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Neural stem cells in aging

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ABSTRACT

Aging is intricately linked to cognitive decline and neurodegenerative diseases, with neural stem cells (NSCs) playing a crucial role in brain function maintenance and repair. We examine the age-related metabolic shifts in NSCs, such as alterations in mitochondrial dynamics and protein expression, and how these changes affect NSCs' function of neurogenesis. We discuss the functional decline in NSCs' proliferation and self-renewal capacity, mainly in the hippocampus, and their implications for cognitive function and emotional regulation. We also highlight the potential of understanding these cellular changes within NSCs to develop novel therapeutic strategies for neurodegenerative diseases and brain injuries, emphasizing the importance of harnessing NSC therapy in aging-related conditions.

1. Introduction

Stem cells are known for their ability to divide without differentiation and their potential to differentiate into various types of cells or organs. According to the extent of this ability and potential, stem cells can be classified into totipotent stem cells, pluripotent stem cells, multipotent stem cells, oligopotent stem cells, and unipotent stem cells, all of which have varying levels of self-renewal and proliferation [1]. The ability of stem cells to proliferate and self-renew is so important to life activity that age-related changes of stem cells, stem cell exhaustion, are listed as one of the 12 hallmarks of aging [2].

Aging is accompanied by declined cognitive ability and a high risk of neurodegenerative diseases, indicating the important role that neural stem cells (NSCs) play in their potential to generate new neurons [3]. NSCs are multipotent stem cells, the differentiation of which begins with the activation of quiescent NSCs (qNSCs), a distinct population of NSCs found predominantly in specific regions of the adult mammalian brain, including the sub-ventricular zone (SVZ) of the lateral ventricles and the dentate gyrus (DG) of the hippocampus [4–6]. It is worth mentioning that the presence of NSCs in the SVZ region in humans is still controversial [4–6]. While most adult qNSCs stay in long cell cycles, upon activation, qNSCs turn into activated NSCs (aNSCs) thus entering cell cycles and gaining the potential to differentiate into various types of nerve cells. Appropriate maintenance and activation of qNSCs are essential for long-term stem cell pools and generating new neurons and glial cells [4–7], and are significantly influenced by the surrounding niches [3,8,9] and intracellular and extracellular signaling [10–12]. While the microenvironment around NSCs experiences continuous alterations throughout aging, NSCs undergo a series of changes and tackle difficulties in maintaining their physiological functions during aging [9,13].

The process by which NSCs generate new neurons in adults, is known as adult neurogenesis. Adult neurogenesis used to be a controversial topic in mice and humans. Research has presented varying findings, with some studies indicating that new neurons are generated in the hippocampus of adult humans [14] while others disagree that neurogenesis exists throughout life [15]. In recent years, substantial evidence indicated adult neurogenesis in various mammalian species, mainly in the hippocampus, including humans, which significantly declines in age-related pathological changes [13,14,16,17]. The implications of adult neurogenesis for cognitive and affective functions are significant, especially in the hippocampus where new neurons differentiated from NSCs contribute to cognitive processes such as learning and memory [17,18]. Although some questions about NSCs to generate new neurons in adults (neurogenesis) remain a mystery, we believe that

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understanding the changes of NSCs in aging is of great significance to unravel the aging mystery and identify potential regulatory targets for aging-related diseases [19].

In this review, we summarize the changes in NSCs during aging, mainly in the hippocampus, and how these changes lead to aging-related brain impairments in return, focusing on the changes within the cell and some functional deterioration, as seen in Fig. 1.

2. NSCs changes during aging

2.1. Surrounding microenvironment changes

NSCs are significantly influenced by the microenvironment, known as the "niche," which undergoes various changes with aging. The NSC niche, which is dynamic and interactive in the SVZ and DG, comprises not only NSCs, but also neurons, glial cells, immune cells, and blood vessels [9,20,21]. During aging, NSCs surrounding the microenvironment undergo dramatic changes that can negatively impact their function (Fig. 2). Examples of alterations in microglia and vasculature are as follows.

Microglia, the resident immune cells in the CNS, fundamentally alter the brain microenvironment; therefore, abnormal condition of microglia during aging results in age-related neurodegenerative conditions and transcriptional changes in NSCs, especially in the hippocampus [22,23]. Moreover, during neuroinflammation, which is often exacerbated in aging, microglia can adopt an activated state that releases pro-inflammatory cytokines, such as IL-1β and TNFα, which have been shown to negatively affect NSC proliferation and neurogenesis [9].

