on the driver of senescence induction, NSCs may express a distinct senescent signature, which may or may not resemble the changes observed in vivo with aging in these stem cells.

Although an increase in p21 following activation of p53 appears to be a driver of senescence, NSCs exhibit p53-independent high levels of p21 that are essential for the maintenance of their stem properties [134,135].

Furthermore, senescent NSCs and NPCs have also been identified in aged animal models. In 12-month-old p16–3MR mice, an increased number of SA-β-gal-positive NPCs were observed, along with a loss of lamin B1 within the SGZ [18]. Similarly, in 22-month-old C57BL/6JRj mice, elevated levels of both SA-β-gal and $p16^{INK4a}$ were detected in the SGZ [136]. Interestingly, deletion of $p16^{INK4a}$ in the SVZ of aged mice resulted in increased neurogenesis, whereas the same effect was not observed in the SGZ [133]. This finding suggests that elevated $p16^{INK4a}$ expression during aging elicits region-dependent responses in neural progenitors, suggesting that the impact of ageing on neurogenesis is not uniform across the brain. However, a critical yet largely unexplored aspect of senescent NSCs may be their SASP. If aging renders NSCs senescent, this could potentially alter the NSC secretome, which, in turn, could disrupt proper NSC activity regulation and contribute to the spread of senescence, ultimately fostering neurogenic deterioration with aging. which could potentially offer valuable insights into therapeutic strategies for mitigating age-related cognitive decline. Given the potential of the SASP to modulate the neurogenic niche, further investigation into the secretory phenotype of senescent NSCs may provide important insights into the mechanisms underlying age-related neurogenic decline and reveal novel targets for therapeutic intervention.

Rejuvenation of aged NSCs and their secretome in aged models

Reactivation of deeply quiescent NSCs

The reactivation of quiescent NSCs aims to push these cells out of the G0-G1 phase by inducing transcriptomic and metabolic changes that promote their proliferation. Restoring growth factor levels in the neurogenic niche has been shown to effectively enhance NSC proliferation. For example, infusion with FGF and EGF restores NSC proliferation in the subgranular zone (SGZ) and subventricular zone (SVZ) of 20-month-old mice to levels comparable to those observed in 3-month-old mice [123]. Additionally, FGF/EGF treatment reduces the expression of Notch1 and its downstream effector gene, Hes5 [137], which could transiently enhance NSC activity and restore neurogenesis in aging brains but may pose a risk of depleting the NSCs reservoir if not precisely regulated. In a general way, exposure of aged NSC to youthful circulating factors, such as GDF11 and TIMP2, has been demonstrated to rejuvenate the aged NSC populations and enhance neurogenesis[14,132,138]. Several metabolic and genetic interventions have also been shown to enhance the reactivation of quiescent NSCs in the aged brain. For instance, the overexpression of transcription factor EB (TFEB) in

qNSCs from aged SVZs improves their ability to exit quiescence, suggesting that targeting the lysosome-autophagy pathway could promote qNSC reactivation in older mice [121]. Furthermore, treatment of qNSCs with malonyl-CoA is sufficient to activate qNSCs and shift their metabolism from fatty acid oxidation to de novo lipogenesis [139]. A recent genome-wide CRISPR-Cas9 screen comparing old and young qNSCs revealed that knocking out Slc2a4, which encodes GLUT4, significantly increased the activation rate of old qNSCs [140].

Clearance of senescent NSCs

Senolytics are a class of drugs that selectively induce apoptosis in senescent cells, thereby improving tissue function and promoting regeneration. In the aging brain, the removal of senescent cells has been shown to enhance cognitive function by reducing inflammation, enhancing neuronal plasticity, and stimulating neurogenesis [18,99,127]. Furthermore, senolytic treatments not only provide insights into the mechanisms underlying cellular senescence but also hold significant therapeutic potential for mitigating age-related cognitive decline. Due to their promising preclinical efficacy, the senolytic drug combination of Dasatinib and Quercetin (D/Q) is currently being evaluated in clinical trials for early-stage Alzheimer's disease.

