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Ageing and Neurodegenerative Diseases

Review

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Advances in neural stem cells in aging and age-related neurodegenerative diseases

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Abstract

With aging, neural stem cells (NSCs) undergo age-related changes, including metabolic abnormalities, disrupted protein homeostasis, mitochondrial dysfunction, reduced genetic stability, and more notably, a diminished capacity for proliferation and differentiation. These changes may contribute to the development of age-related neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). In these conditions, disease-specific pathological changes may interact with age-related alterations of NSCs, resulting in impairment of neurogenesis, which further leads to cognitive, mood, and motor decline. Based on these changes, potential therapeutics targeting neurogenesis and stem cell-based therapies may restore the functions of NSCs and replace the degenerated neurons, aiming to ameliorate functional decline in these neurodegenerative diseases. While stem cell-based therapies, including stem cell transplantation and stem cell secretome therapy, show great potential in the treatment of neurodegenerative diseases, challenges in tumorigenesis, immune rejection, and extraction or storage of the stem cell secretome need to be further addressed. A better understanding of age- and disease-related changes in NSCs, the underlying mechanism driving these changes, and the benefits and drawbacks of the therapeutic approaches may provide insights for novel disease-modifying interventions for the future treatment of these diseases.

Keywords: Aging, neural stem cells, neurogenesis, neurodegenerative diseases, stem cell therapy

INTRODUCTION

Stem cells play an important role in the development, renewal, and regeneration of diverse tissue types, including the brain[1]. These cells have the unique ability to self-renew and differentiate, enabling them to repair damaged tissues in response to changes in the systemic or local environment[2]. However, the self-renewal capacity and differentiation potential differ significantly across different stem cell types. In contrast to stem cells in other tissues, such as skin or liver, neural stem cells (NSCs) typically remain in a relatively quiescent state, exhibiting minimal or no division in normal conditions[3,4]. However, contrary to the prevailing view that neurogenesis occurs only during early development, evidence has shown that neurogenesis continues into adulthood, although at a much lower rate and in specific brain regions. NSCs divide *in situ*, resulting in the generation of new neurons in the subgranular zone (SGZ) of the hippocampal dentate gyrus (DG) and subventricular zone (SVZ) of the lateral ventricles[1,5]. In the hippocampus, radial glial stem cells residing in the SGZ are activated and start to divide asymmetrically into intermediate progenitor cells in response to physiological and pathological stimuli. These progenitor cells are highly proliferative amplifying stem cells and subsequently generate neuroblasts. Then, the new-generated neurons migrate into the granule cell layer and differentiate into granule neurons. The granule neurons can integrate into the hippocampal circuit, contributing to function in learning and memory[6-8]. In SVZ, NSCs located in "pinwheel" structures can also be activated upon environmental stimuli and injury. Newly generated neuroblasts from these NSCs migrate to the olfactory bulb to become granule and periglomerular neurons, contributing to various olfactory functions, such as odor discrimination and olfactory learning[1,9]. These processes are supported by evidence from human and animal studies[10-13].

Like other types of cells, NSCs accumulate damage and undergo a decline in number and function with age[5,14]. They exhibit alterations in metabolism, protein homeostasis, mitochondrial function, genetic stability, and notably, a reduction in proliferation and differentiation[15]. A deeper comprehension of the alterations, regulatory processes, and mechanisms underlying these age-related changes in NSCs may offer novel therapeutic targets for age-related disorders, including neurodegenerative diseases. Here, we summarize recent advances in the field of NSC research in two sections. Section "REGULATION OF NEUROGENESIS AND NSC CHANGES IN HEALTHY AGING" discusses the regulation of adult neurogenesis and NSC changes in healthy aging. Section "AGING AND NSCS IN AGE-RELATED NEURODEGENERATIVE DISEASES" includes age- and disease-related alterations of NSCs and potential therapeutics targeting NSCs in neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and Huntington's disease (HD). It is hoped to bring new insights for mechanism research and clinical treatment development in the future.

REGULATION OF NEUROGENESIS AND NSC CHANGES IN HEALTHY AGING

Regulation of adult neurogenesis

Adult neurogenesis is a tightly regulated process influenced by extrinsic and intrinsic factors. Firstly, intrinsic factors are critical for the proliferation and differentiation of NSCs, including (1) Transcription factors: In addition to the well-known transcription factors that regulate stem cell function, such as neuronal differentiation 1, prospero homeobox protein 1, members of SRY-related high-mobility group box family and forkhead O-box transcription factor family, *etc.*[16], several other transcription factors, such as zinc-finger E-box binding homeobox 1[17], Kruppel-like factor 9[18], BCL6 transcription repressor[19], and others, have also been documented; (2) Cell cycle regulators: cyclins, cyclin-dependent kinases (CDKs), CDK inhibitors, and Rb proteins play important roles in the regulation of NSC proliferation and the exit from the cell cycle to differentiation[20]; (3) Epigenetic modifications: DNA methylation, histone post-translational modifications, and chromatin remodeling are critical regulators of adult neurogenesis through their impact on gene expression[21]. Secondly, extrinsic factors within the microenvironment (niches) and

other factors from the external environment are also of critical importance for the regulation of adult neurogenesis in the hippocampus, including neurotransmitters, such as serotonin[22], dopamine[23], and acetylcholine[24]; neurotrophic and growth factors, such as brain-derived neurotrophic factor (BDNF)[25], bone morphogenetic protein[26], and vascular endothelial growth factor (VEGF)[27]; hormones, such as growth hormone, estradiol, testosterone, and cortisol[28]; neuroinflammation, such as microglia activation and inflammatory cytokines[29], and other external factors, such as caffeine[30], gut microbiota[31], selenium[32], physical exercise[33], and enriched environments[34]. Thirdly, neural circuit activity can influence nearby NSCs. For example, hippocampus-dependent learning tasks, which are based on hippocampal circuit activity, have been demonstrated to promote adult neurogenesis, and processes involved in learning and memory, such as long-term potentiation, are associated with the integration of newborn neurons into existing networks[35]. Evidence also shows that stimulation of neurons outside the hippocampus, such as supramammillary nucleus neurons in the hypothalamus[36], promotes hippocampal neurogenesis. Lastly, pathological conditions, such as chronic stress[37], depression[38], and neurodegenerative diseases including AD[39,40] and PD[41], may impair hippocampal neurogenesis.