The vasculature within the NSC niche is also affected by aging. Aging can lead to changes in blood flow and vascular permeability, which may affect the delivery of nutrients and signaling molecules to NSCs [9]. Interestingly, during the aging process, the vascular structural changes in the ventricular-subventricular zone that affect the function of NSCs are more pronounced in male mice, such as the decrease in vessel diameter, increase in tortuosity, and elevation of vessel density, which are accompanied by a significant decline in the number of NSCs, reduced progenitor cell proliferation, and more disorganized migration of neuroblast chains in male mice [21].

2.2. Different metabolic patterns

qNSCs predominantly use glycolysis for energy metabolism which is oxygen-independent and uses glucose as energy resource, while aNSCs turn to oxidative phosphorylation which is more efficient and oxygen-dependent [3]. Aging affects this metabolic switch, potentially impacting the energy supply for neurogenesis [24,25] (Fig. 1). More than early neurodevelopment, metabolic patterns are important for age-related NSC fate decisions and functional changes within cells [26,27]. The abnormal metabolic patterns, such as aberrant lipid metabolism, can result in brain diseases including neurodegenerative diseases and emotional disorders [28–31].

Changes in protein levels and gene expression associated with aging often affect the metabolic pattern of NSC. A recent study published in Nature confirmed that the knockout of Slc2a4, the gene encoding the glucose transporter GLUT4, or by glucose starvation in NSCs located in the SVZ, can increase the activation of aged NSCs and migration of newborn neurons from SVZ-derived NSC to the olfactory bulb [32]. Also, a proteomic analysis found a protein network module linked to sugar metabolism related to Alzheimer's disease (AD) and cognitive decline that is increased in cerebrospinal fluid in individuals with AD, even increased in the asymptomatic stage of the disease, indicating early changes in energy metabolism [33]. As for gene expression, tracking cell line

