Neural stem cells promote neuroplasticity: a promising therapeutic strategy for the treatment of Alzheimer's disease

Jun Chang[1, 2], Yujiao Li[1, 2], Xiaoqian Shan[1, 2], Xi Chen[1, 2], Xuhe Yan[1, 2], Jianwei Liu[3, *], Lan Zhao[1, 2, *]

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Abstract

Recent studies have demonstrated that neuroplasticity, such as synaptic plasticity and neurogenesis, exists throughout the normal lifespan but declines with age and is significantly impaired in individuals with Alzheimer's disease. Hence, promoting neuroplasticity may represent an effective strategy with which Alzheimer's disease can be alleviated. Due to their significant ability to self-renew, differentiate, and migrate, neural stem cells play an essential role in reversing synaptic and neuronal damage, reducing the pathology of Alzheimer's disease, including amyloid-β, tau protein, and neuroinflammation, and secreting neurotrophic factors and growth factors that are related to plasticity. These events can promote synaptic plasticity and neurogenesis to repair the microenvironment of the mammalian brain. Consequently, neural stem cells are considered to represent a potential regenerative therapy with which to improve Alzheimer's disease and other neurodegenerative diseases. In this review, we discuss how neural stem cells regulate neuroplasticity and optimize their effects to enhance their potential for treating Alzheimer's disease in the clinic.

Key Words: Alzheimer's disease; amyloid-β; cell therapy; extracellular vesicle; neural stem cell; synaptic plasticity; tau

From the Contents

Introduction

Alzheimer's disease (AD) is a destructive neurodegenerative disease that is characterized by progressive cognitive impairment an poses a severe threat to the life and health of patients (Tang et al., 2017; Hayashi et al., 2020; Huang et al., 2021; Terreros-Roncal et al., 2021). AD affects more than 50 million people worldwide; this figure is expected to exceed 152 million by 2050 (Livingston et al., 2020). The drugs that are currently approved by the US Food and Drug Administration for the treatment of AD have limited effects and are unable to reverse the loss of synapses and neurons; in addition, these drugs have notable side effects (McGinley et al., 2016; Kizil and Bhattarai, 2018; Park et al., 2020; Zhao et al., 2021). The strategies used to reduce amyloid-β (Aβ) or tau have no obvious effect on AD and are unable to restore damaged nerve tissue (Blurton-Jones et al., 2014; Hunsberger et al., 2016; Yan et al., 2016; Gao et al., 2022). Consequently, there is an urgent need to develop safe and effective drugs. Neural stem cells (NSCs) can undergo renewal, differentiation, migration, and can thus enhance synaptic plasticity and neurogenesis. Accordingly, NSCs are considered as an attractive regenerative treatment for AD.

Herein, we review the manifestation of impaired neuroplasticity in AD and summarize how NSCs can regulate neuroplasticity and induce beneficial effects. We also discuss the current situation and challenges of NSCs in clinical treatment to provide a theoretical basis for the clinical transformation of NSCs and to bring new hope for the clinical treatment of AD.

Literature Retrieval Strategy

The studies cited in this review were retrieved from the PubMed database. Most of the elected studies (80% of all references) were published between May 2017 and September 2022. Different combinations of the following text words were used to search the existing literature: "neural stem cell," "Alzheimer's disease," "neuroplasticity," "neurogenesis," and "synaptic plasticity." Only studies investigating the relationship between neuroplasticity and NSCs in AD were included so that our analysis focused specifically on the neuroplastic effects of NSCs on AD.

Impairments of Neuroplasticity in Alzheimer's Disease

Neuroplasticity is an integral aspect of cognitive and emotional functionality in healthy individuals. Over recent years, neuroplasticity has become a significant hotspot for brain injury research. Neuroplasticity in the adult central nervous system (CNS) is primarily characterized by synaptic plasticity and neurogenesis (Mango et al., 2019; Colom-Cadena et al., 2020; Chipika et al., 2022). Deficits in synaptic plasticity and neurogenesis in the hippocampus (HIPP) is known to make a significant contribution to cognitive impairment (Boldrini et al., 2018; Berger et al., 2020; Liu et al., 2020a; Mercerón-Martínez et al., 2021).