NSCs in healthy aging

During healthy aging, NSCs show age-related changes as other cells, such as the accumulation of DNA damage, telomere shortening, and mitochondrial dysfunction leading to increased oxidative stress and decreased energy metabolism[15]. However, NSCs also experience age-related alterations in their proliferation and differentiation properties. Firstly, aging NSCs show declined proliferation and imbalanced differentiation. Their ability to efficiently enter the cell cycle and proliferate diminishes with age, as evidenced by prolonged quiescence, decreased cell numbers, and impaired self-renewal[1,5,9,14,42]. Additionally, there is a shift toward differentiating into astrocytes with age[43,44]. Secondly, epigenetic modifications in NSCs are altered during aging, including changes in DNA methylation, histone modifications, and non-coding RNAs, leading to changes in promoter accessibility and the silencing of genes critical for neurogenesis[9,45-47]. Thirdly, the niche signaling of NSCs shows age-related changes, including alterations in the microenvironment with less supportive factors, such as growth factors[42], and chronic inflammation, such as immune cell infiltration and increased levels of inflammatory cytokines[9,48]. Fourthly, the aging of NSCs is associated with disruptions in protein homeostasis and autophagy, resulting in an increased accumulation of protein aggregates[5,49]. Lastly, the response of aging NSCs to injury and pathological changes is impaired[9,50]. Even when new neurons are generated, they develop more slowly with age, accompanied by a reduced capacity to integrate into existing neural circuits due to altered synaptic transmission and synapse loss[51].

NSC function and neurogenesis are under strict regulation in the brain. Aging NSCs are characterized by reduced proliferation, imbalanced differentiation, epigenetic changes, alteration in metabolism, and neuroinflammation in the niches. These changes contribute to a decline in neurogenesis, which impacts learning, memory, mood regulation, and cell repair and replenishment after brain injury or in disease condition [Figure 1]. Understanding these mechanisms is essential for developing interventions to mitigate functional decline in neurodegenerative diseases. Advanced lineage tracing tools with clustered regularly interspaced short palindromic repeat (CRISPR)-Cas9 technology to visualize NSC activation and differentiation *in situ* may provide novel methods to track changes in NSC niches for a better understanding of the underlying mechanisms of NSC aging[9]. The rejuvenation of aged stem cells, including dietary and exercise interventions, microbiome transfer, and *in vivo* partial reprogramming, may provide insight into new therapeutic strategies for age-related neurodegenerative diseases[9]. CRISPR-Cas9 mediated genome editing might be used to target genes in neurodegenerative diseases, such as correction of mutant amyloid precursor protein (*APP*) gene in AD[52], and it has the potential to introduce support genes into NSCs, such as nerve growth factors, thereby facilitating neuronal regeneration. However, it should be noted that

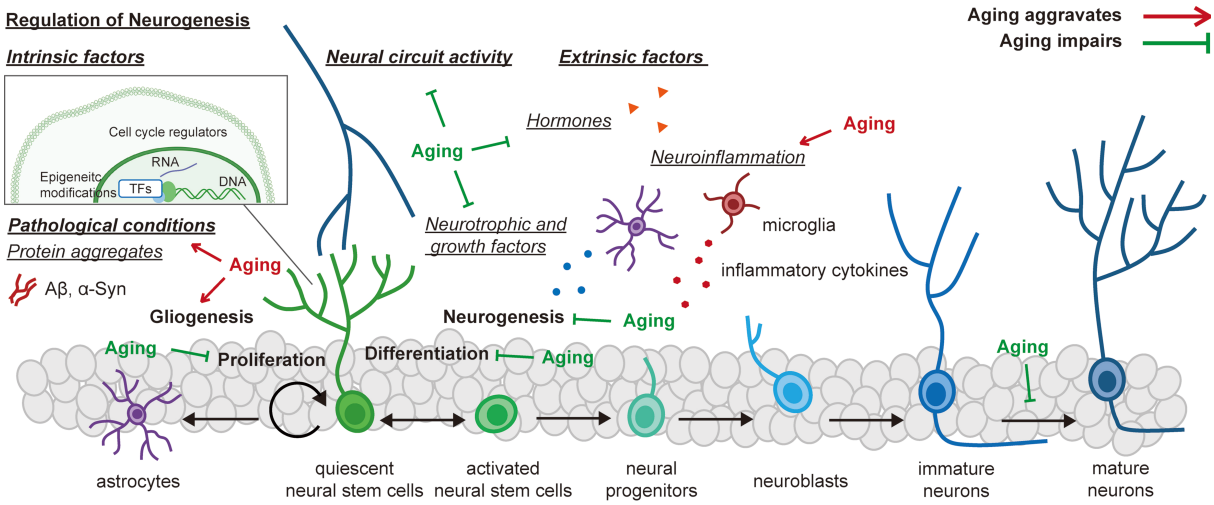

Figure 1. Regulation of neurogenesis and NSC changes in healthy aging. Regulation of neurogenesis includes intrinsic factors (transcription factors, cell cycle regulators, epigenetic modifications), extrinsic factors (neurotransmitters, neurotrophic and growth factors, hormones, neuroinflammation, and other external factors), neural circuit activity, and pathological conditions. In aging, NSCs show a decline in proliferation, imbalanced differentiation favoring gliogenesis and preventing neurogenesis, age-related epigenetic modifications, changed niche signaling with less supportive factors and chronic inflammation, alterations in protein homeostasis and autophagy, and declined response to injury and diseases. NSC: Neural stem cell; Aβ: amyloid β; α-Syn: α-synuclein; TFs: transcription factors.

significant challenges, including ethical issues and off-target effects, remain to be overcome before this approach can be finally adopted.

AGING AND NSCS IN AGE-RELATED NEURODEGENERATIVE DISEASES

In age-related neurodegenerative diseases, the changes in NSCs with age may interact with or be affected by different pathological changes in these diseases. A better understanding of NSC alterations in disease conditions, their mechanisms, and the advantages and disadvantages of potential therapeutics will benefit the treatment of these diseases. There are pharmacological and non-pharmacological interventions targeting neurogenesis, and stem cell-based therapies. The current stem cell-based therapies encompass cell transplantation, stem cell secretome therapy, and stem cell gene editing[53,54].

Cell transplantation involves the transplantation of stem cells or differentiated cells into the brain, providing a direct replacement for damaged neuronal or glial cells[55]. Stem cell transplantation for neurodegenerative diseases has made great advances in recent years and is becoming one of the most promising treatments. Firstly, stem cell transplantation can be divided into two categories according to the cell source: allogeneic or autologous transplantation. Allogeneic transplantation, combined with immunosuppression, is a classical regimen primarily based on fetal-derived human pluripotent embryonic stem cells (ESCs)[56,57]. The drawbacks of allogeneic transplantation are insufficient cell sources, adverse effects of immunosuppression, and ethical concerns[57]. Autologous transplantation utilizes induced pluripotent stem cells (iPSCs) reprogrammed from a patient's somatic cells. Although autologous iPSC transplantation could alleviate immune rejection and obviate the necessity for major histocompatibility complex matching theoretically, there are still concerns regarding uncertain changes in cell immunogenicity during *in vitro* growth, expansion, and differentiation of iPSCs[58]. Secondly, the delivery method of stem cell transplantation mainly relies on direct injection. Intracerebral or intraneural injection can target precisely but have the risk of neurological complications or nerve injury, while intrathecal or intracerebroventricular injection have direct access to cerebrospinal fluid but may have challenges in cell retention and potential off-target effects[59].