The ablation of NSCs and their SASP using the senolytic drug ABT-263 (Navitoclax) has been shown to enhance hippocampal neurogenesis and improve spatial learning and memory in aged mice [18]. While the precise cellular mechanism by which ABT-263 eliminates senescent NSCs and their SASP remains unclear, it is well established that ABT-263 targets the BCL-2 family of proteins, inducing apoptosis in senescent cells. Beyond its effects on NSCs, ABT-263 has also demonstrated efficacy in clearing senescent glial cells in tau-dependent neurodegenerative conditions, leading to improvements in short-term memory [141]. Additionally, ABT-263 has been shown to eliminate senescent endothelial cells, thereby restoring blood–brain barrier (BBB) integrity, which correlates with improved cognitive function [142]. Collectively, these findings suggest that senolytic drugs like ABT-263 could represent a promising therapeutic strategy to enhance neurogenesis and mitigate age-related cognitive decline.

Interestingly, systemic factors such as GDF11 can mimic the effects of senolytic drugs. Restoring serum levels of GDF11 in aged mice has been shown to eliminate senescent cells in the hippocampal SGZ by reducing the expression of senescence markers SA-β-gal, $p16^{INK4a}$ and $p21^{WAF1/Cip1}$. These changes correlate with improvements in memory and a reduction in age-related depressive symptoms [136]. This evidence suggests that blood-borne factors can physiologically modulate cellular senescence during aging, and they may represent a promising alternative approach for eliminating senescent NSCs.

Blood-borne pro-youthful factors, such as GDF11, TIMP2, and oxytocin, have been shown to enhance regeneration in the aged brain by reactivating quiescent neural stem cells (NSCs) and improving neurogenesis [14,138,143]. However, their effects are often transient and require repeated administration, with limited mechanistic clarity and potential off-target systemic effects. In contrast, senolytic drugs selectively eliminate senescent cells and reduce SASP-driven inflammation, thereby restoring tissue homeostasis and regenerative capacity [144]. Nonetheless, they may also remove beneficial senescent cells involved in tissue repair and exhibit limited blood–brain barrier permeability [145]. A combined approach—first targeting senescent cells, then introducing pro-youthful factors—may offer a synergistic strategy to enhance regeneration and mitigate cognitive decline in aging.

Conclusion

NSCs have been known to be central to adult neurogenesis, however lately it becomes increasingly evident that they also act as key regulators of the neurogenic process through the secretion of bioactive factors. These secreted molecules influence critical processes such as neuroblast proliferation, differentiation, and migration, underscoring the importance of the NSC secretome in maintaining neurogenic homeostasis.

However, with aging, the population of NSCs declines and those that persist tend to enter a deeper state of quiescence. This shift is accompanied by a reduction in neurogenesis and subsequent cognitive decline, but also leads to changes in the composition and function of the NSC secretome.

An increasing number of studies sugget that NSCs may adopt a senescent fate with aging. Such a phenotype may potentially impair their secretome, disrupt local signaling networks, damage the supportive microenvironment, and propagate senescence to neighboring cells, thereby contributing to the dysregulation of the neurogenic process. In this context, pharmacological interventions aimed at restoring the neurogenic potential of aged NSCs have gained considerable interest. Senolytic drugs, and pro-neurogenic blood-borne factors have been shown to improve neurogenesis and attenuate markers of senescence in NSC populations and appear as promising interventions highlighting the therapeutic potential of targeting both cellular and secretory components of the aging neurogenic niche.

Despite these promising insights, our understanding of how the NSC secretome evolves with age remains limited. Specifically, distinguishing the secretory profiles of quiescent versus activated NSCs in young and aged brains could provide critical information on how niche signaling is disrupted over time. Such knowledge may not only elucidate fundamental mechanisms underlying age-related neurogenic failure but also guide the development of targeted strategies to rejuvenate endogenous stem cell function. As neurogenesis plays an important role in cognitive flexibility, mood regulation, and brain repair, preserving or restoring NSC functionality through modulation of their secretome represents a compelling direction for combating neurodegenerative diseases and cognitive decline in aging.

CRediT authorship contribution statement

Soumia Abdellaoui: Writing – original draft. **Lida Katsimpardi:** Writing – review & editing, Validation, Supervision, Funding

acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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