The impairment of synaptic plasticity in AD

Synaptic plasticity is the neurobiological basis of cognition, learning, and memory (Marsh and Blurton-Jones, 2017; Toda et al., 2019; Zhang et al., 2019; Montero-Crespo et al., 2021; Cornell et al., 2022). Synaptic plasticity is represented by long-term potentiation (LTP) and long-term depression;

[1]First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, China; [2]National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin, China; [3]Tianjin University of Traditional Chinese Medicine, Tianjin, China

*Correspondence to: Lan Zhao, PhD, lanzhao69@163.com; Jianwei Liu, PhD, 13389915877@126.com.

https://orcid.org/0000-0002-7449-2947 (Lan Zhao); https://orcid.org/0000-0001-7120-2951 (Jianwei Liu); https://orcid.org/0000-0001-7800-7286 (Jun Chang); https://orcid.org/0000-0003-4949-2942 (Yujiao Li); https://orcid.org/0000-0002-9473-0949 (Xiaoqian Shan); https://orcid.org/0000-0003-4179-0240 (Xi Chen); https://orcid.org/0000-0002-3178-0463 (Xuhe Yan)

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these are considered as important signals of synaptic survival and death, respectively. Promoting LTP and inhibiting long-term depression can serve as protective mechanisms that are essential for learning and memory (Pozueta et al., 2013; Nam et al., 2015; Mango et al., 2019). LTP functionality has shown to be reduced in a triple transgenic mouse model of AD (3×Tg) and in amyloid precursor protein/presenilin-1 (APP/PS1) mice (Oddo et al., 2003; Zhang et al., 2014b; Wang et al., 2020).

Synaptic function is closely related to synaptic size, number, density, and connectivity (Terry et al., 1991; Wu et al., 2021), and is a valid predictor of cognitive deficits (Zhang et al., 2019; Colom-Cadena et al., 2020). Compared with patients with Aβ plaques and neurofibrillary tangles lesions but without symptoms of dementia, patients with a combination of these lesions and symptoms of dementia were found to exhibit impaired synaptic function; these data suggested that impaired synaptic function may contribute to dementia (Gómez-Isla and Frosch, 2022). Research has also demonstrated that synaptic loss is the underlying cause of impaired synaptic function in patients with AD (Selkoe, 2002; Ager et al., 2015; Wu et al., 2016; Duncan and Valenzuela, 2017) and that numerous synapses in the HIPP and cerebral cortex (CTX) are lost (Yamasaki et al., 2007; Mecca et al., 2022). The size of synapses is closely related to their function; previous research has demonstrated a reduction in the number of synapses in patients with AD along with fewer large synapses (Berger et al., 2020; Moreno-Jiménez et al., 2021). Synaptic density has been shown to correlate positively with cognitive ability and is therefore a useful predictor of cognition (Yamasaki et al., 2007; Mecca et al., 2022). AD patients have been shown to exhibit reduced synaptic density in the HIPP; this change could be used to predict executive function, processing speed, and visuospatial and verbal memory. Furthermore, synaptic density is known to positively correlate with global cognition in the prefrontal, temporal, parietal, and occipital cortices (Mecca et al., 2022). Similar studies have recorded a reduction in the levels of presynaptic and postsynaptic markers in patients with AD (Babcock et al., 2021; Gómez-Isla and Frosch, 2022). The synaptic connection is the structural basis of signal transmission between neurons and is predominantly mediated by neurotrophins (NTs). The brain-derived neurotrophic factor (BDNF) and tyrosine kinase receptor B (TrkB) pathways are also involved in promoting the survival of neurons and the establishment of synaptic connections between neurons and target cells (Poo, 2001; Kowiański et al., 2018; Gao et al., 2022). However, the synaptic connections between HIPP and CTX are known to be reduced in patients with AD (Du et al., 2018; Babcock et al., 2021). Furthermore, researchers have reported reduced expression levels of BDNF and TrkB in the HIPP and CTX, as well as in the cerebrospinal fluid and peripheral blood (Du et al., 2018; Wu et al., 2021).