Moreover, minimally invasive surgery can be used to reduce damage. Intranasal delivery of stem cells is non-invasive but limited by variable absorption[59]. Thirdly, the safety and efficacy evaluation of stem cell transplantation is of great importance in clinical trials. Death and other acute severe complications are closely monitored immediately after the surgery, and chronic complications such as tumorigenicity and undesirable distribution are continuously checked following 12 months or longer[60]. Imaging techniques with specific tracers are used to assess the survival and function of cells after transplantation[61]. The long-term efficacy of therapy could be evaluated by clinical scales and cognitive or motor function measures, along with a series of examinations of imaging and fluid biomarkers[60].

Stem cell secretome therapy utilizes various bioactive molecules secreted by NSCs, such as growth factors, cytokines, and extracellular vesicles, to promote neural repair, regeneration, and anti-inflammation, and to enhance the blood-brain barrier function[62-64]. This therapy overcomes the problems associated with cell transplantation, but it faces challenges in the extraction and storage of the secretions, as well as difficulties in determining the treatment dosage. Additionally, the efficacy may vary due to the instability of the secretions[65].

Stem cell gene editing refers to the combination of stem cell therapy with gene editing technology. As mentioned in the previous section, specific genes can be introduced into NSCs, enabling them to express therapeutic proteins or factors post-transplantation, thereby enhancing the precision of treatment or diminishing the likelihood of immune attack[66-68].

In the following section, we will discuss in detail the recent advances in NSC alterations and the potential therapeutics targeting neurogenesis in age-related neurodegenerative diseases.

AD

AD is the most common form of dementia among the older population. It is clinically manifested as progressive cognitive decline and behavioral abnormalities and pathologically characterized by amyloid β (Aβ) plaques, hyperphosphorylated tau neurofibrillary tangles, and neuronal loss[69].

Studies have indicated that hippocampal neurogenesis declines with age in AD patients[70,71] and AD mouse models[72,73]. In AD brains, hippocampal neurogenesis is impaired even before the presence of Aβ plaques or neurofibrillary tangles in the DG[70], or in early postnatal AD mice[74]. AD brains have a remarkably decreased number of doublecortin/proliferating cell nuclear antigen-positive ($DCX^+/PCNA^+$) neuroblasts and newborn DCX^+ neurons, and the maturation of these DCX^+ neurons is also impaired[70,71]. As in healthy aging, NSCs in AD show an imbalanced differentiation favoring gliogenesis rather than neurogenesis[75] and the functional integration of newborn neurons is also impaired[76]. Evidence from human iPSCs shows that hippocampal progenitors and neurons derived from iPSCs from familial and sporadic AD patients exhibit impaired neurogenesis with dysregulation of c-Jun-cGAS–STING and WNT/JNK pathways[77]. Extracellular vehicles from different iPSC-derived cells, including excitatory neurons, astrocytes, microglia-like cells, and oligodendrocyte-like cells, also show disease-specific molecules associated with AD pathology and cognitive impairment[78].

Aβ toxicity and tau pathology

Aβ is produced by sequential proteolytic cleavage of APP by β- and γ-secretase, which is believed to induce toxicity in cellular systems through membrane disruption and organelle dysfunction, and spread through cell-to-cell transmission[79]. Regarding neurogenesis, Aβ impairs the proliferation and differentiation and accelerates the senescence of the NSCs in AD[80]. For example, Aβ hinders the proliferation of neural

precursors and neuronal differentiation in DG by downregulating microRNA (miR)-132. miR-132 is recruited by adult NSCs and progenitors as part of the response to exercise- or aging-related stimuli but compromised under Aβ pathology[81]. Besides Aβ, APP and the secretases also contribute to abnormal neurogenesis in AD; for example, APP is reported to favor the differentiation of NSCs toward glial cells and prevent the differentiation toward neurons through APP/APP intracellular domain/glycogen synthase kinase-3β system[75]. Mutations of Presenilin 1, one of the four core proteins in the γ-secretase, cause premature neurogenesis driven by reduced Notch signaling[82].

Tau is a microtubule-associated protein that plays a role in tubulin polymerization, microtubule stabilization, and axonal transport, and is hyperphosphorylated in AD to aggregate as neurofibrillary tangles[83]. It is reported that accumulation of phosphorylated tau in hippocampal DG GABAergic interneurons induces neurogenesis deficits and astrogliosis through local neural network hyperactivation[84]. Anti-aggregating tau mutation or tau deficiency promotes hippocampal neurogenesis[85,86].

Neuroinflammation

Neuroinflammation has a prominent role in the pathogenesis of AD. The pathological protein aggregations of Aβ and tau induce excessive activation of glial cells and the release of proinflammatory cytokines, which contributes further to neuronal loss in AD[87]. Neuroinflammation can impact various stages of neurogenesis, including cell proliferation, differentiation, migration, the survival of newborn neurons, maturation, synaptogenesis, and neuritogenesis[88]. For example, the proinflammatory cytokine interleukin 1 β (IL-1β) causes a reduction in the number of immature neurons and impairment in their morphological development, leading to cognitive deficits[89]. IL-6 has been demonstrated to inhibit neurogenesis in NSCs via the JAK2/STAT3 signaling[90]. Even peripheral infection and inflammation, such as exposure to coronavirus disease 2019, can affect hippocampal neurogenesis[91].

Epigenetic modifications

In AD, NSCs show disease-specific epigenetic changes, such as altered DNA methylation and histone modifications. A study profiling genome-wide DNA methylation levels in hippocampal samples from AD patients shows that 118 AD-related differentially methylated positions are identified, preferentially involving neurodevelopmental and neurogenesis-related genes[92]. Another study shows that 5-hydroxymethylcytosine is significantly altered in developmentally programmed intragenic regions within defined fetal histone marks and enhancers in AD organoids[93].

Changed niche signaling

AD and its pathological changes affect the niche signaling of the NSCs, such as disrupted growth factor levels and vascular dysfunction. Several growth factors including BDNF[94], insulin-like growth factor 2[95], and transforming growth factor-β (TGF-β)[96] are reported to be dysregulated in the AD brain. Restoring the level of these growth factors or stimulating their signaling pathways ameliorates hippocampal neurogenesis in AD[97-99]. On the other hand, vascular dysfunction including endothelial dysregulation and age-related changes in blood and plasma also impair neurogenesis and hippocampal neural precursor activity[100,101].

Potential therapeutics targeting neurogenesis in AD

Pharmacological interventions targeting Aβ pathology, neuroinflammation, and growth factors are applied to modulate neurogenesis in AD, with the objective of improving cognitive function[10,102,103]. For example, soluble APP-α, a product of APP cleavage by α-secretase, may restore the proliferation of neural progenitor cells (NPCs) in SGZ and be therapeutic for the cognitive decline in AD[104]. CHF5074, a γ-secretase modulator, restores hippocampal neurogenesis and reverses memory deficit in an AD mouse model[105].