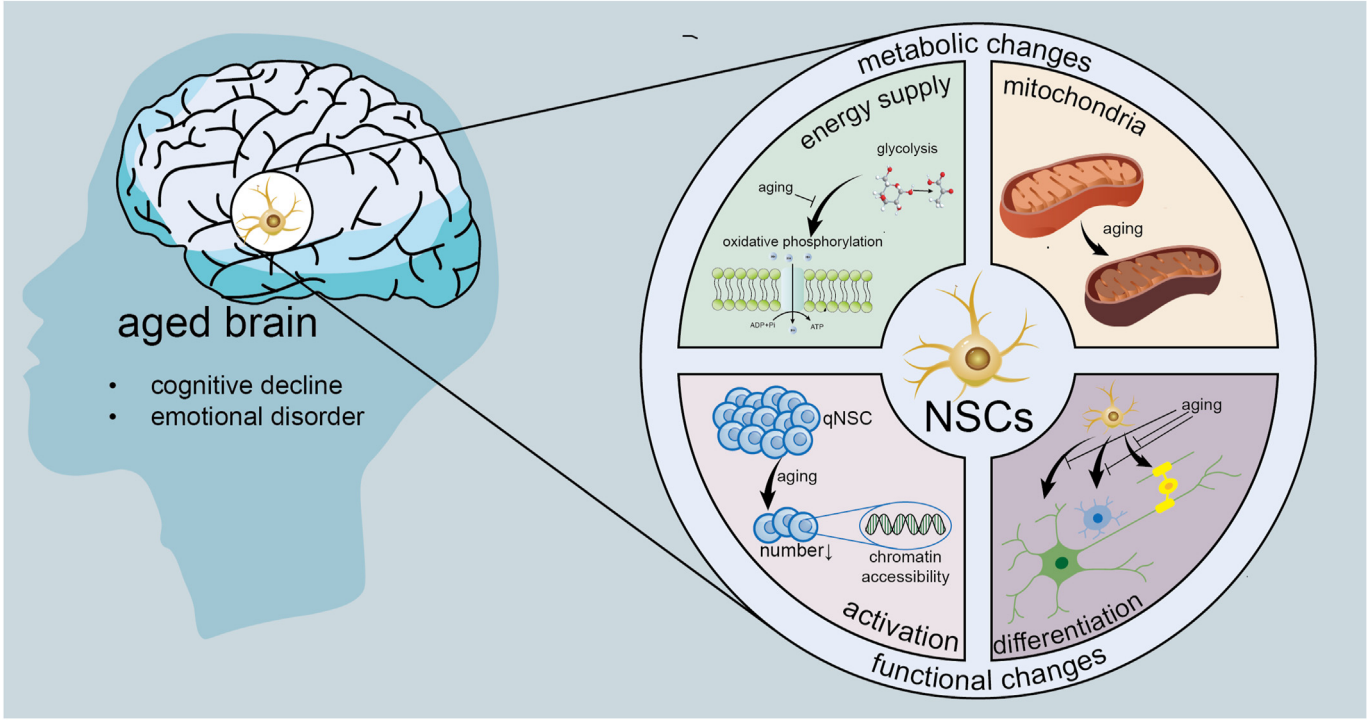

Fig. 1. NSCs undergo metabolic and functional changes in the aged brain. In the aged brain, hippocampal NSCs undergo several changes that are related to cognitive decline and emotional disorder: 1) Aging impedes the transformation of metabolic patterns during qNSC activation, thus affecting the energy supply for neurogenesis. 2) Mitochondrial dynamics change during aging, ultimately contributing to cognitive decline and emotional disorders. 3) During aging, the number and function of qNSCs drop, which may be related to changed chromatin accessibility. 4) Aging impairs the adult hippocampal neurogenesis (AHN) and prevents the differentiation of NSCs into neurons and glial cells.

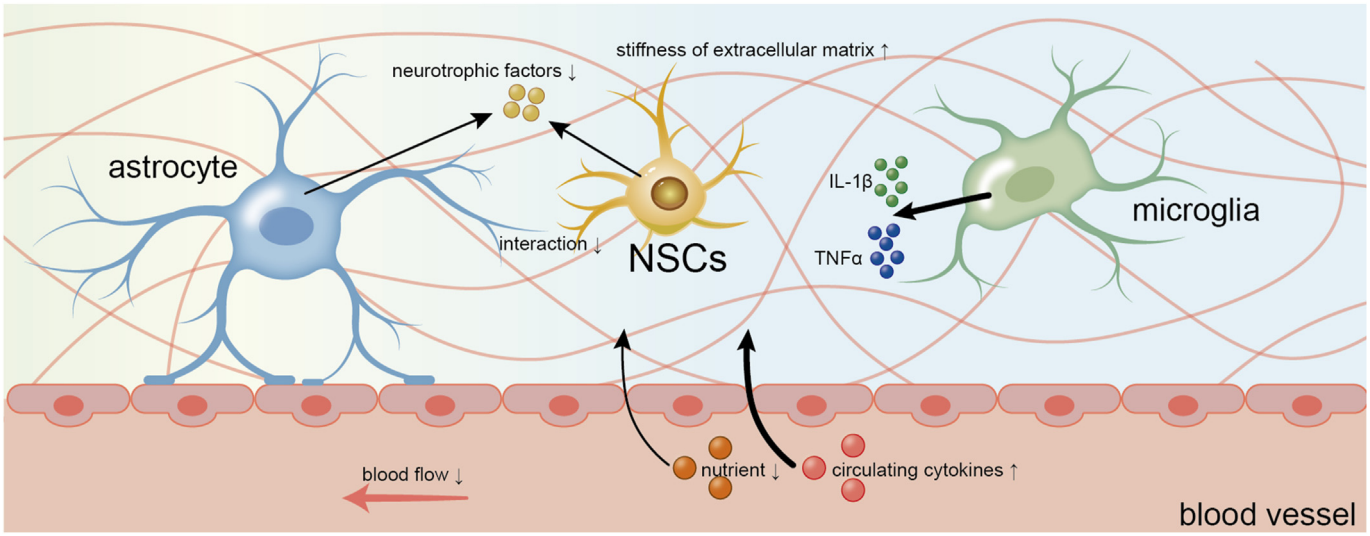

Fig. 2. NSC niche changes during aging. During aging, astrocytes release fewer neurotrophic factors and interact with NSCs less while activated microglia release more pro-inflammatory cytokines, such as IL-1β and TNFα. Also, aging leads to lower blood flow and vascular permeability changes which means less nutrients and more circulating cytokines go into the NSC niche. Lastly, the extracellular matrix becomes stiffer during aging. The thickness of arrow represents intensity or severity.

differentiation uncovered aging downregulated genes including genes related to cell proliferation and neurogenesis regulation, which implicates downregulated self-renewal potential and the depleted NSC pool in the aged brain [34]. Other research also supported the idea that gene expression changes with age, which means aged NSCs do have a specific aging signature and can be used to predict the chronological or biological age of cells, and potential rejuvenation interventions as well [35–37].