JC124, an inhibitor of NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome, reduces microglia activation and astrogliosis, increases hippocampal neurogenesis, and improves synaptic plasticity and cognitive function in AD mice[106]. Curcumin improves neurogenesis by upregulating Wnt/β-catenin and BDNF in AD[107]. Other therapeutics, such as RNA-binding protein 8A[108], vitamin D[109], and Ω-3 polyunsaturated fatty acids[110], also show beneficial effects in improving hippocampal neurogenesis in AD.

Non-pharmacological treatments are also used to potentially modulate neurogenesis in AD. Exercise or physical activity is a widely studied intervention to modulate neurogenesis in diseases such as AD, the mechanism of which may include increased BDNF levels via the release of various cytokines or metabolic products (such as cathepsin B, irisin, lactate, and ketone bodies) during exercising [111]. Recent studies show that blood plasma from exercised human subjects or animals may promote hippocampal neurogenesis and rescue cognitive decline in AD[112,113]. Photobiomodulation therapy is reported to promote interferon-γ (IFN-γ)/IL-10 release from $CD4^+$ T cells to modulate neurogenesis and ameliorate cognitive deficits in AD mouse models[114]. Patterned optogenetic stimulation applied to the hypothalamic supramammillary nucleus has been shown to enhance hippocampal neurogenesis in 5×FAD and 3×Tg-AD mouse models[115].

NSC transplantation has been applied as a potential therapeutic for replenishing the reduced NSC pool in the hippocampus, aiming to ameliorate cognitive impairment in AD[116,117]. Treatments aimed at improving the microenvironment or employing different delivery methods, such as pharmacological inhibition of the asparaginyl endopeptidase[118], nanomaterial formulation[119], and intranasal transplantation[120], are used to improve the efficacy of NSC transplantation. NSC-derived extracellular vesicles that can modulate the local microenvironment and distant neuronal functions are used as a "cell-free" therapy for central nervous system diseases including AD[121]. RNAs and proteins in these extracellular vesicles show anti-apoptotic, antioxidant, anti-inflammatory, and neurogenic properties, which may enhance the hippocampal neurogenesis, mitigate Aβ accumulation, protect against synaptic loss, and improve cognitive function in the AD brain[122,123].

Other rejuvenation strategies targeting NSCs are also applied in AD. For example, dasatinib and quercetin, a cocktail of two U.S. Federal Drug Administration-approved "senolytic" compounds, are reported to be administrated for selectively eliminating Aβ-associated senescent oligodendrocyte progenitor cells, reducing neuroinflammation and Aβ load, and ultimately improving cognitive deficits in AD mice[124]. The age-related changes in NSCs in AD and potential therapeutics targeting NSCs, as well as their advantages and disadvantages, are illustrated in Figure 2.

PD

PD is clinically characterized by parkinsonian motor symptoms, including bradykinesia, muscular rigidity, rest tremor, and postural, gait impairment, and non-motor symptoms, such as olfactory dysfunction, cognitive impairment, psychiatric symptoms, sleep disorders, and others[125].

A few studies indicate a dysregulated adult neurogenesis in the brain of PD patients[126,127] and PD rodents[128,129]. However, one study demonstrates no change in NSC proliferation in PD brains compared with control ones[130]. PD brains show increased densities of HuC/HuD^+ proliferative neuroblasts and DCX^+ immature DG cells with morphological abnormalities and reduced expression of neuronal nuclei (NeuN), which implies deficits in the maturation of newborn neurons in PD[131]. Deficiencies in neurogenesis in different brain areas may be a possible pathophysiological mechanism for non-motor symptoms in PD; for example, impairment of neurogenesis in the hippocampus and olfactory bulb may be associated with depression and olfactory dysfunction in PD, respectively[132,133].

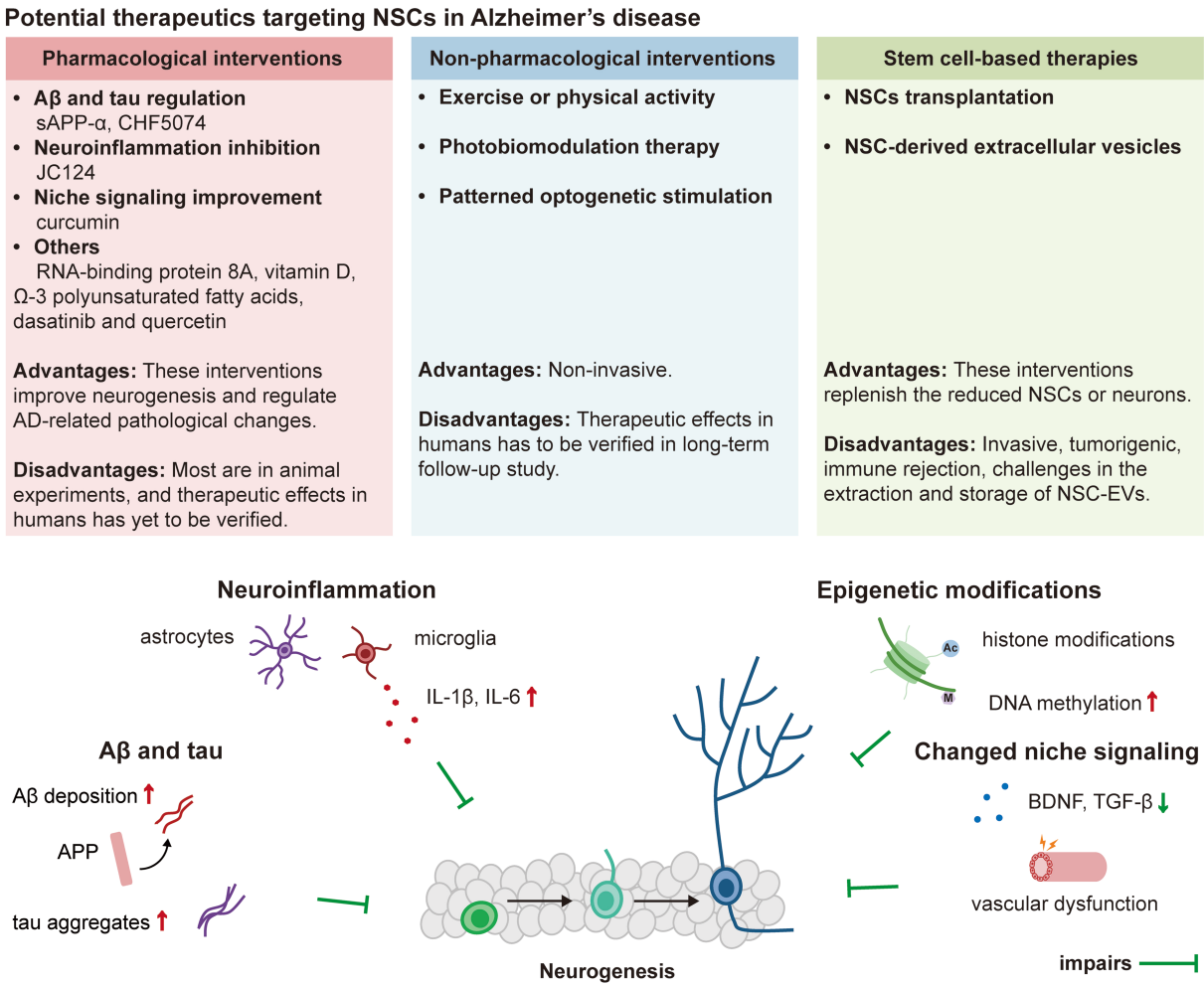

Figure 2. Potential therapeutics targeting NSCs in AD. Pharmacological (agents targeting Aβ and tau, neuroinflammation, and improving niche signaling), non-pharmacological interventions (exercise, photobiomodulation, optogenetic stimulation) and stem cell-based therapies show potential in improving neurogenesis in AD. NSCs: Neural stem cells; AD: Alzheimer's disease; Aβ: amyloid β; APP: amyloid precursor protein; BDNF: brain-derived neurotrophic factor; IL-1β: interleukin 1β; IL-6: interleukin 6; NSC-EVs: neural stem cell-derived extracellular vesicles; sAPP-α: soluble amyloid precursor protein-α; TGF-β: transforming growth factor-β.

Dopamine signaling deficiency and α-synuclein toxicity

The loss of dopaminergic neurons in the substantia nigra pars compacta is the key pathological change in PD[134]. However, dopamine signaling from the midbrain plays a crucial role in modulating neurogenesis in SGZ and SVZ[126,135]. Dopamine may promote the proliferation and differentiation of NSCs and progenitor cells and increase neurogenesis[136]. Deficiency of dopamine signaling from the midbrain decreases NSC proliferation in both SGZ and SVZ[126,135], and selective agonism of D2-like receptors restores the proliferation of the progenitor cells[126].

On the other hand, the pathological hallmark of PD is Lewy pathology consisting of abnormal aggregates of α-synuclein (α-Syn)[134]. α-Syn, as a synaptic regulator, is believed to be essential for the maintenance of subependymal NSCs[137]. Post-translational modifications of α-Syn, including phosphorylation, promote its misfolding and aggregation, and contribute to its toxicity affecting cellular processes, such as protein degradation and autophagy, mitochondrial function, and oxidative stress[138]. Besides this toxicity, α-Syn aggregation impairs neuronal differentiation, induces differentiation toward non-neuronal fates, and

impairs the survival of NSC-derived neurons, especially dopaminergic neurons in iPSC-derived NSCs[139]. α-Syn aggregation also affects neurogenesis in the olfactory system, as evidenced by a decrease in newly generated interneurons in the olfactory bulb in the early and late stages of PD motor progression[133].

Genetic factors

Several genes linked to monogenic PD, including alpha-synuclein (*SNCA*), leucine-rich repeat kinase 2 (*LRRK2*), Parkin, and PTEN-induced putative kinase 1 (*PINK1*), are genetic risk factors contributing to the incidence of PD[134]. These genes play important roles in maintaining synaptic and mitochondrial functions and may also regulate neurogenesis. For example, PD-associated LRRK2-G2019S mutation induces early cell cycle exit, loss of stemness, and decreased viability in differentiating NSCs[140]. Parkin knockout causes accumulation of p21 in NSCs, which further results in the loss of cell differentiation ability and lowers neurogenesis[141]. PINK1 deficiency is reported to be associated with deficits of hippocampal neurogenesis[142].

Neuroinflammation

Numerous studies suggest that neuroinflammation is associated with PD pathogenesis; for example, misfolded α-Syn can activate microglial nuclear factor-κB through toll-like receptors, resulting in the production of IL-1β and tumor necrosis factor-α (TNF-α)[143]. Excessive activation of microglia and dysregulation of the release of proinflammatory cytokines may contribute to the development of PD[144]. Evidence indicates a crucial role of neuroinflammation in the regulation of neurogenesis and dopaminergic differentiation. Two α-chemokines, chemokine ligand 6 (CXCL6) and CXCL8, are reported to promote the proliferation and differentiation of ventral midbrain precursors and increase the number of dopaminergic neurons *in vitro*[145]. Microglia-secreted factors, such as IL-1β, TNF-α, and insulin-like growth factor 1, are shown to increase dopaminergic differentiation of human ventral mesencephalic NSCs[146]. Integration of iPSC-derived microglia into midbrain organoids affects synaptic remodeling and increases neuronal excitability, further leading to increased neuronal maturation and functionality[147].

Impaired niche signaling

Exposure to environmental factors such as pesticides is an important risk factor for the development of PD[134]. At the same time, exposure to environmental toxicants also affects the neurogenesis in PD. For example, combined exposure to maneb and paraquat is reported to have a synergistic effect with α-Syn accumulation, resulting in a significant reduction in neuronal precursors and proliferating cells through transcriptional alteration of genes regulating neurogenesis[148]. Circulating hormones are also modulators of neurogenesis. Unacylated ghrelin, a stomach hormone, is shown to inhibit hippocampal neurogenesis and reduce the number of newborn neurons, and its level is dysregulated in PD dementia patients[149].

Potential therapeutics targeting neurogenesis in PD

Pharmacological treatments regulating the dopaminergic system, modulating hormone signaling, or providing neuroprotective effects are used in PD to enhance neurogenesis to improve dopaminergic pathways and non-motor symptoms[150-152]. For example, agonists of dopamine D2/D3 receptors show a promoting effect of neurogenesis by enhancing the secretion of BDNF, ameliorating neuroinflammation, and alleviating oxidative stress[126,150]. A synthetic estrogen-related receptor γ ligand is shown to enhance neurogenesis in the hippocampus of female LRRK2-G2019S mice, as evidenced by the increased number of DCX^+ cells and bromodeoxyuridine (BrdU)/NeuN-positive cells in DG[151]. Glucagon-like peptide 1, a hormone regulating blood glucose levels and appetite, has shown neuroprotective effects in preclinical studies and may play beneficial roles in enhancing neuronal insulin sensitivity and energy metabolism, increasing the synthesis of BDNF and glial cell line-derived neurotrophic factor (GDNF), and promoting

neurogenesis in AD and PD[153]. Intranasal administration of gangliosides GD3 and GM1 can increase the number of BrdU/Sox2$^+$ NSCs in the SVZ and DCX$^+$ immature neurons in the olfactory bulb and restore impaired neurogenesis in A53T α-Syn-expressing mice[152]. miR-124-3p-enriched small extracellular vesicles are reported to induce neuronal differentiation in SVZ NSCs *in vitro* and offer a protective effect on dopaminergic neurons *in vivo*[154].

Non-pharmacological interventions are also applied to modulate neurogenesis in PD. Exercise is believed to improve the production of neurotrophic factors, neurotransmitters, and hormones to enhance neurogenesis[155]. Environmental enrichment, including physical exercise, cognitive stimulus, and social interactions, has beneficial effects on neurogenesis through the regulation of neurotransmitters and neurotrophic factors in PD, such as dopamine, BDNF, and GDNF[156]. Electroacupuncture is reported to increase the expression of BDNF and restore the number of BrdU+ and BrdU/DCX$^+$ cells in the SVZ in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD mouse model[157].