This kind of process is like a chain reaction towards aging—different metabolic patterns accompany the state of NSCs while metabolic changes influence NSCs' activation and differentiation (Fig. 1). Previously, researchers found intracellular reactive oxygen species a cellular signaling event greatly influencing NSC niches [38].

More significantly, mitochondrial dynamics are crucial for NSCs' energy metabolism and NSCs' fate decisions [39,40], ultimately contributing to cognitive decline and emotional disorders [41–43] (Fig. 1). One study showed that the loss of Opa1, a regulator of mitochondrial structure and function, leads to a decline in neurogenesis due to impaired stem cell activation and progenitor proliferation. Another research supports mitochondria's significant role in NSCs' mitochondrial dynamics changes [39]. The research by Na et al. (2023) demonstrated that the knockout of the Dnm1l, a key regulator of mitochondrial fission, results in altered mitochondrial function and an accelerated aging phenotype in NSCs [44]. Mitochondrial dynamics, to be more specific, the mitochondrial structure, function, and morphology, are closely related to NSC changes in the aging process [24,39,44–46]. That makes mitochondrial function and dynamics a novel strategy to promote healthy brain aging by enhancing NSCs' ability. Four regulators affecting NSCs through mitochondrial dynamics are seen in Fig. 3.

2.3. Altered NSCs function (decreased ability of proliferation and self-renewal)

Learning and memory mechanisms include synaptic plasticity, adult neurogenesis, neuromodulation, sleep, and epigenetics [47,48]. During aging, learning and memory deficits and cognitive decline are affected by several changes related to the above mechanisms, one of which is the decreased ability of NSCs and adult hippocampal neurogenesis (AHN) [49], and other changes involve glia-regulated synaptic plasticity [50,51], epigenetic modification [52,53], neuromodulation or neurotransmitters and their receptors [54]. What's more, changes like synaptic plasticity and neurotransmitter receptors, such as α1 GABAA receptor, can also be modulated by NSCs– The expression of α1 GABAA receptor is increased in AD but is decreased when deleting aNSCs which may cause the improved LTP after ablation of aNSCs [55]. The function of NSCs is so important that it is strongly associated with age-related learning and memory deficits and cognitive decline.

NSCs divide symmetrically to self-renew at the early stage and then divide asymmetrically to differentiate [56], during which some would differentiate into neurons and this process is otherwise known as neurogenesis. Aging negatively affects NSCs' ability to generate new neurons, with dramatically reduced neurogenesis [3,13,57,58] and smaller NSCs pool both in the SVZ of the lateral ventricles and the DG of the hippocampus [59,60] (Fig. 1). Past studies indicate the persistence of AHN until at least the 10th decade of human life [14,61,62]. However, there is a marked impairment in this process in patients with Alzheimer's disease, suggesting that the rate of neurogenesis may decline with age or be impacted by certain neuropathological conditions [17,58,61–63]. It is important to note that while there is evidence for a decline in AHN with aging, the precise timing and the extent of this decline can vary between individuals and may be influenced by various factors, including overall health, cognitive activity, and possibly lifestyle factors.

Focusing on the process of how qNSCs activate to differentiate, we examine altered NSCs' function in more detail. The maintenance of qNSCs is essential for the long-term maintenance of NSC pools while the activation of qNSCs is essential for differentiation [64]. However, the aged qNSCs undergo dramatic changes in cell number and function [5,6,65], which may be related to changed chromatin accessibility [64,66,67], such as glucocorticoid-mediated epigenetic alteration [68] (Fig. 1). Studies have reported that aged qNSCs exhibit a decline in number both in the SVZ and the DG of the hippocampus [60], a reduced capacity to activate in response to neurogenic signals [60], and a diminished potential to differentiate into neuronal and glial lineages [69].

In summary, the aging process contributes to NSCs' intrinsic and

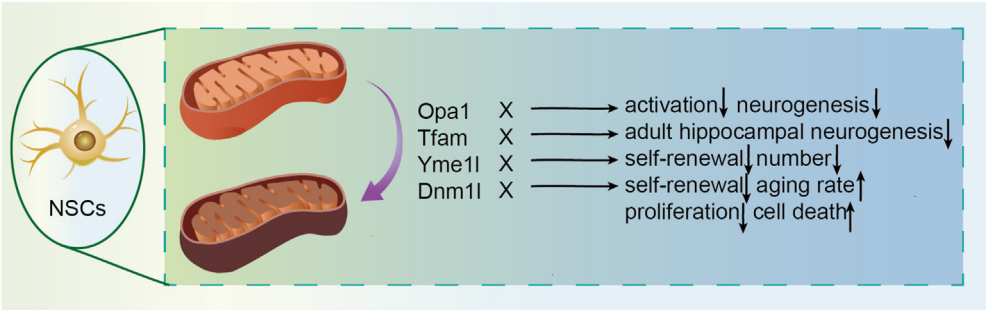

Fig. 3. Four regulators affect NSCs through mitochondrial dynamics. The knockdown or knockout of four regulators related to mitochondrial dynamics can lead to a decline in NSC function and AHN.

extrinsic alterations, thus leading to their functional changes, especially a distinct decrease in their regenerative potential and AHN.