Stem cell transplantation is also applied in PD. A study using intraspinal transplantation of hypoxia-preconditioned olfactory mucosa mesenchymal stem cells shows improved neural functional recovery in PD animal models and patients through secretion of TGF-β[158]. Concurrently, stem cells are employed to replace dopamine neurons in PD, but the source of stem cells and therapeutic effects remain uncertain. With the development and improvement of reprogramming and differentiating technologies, dopaminergic progenitor cells or dopamine neurons derived from human ESCs or iPSCs are now being used for cell replacement therapy in PD. Stem cell-derived midbrain dopamine neurons are tested to restore functionality of the nigrostriatal circuit to improve motor function in PD animal models[159]. The safety and quality of stem cell-derived ventral midbrain progenitor cells have been demonstrated in a 39-week safety study for toxicity, tumorigenicity, and biodistribution, with no adverse effects observed. These cells are now being used in a clinical trial of patients with moderate PD[160]. On the other hand, *trans*-differentiation approaches for switching somatic cells, such as midbrain astrocytes, into dopaminergic neurons *in situ* have shown potential to reconstruct the nigrostriatal circuit, restore dopamine levels, and rescue motor deficits in PD[161]. The alterations of NSCs in PD and potential therapeutics targeting NSCs, as well as their advantages and disadvantages, are illustrated in Figure 3.

Other neurodegenerative diseases

ALS

ALS is a fatal neurodegenerative disease characterized by a combination of upper and lower motor neuron dysfunction, resulting in progressive weakness of the voluntary skeletal muscles involved in limb movement, swallowing, speech, and respiratory function[162]. The pathological hallmark of ALS is transactive response DNA-binding protein 43 (TDP-43) proteinopathy[162]. Studies in ALS patients and animal models have indicated alterations in NSC proliferation in SVZ, SGZ, and the olfactory bulb[163]. TDP-43 Q331K knock-in induces a reduction in immature neurons in DG, indicating impaired adult neurogenesis in TDP-43 proteinopathies including ALS and frontotemporal dementia[164].

For therapeutics targeting neurogenesis in ALS, the peptide drug GM6 (GM604 or Alirinetide), a candidate for ALS therapy, is reported to induce an upregulation of Notch and hedgehog signaling, and increase the expression of genes associated with neurogenesis and axon growth[165]. For non-pharmacological interventions, physical exercise is shown to improve skeletal muscle metabolism and regeneration, neurogenesis, mitochondrial biogenesis, and antioxidant defense in ALS[166]. Clinical trials of stem cell transplantation have been conducted and shown therapeutic potential in ALS. Recent clinical trials indicate that mesenchymal stem cells injected intrathecally may provide a beneficial effect to decrease the

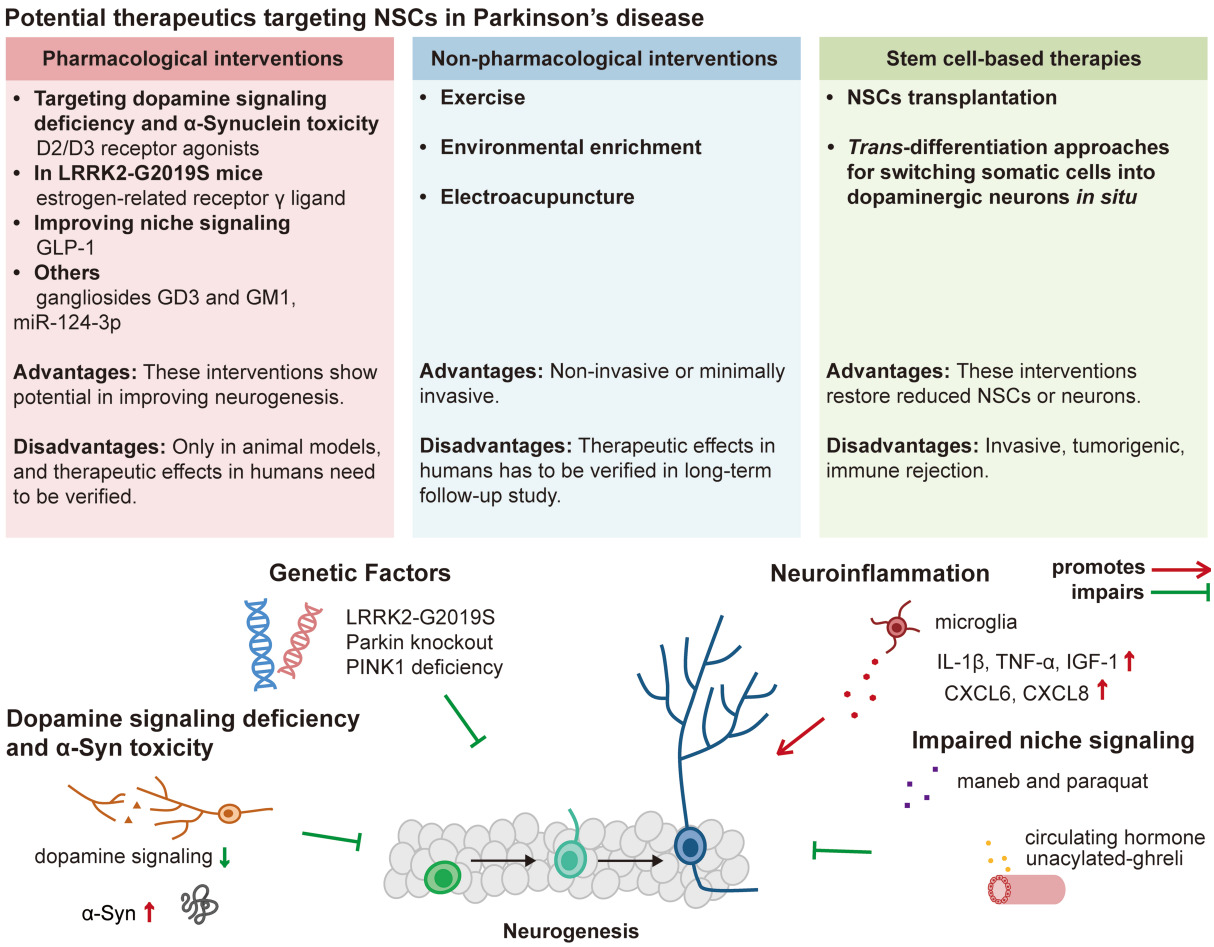

Figure 3. Potential therapeutics targeting NSCs in PD. Pharmacological (agents targeting dopamine signaling deficiency, improving niche signaling), non-pharmacological interventions (exercise, environmental enrichment, electroacupuncture) and stem cell-based therapies show potential in improving neurogenesis in PD. NSCs: Neural stem cells; PD: Parkinson's disease; α-Syn: α-synuclein; CXCL6: chemokine ligand 6; CXCL8: chemokine ligand 8; GLP-1: glucagon-like peptide 1; IGF-1: insulin-like growth factor 1; IL-1β: interleukin 1β; LRRK2: leucine-rich repeat kinase 2; PINK1: PTEN-induced putative kinase 1; TNF-α: tumor necrosis factor-α.

progression of the disease by secreting neurotrophic factors; however, the therapeutic efficacy remains uncertain[167,168]. Another recent trial transplanted human NPCs into the lumbar spinal cord, where they provide new support cells and delivery of GDNF to ALS patients[169]. On the other hand, iPSCs from ALS patients are used for drug screening for the disease therapy, providing candidates for further clinical trials[170,171].

HD

HD is an autosomal dominant neurodegenerative disease caused by a CAG repeat expansion in the first exon of the Huntington (*HTT*) gene[172]. GABAergic medium spiny neurons in the striatum, cerebral cortex, thalamus, and hypothalamus are especially vulnerable to the toxicity of mutant HTT, and the degeneration of these neurons causes motor, cognitive, and psychiatric symptoms with slowly progressive decline over two decades[172,173]. Deficits in adult neurogenesis have been shown in the R6/2 HD mouse model[174,175]. On the other hand, chromosomal instability in neurogenesis during development causes morphological defects in forebrain neurons, which further disrupts the normal function of neural circuits in HD[176]. Treating early postnatal circuit defects may delay the onset and pathology of the disease[177].

Environmental enrichment and exercise may provide beneficial effects on neurogenesis in HD by improving mitochondrial function, decreasing cell death, and increasing the level of neurotrophic factors such as BDNF[178,179]. NSCs taken from a fetal brain, iPSCs, ESCs, and progenitor cells derived from these cells are used as cell-based therapy for HD[173]. These cells are expected to differentiate into medium spiny neurons, thereby improving motor function in HD. Genetically engineered stem cells to overexpress BDNF are also applied to improve the outcome of the stem cell therapy[173].

SUMMARY

As they age, NSCs undergo a series of age-related changes, such as a decline in proliferation, imbalanced differentiation, altered epigenetic modifications, impaired niche signaling, compromised protein homeostasis, and decreased response to injury. These NSC changes may play an important role in the development of age-related neurodegenerative diseases, including AD, PD, ALS, and HD. Pathological changes in these diseases affect the proliferation and differentiation of NSCs and contribute to alterations in epigenetics, dysregulation of neuroinflammation, and decreased levels of neurotrophic factors, further leading to cognitive, mood, and motor symptoms.

Potential therapeutics including medicine targeting disease-specific pathologies, neurotrophic regulators, non-pharmacological interventions, and stem cell-based therapy may modulate neurogenesis in the brain to replace degenerated neurons and reconstruct functional circuits to alleviate cognitive or motor decline. However, most studies discussed above have only been conducted on animal disease models. Although these animal models are widely employed in neurodegenerative disease research due to the easy access to brain tissues and success in genetic modeling, their discrepancies from actual human conditions may limit the reproducibility and practical applicability of certain findings[180]. Human iPSCs are reprogrammed from patient-specific cells with a human genetic background and successfully applied in drug screening and mechanism research, but they cannot fully replicate the complex *in vivo* environment and have variations of differentiated cells depending on the protocol[180]. Organoid and organoid-on-chip hold the ability to mimic the cellular environment in 3D structure and are cost-effective, time-efficient, easy to establish and maintain, and easy for genetic manipulation and genome-wide screening[181]. The U.S. Food and Drug Administration and the U.S. National Institutes of Health have provided project support for tissue chips for drug screening. These techniques are expected to provide a novel platform for developing therapeutics targeting neurogenesis.

For stem cell-based therapy, a summary of clinical trials in age-related neurodegenerative diseases is shown in Table 1. Despite clinical trials that have been conducted, there are potential safety issues of stem cell transplantation, including the development of tumors and immune response to transplant. Using undifferentiated cells such as ESCs would be tumorigenic, but pre-differentiated cells such as neurons suffer a single fate and might encounter challenges in adapting to the complex cellular microenvironment[182]. NPCs, for example, midbrain dopaminergic progenitor cells for PD, which retain the ability to differentiate into different cells with lower tumorigenicity, might be a solution for this problem. For immune response to the transplant, several inflammatory factors including TNF-α, IL-1β are reported to be increased after the transplantation[183]. Autologous transplantation of personalized iPSC-derived NPCs may be used to minimize the immune response to the transplant.

Compared with stem cells, stem cell-derived extracellular vesicles (SC-EVs) possess the ability to cross the brain-blood barrier with several advantages, such as immuno-regulating characteristics, no immunogenicity, no infusion toxicity, and no tumorigenic potential, and execute functions including neuroprotection, angiogenesis, preservation of brain-blood barrier integrity, and alleviation of

Table 1. Clinical trials of stem cell-based therapy in age-related neurodegenerative diseases

Diseases	Clinical trial	Stem cell-based therapy	Last updated	Status
AD	NCT02054208, Phase1/2; NCT03172117, Phase1/2	NEUROSTEM (human umbilical cord blood derived mesenchymal stem cells) or placebo. Three repeated administrations into the lateral ventricle via an Ommaya reservoir were feasible, safe, and well-tolerated. Extended follow-up study for Phase 2a trial is undergoing. [Published in PMID34521461]	2020-08-28 2023-03-15	Completed
AD	NCT03117738, Phase1/2	AstroStem (autologous adipose tissue-derived mesenchymal stem cells) or placebo	2021-08-10	Completed
AD	NCT02600130, Phase1	Longeveron mesenchymal stem cells or placebo	2021-12-14	Completed
AD	NCT04040348, Phase1	Allogeneic human mesenchymal stem cells	2023-07-14	Completed
AD	NCT02833792, Phase2	Allogeneic human mesenchymal stem cells or placebo	2022-10-28	Recruiting
AD	NCT05667649, Phase1	Autologous activated adipose-derived stem cells	2024-02-12	Recruiting
AD	NCT02899091, Phase1/2	CB-AC-02 or placebo	2024-04-09	Active, not recruiting
AD	NCT06632470, Phase1	Human umbilical cord mesenchymal stem cell-derived secretome injection or Vitamin B12	2024-10-09	Not yet recruiting
PD	NCT04414813, Phase1	Human amniotic epithelial stem cells	2023-04-12	Completed
PD	NCT06142981	Autologous platelet-rich plasma and peripheral blood-derived very small embryonic-like stem cell therapy	2023-11-22	Completed
PD	NCT02611167, Phase1	Allogeneic bone marrow-derived mesenchymal stem cells	2023-11-29	Completed
PD	NCT04928287, Phase2	Autologous Hope Biosciences adipose-derived mesenchymal stem cells or placebo. [Results posted on ClinicalTrials.gov]	2024-05-20	Completed
PD	NCT04506073, Phase2	Allogeneic bone marrow-derived mesenchymal stem cells or placebo	2024-07-26	Completed
PD	NCT05691114, Phase1	Human amniotic epithelial stem cells	2023-02-17	Recruiting
PD	NCT05901818, Phase1	Autologous induced NSC-derived dopaminergic precursor cells	2023-06-22	Recruiting
PD	NCT05635409, Phase1	STEM-PD (ventral midbrain dopaminergic progenitor cells derived from the clinical-grade hESC line RC17)	2024-02-29	Recruiting
PD	NCT04995081, Phase2	Autologous Hope Biosciences adipose-derived mesenchymal stem cells or placebo	2024-06-21	Recruiting
PD	NCT06167681, Phase1/2	NouvNeu001 (human dopaminergic progenitor cells injection)	2024-07-08	Recruiting
PD	NCT06482268, Phase1	CT1-DAP001 (human iPSC-derived dopaminergic progenitors)	2024-09-20	Recruiting
PD	NCT06608355, Phase1	NouvNeu001 (human dopaminergic progenitor cells injection)	2024-09-23	Recruiting
PD	NCT06141317, Phase1/2	Pluripotent adipose-derived stem cells or placebo	2023-12-01	Active, not recruiting
PD	NCT05887466, Phase1/2	A9-DPC (allogenic ESC-derived A9 dopamine progenitor cell)	2024-06-24	Active, not recruiting
PD	NCT06477744	A9-DPC (allogeneic ESC-derived A9 dopamine progenitor cell)	2024-07-26	Active, not recruiting
PD	NCT05152394, Phase1	AlloRx (cultured allogeneic adult umbilical cord-derived mesenchymal stem cells)	2022-01-28	Not yet recruiting
PD	NCT06145711	Human iPSC-derived dopaminergic neural precursor cells	2023-11-24	Not yet recruiting