3. Impact of NSC changes on aging

The cellular alterations of NSCs caused functional decline, thus resulting in aging-related dysfunction and diseases. Neurodegenerative diseases and emotional disorders are two known results of the impact of NSC changes.

3.1. Cognitive decline and neurodegenerative diseases

The alterations of NSCs bring a higher risk of cognitive decline and neurodegenerative diseases, exhibiting a smaller NSC pool and waning adult neurogenesis [13,59,60,70]. Neuronal loss and impaired neurogenesis cause a reduction in hippocampal volume, which contributes to hippocampal atrophy and exhibits cognitive impairment [71]. Meanwhile, restoring the ability of neurogenesis and exploring the potential function of NSCs can rescue such decline and AD neuropathologies [17]. Previous research found that exercise enhances neurogenesis and ameliorates cognitive deficits associated with aging by changing systemic environment such as the release of the antioxidant selenium transport protein, selenoprotein P (SEPP1) and by reactivating qNSCs in the hippocampus [72]. Another research focusing on the AD model demonstrated that extracellular vesicles derived from human NSCs ameliorate both behavioral and molecular neuropathologies in AD, indicating the neuroprotective potential of NSCs [73].

More intriguingly, NSC-related therapy offers many potential AD intervention therapies. Studies in rodent models have shown that NSC transplantation can lead to reduced amyloid-beta levels, decreased tau phosphorylation, and improved cognitive function [74]. There is still a long way to bridge the gap between these preclinical findings and their application in AD patients, considering the difference between animal models and human patients. For another neurodegenerative disease, Huntington's disease, human NSC transplantation could also be a potential therapy [75]. Except for NSC transplantation, NSCs can secrete therapeutic factors that support neuronal survival and promote the growth of new neurons and synapses [74,76]. The researchers also found that induced pluripotent stem cell (iPSC)-derived cortical neural stem cell secretome (CNSC-SE) could be a promising therapy for AD by reducing neuroinflammation and improving the neuroprotective environment [76].

3.2. Emotional disorders

Some researchers argue that emotional disorders, such as stress, anxiety, and depression, are detrimental to NSCs and neurogenesis, which ultimately lead to cognitive decline [18,77,78]. The chronic restraint stress model of depression with mice induces autophagic cell death of hippocampal NSCs thus leading to a decline in AHN [77]. Antidepressant treatment, particularly with selective serotonin reuptake inhibitors (SSRIs), has been shown to increase hippocampal neurogenesis markers and potentially improve mood and cognitive symptoms in MDD patients [18]. Meanwhile, transplantation of neural progenitor cells (NPCs) in vitro differentiated from human iPSCs, could promote regeneration and motor function recovery in the post-traumatic stress disorder model [79].

4. Conclusion and prospects

Several questions remain in the maintenance and activation of NSCs during aging. Right now, many researchers are concerned with the exact regulatory mechanism behind the transition from quiescent NSCs to activated NSCs, especially during aging [5,58,80]. Also, they intend to find out how NSCs maintain their proliferative potential throughout our lifespan and whether the NSCs pool could be restored. Among these mechanisms, mitochondria have a wide influence on NSCs' fate decisions and aging [40,46]. However, it is still unclear whether the structural and functional changes of mitochondria are a consequence of NSCs' aging or an initiation factor. What role do immune factors play in NSCs during aging? As NSCs attract more and more attention for their potential to treat neurodegenerative diseases and spinal cord injuries, we expect further research to uncover the mysteries of NSCs in aging. Understanding how NSCs change throughout physiological and pathologic aging might provide novel ways to activate and maintain the generation and maturation of new neurons for NSC therapy.

CRediT authorship contribution statement

Zhi-Xia Li: Writing – original draft. **Jing-Dong J. Han:** Writing – review & editing.

Conflict of interest statement

We declare that we have no conflict of interest.

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