PD	NCT05094011, Phase1	Adipose-derived mesenchymal stem cells	2024-04-11	Not yet recruiting
ALS	NCT02943850, Phase1	CNS10-NPC-GDNF (Human neural progenitor cells secreting glial cell line-derived neurotrophic factor). One administration of engineered neural progenitors can provide new support cells and GDNF delivery to the ALS patient's spinal cord. [Published in PMID 36064599]	2020-07-15	Completed
ALS	NCT03482050, Phase1/2	AstroRx (Astrocytes derived from human ESCs)	2021-01-15	Completed
ALS	NCT04821479, Phase1/2	Autologous bone marrow-derived mesenchymal stem cells. Repeated intrathecal injections were safe and provided indications of medium-term clinical benefits. 13 patients had a > 25% improvement in the slope of progression of Amyotrophic Lateral Sclerosis Functional Rating Scale Revised. [Published in PMID34719198]	2021-03-29	Completed
ALS	NCT01363401, Phase1/2	HYNR-CS (autologous bone marrow-derived stem cells) or control group. [Results posted on ClinicalTrials.gov]	2022-03-17	Completed
ALS	NCT02290886, Phase1/2	Autologous mesenchymal stem cells or placebo	2022-04-06	Completed
ALS	NCT03280056, Phase3	NurOwn (Neurotrophic factors-secreting mesenchymal stromal cells) or placebo. [Results posted on ClinicalTrials.gov]	2024-02-29	Completed
ALS	NCT02017912, Phase2	NurOwn (Neurotrophic factors-secreting mesenchymal stromal cells) or placebo. [Results posted on ClinicalTrials.gov]	2024-06-06	Completed
ALS	NCT05306457, Phase1	CNS10-NPC-GDNF (Human neural progenitor cells secreting glial cell line-derived neurotrophic factor)	2024-02-06	Recruiting
ALS	NCT06344260, Phase2	Human NSCs or placebo	2024-04-03	Recruiting
ALS	NCT06598202, Phase1/2	hUC-MSC-sEV-001 nasal drops (human umbilical cord mesenchymal stem cell-derived small extracellular vesicles) or placebo	2024-09-19	Recruiting
ALS	NCT04745299, Phase3	Lenzumestrocel (Neuronata-R) (autologous bone marrow-derived mesenchymal stem cells) or riluzole or placebo	2024-10-03	Active, not recruiting
ALS	NCT02478450, Phase1/2	Q-Cells (Human glial-restricted progenitor cells)	2023-08-21	Not yet recruiting
HD	NCT03252535, Phase2	Cellavita HD (mesenchymal stem cells) or placebo	2022-10-28	Completed
HD	NCT02728115, Phase1	Cellavita HD (mesenchymal stem cells)	2022-11-02	Active, not recruiting
HD	NCT06097780, Phase3	NestaCell (human dental pulp stem cells)	2023-10-24	Not yet recruiting
AD, PD	NCT06607900, Phase1	hUC-MSC-sEV-001 nasal drops (human umbilical cord mesenchymal stem cell-derived small extracellular vesicles)	2024-09-25	Not yet recruiting
AD, PD, ALS	NCT02795052	Autologous bone marrow-derived stem cells	2024-04-15	Recruiting

Data were collected from ClinicalTrials.gov from 2020 to 2024. AD: Alzheimer's disease; PD: Parkinson's disease; NSC: neural stem cell; iPSC: induced pluripotent stem cell; GDNF: glial cell line-derived neurotrophic factor; ALS: amyotrophic lateral sclerosis; ESCs: embryonic stem cells; HD: Huntington's disease.

neuroinflammation[184]. Biomedical engineering technology can be further adapted for more particular cell-targeting or more efficient brain-blood barrier crossing to optimize the therapeutic effect of SC-EVs. Although the extraction and preservation of SC-EVs or exosomes remain challenging, clinical trials utilizing EVs or exosomes for neurodegenerative diseases are registered at clinicaltrials.gov (NCT06607900, NCT04388982).

In this review, we have provided a detailed summary of the changes observed in NSCs during normal aging and in the context of age-related neurodegenerative diseases. A deeper understanding of the age- and disease-associated alterations in NSCs, alongside the molecular and cellular mechanisms driving these changes, could offer critical insights into identifying novel therapeutic targets. Additionally, we have discussed potential therapeutics targeting neurogenesis, including stem cell-based therapies, to address these diseases. While stem cell transplantation and SC-EVs hold great potential in the treatment of neurodegenerative diseases, they are accompanied by limitations that necessitate further improvement in clinical application. Therefore, a thorough grasp of the mechanisms, benefits, and drawbacks of these therapeutic approaches is essential for informed treatment selection and critical in guiding the development of innovative therapeutic strategies, ultimately advancing the management of age-related neurodegenerative diseases.

DECLARATIONS

Authors' contributions

Contributed to the writing of the original draft: Zhong R, Huang W, Chen C, Zhang F
Revised and edited the manuscript: Zhong R, Zhang B, Pu J, Zhang F
All authors reviewed and approved the final version of the manuscript.

Availability of data and materials

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

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Consent for publication

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