Dendritic spines are vital components of the synapses formed by neurons and their absence is anatomically responsible for cognitive deficits (Walker and Herskowitz, 2021). The densities of dendritic spines in the HIPP, CTX, and basal nucleus are known to decrease with aging and in patients with AD patients; compared with aging patients, the density of dendritic spines in the HIPP and CTX were significantly reduced in AD patients (Montero-Crespo et al., 2021; Walker and Herskowitz, 2021). A previous study investigated the dendritic spines of pyramidal neurons in layers II and III of the lateral frontal cortex of AD patients using Golgi-Cox staining of 12 age-matched controls without pathology, 8 controls with AD pathology (CAD), and 21 cases with AD (Boros et al., 2017). These researchers showed that the density of dendritic spines was similar among controls and CAD cases but was reduced in AD patients. In addition, there was a significant reduction in the density of both short and thick dendritic spines in patients with CAD and AD. The density of synapses and dendritic spines in the HIPP and prefrontal cortex (PFC) decreased with increasing age and AD symptoms (Pozueta et al., 2013; Babcock et al., 2021; Montero-Crespo et al., 2021; Walker and Herskowitz, 2021).

As specific markers and the main constituent proteins of a synapse, postsynaptic density-95 (PSD-95) and synaptophysin (SYP) play a significant role in cognitive plasticity (Bustos et al., 2017; Moreno-Jiménez et al., 2019; Tobin et al., 2019; Li et al., 2020). These proteins serve as effective anti-AD intervention targets and can also regulate synaptic plasticity. The expression levels of PSD-95 and SYP proteins were shown to be reduced in the HIPP and PFC of patients with AD (Schmitt et al., 2009; Bustos et al., 2017). The levels of SYP protein in the PFC were reduced by 25% in patients with mild AD, and were reduced more significantly in patients with moderate and severe AD; the levels of synaptotagmin protein have also been reported to be reduced in patients with moderate and severe AD. In another study, the levels of growth-associated protein 43 (GAP-43) were shown to exhibit a gradual reduction in patients with mild, moderate, and severe AD (Masliah et al., 2001). The expression levels of SYP protein were shown to be reduced in the HIPP and PFC of patients with sporadic AD; these changes were negatively correlated with the severity of AD symptoms (Martin et al., 2014). Other research has demonstrated reduced expression of SYP and PSD-95 proteins in APP/PS1 mice (Zhang et al., 2014a; Wang et al., 2020). Furthermore, the expression levels of SYP protein in the basolateral amygdala (BLA) and medial prefrontal cortex (mPFC) were shown to be reduced in the early five FAD mutations (5×FAD) mouse model, while levels of SYP in the BLA were reduced significantly in late-stage AD mice (Apodaca et al., 2021). Some studies have shown that the mRNA and protein levels of SYP in the HIPP were reduced in senescence-accelerated mouse prone 8 (SAMP8) mice (Zhao et al., 2020). In addition, Schmitt et al. (2009) demonstrated a reduction of learning, memory, and exploration abilities in SYP-knockout mice.

In conclusion, synaptic plasticity in the HIPP and PFC is known to be impaired in both AD patients and mouse models of AD, including LTP, synaptic density, dendritic spine density, and synaptic connections. Furthermore, AD is associated with reduced protein levels of PSD-95, SYP, BDNF, and TrkB.

Impairment of AD neurogenesis

Neurogenesis is the process by which neural precursor cells (NPCs) proliferate and differentiate into neurons, and then integrate into the existing neural network. Deficiency of adult hippocampal neurogenesis (AHN) is a crucial feature of AD (Liu et al., 2021; Terreros-Roncal et al., 2021). The hippocampal structure is particularly vulnerable to AHN damage, particularly during the early stages of AD (Baglietto-Vargas et al., 2017; Moreno-Jiménez et al., 2019; Tobin et al., 2019; Scopa et al., 2020). It has been reported that AHN decreases sharply in AD patients with the increasing age and increasing severity of AD symptoms (Gage and Temple, 2013; Choi and Tanzi, 2019; Tobin et al., 2019; Cosacak et al., 2020). Bromodeoxyuridine (BrdU)/neuronal nuclei (NeuN) was shown to be reduced in 1.5-month-old amyloid precursor protein (Tg2576) mice, and neurogenesis was impaired in the subventricular zone (SVZ), including the levels of BrdU, glial fibrillary acidic protein (GFAP), SRY-box transcription factor 2, and BrdU/calretinin (Scopa et al., 2020). AHN began to decrease in 5×FAD mice at 2 months-of-age, significantly decreased at 5–6 months-of-age, and eventually failed to form new neurons from 7 months-of-age (Moon et al., 2014; Li Puma et al., 2020; Apodaca et al., 2021). A previous study found that the proliferation of NSCs in the SVZ of early Tg2576 mice decreased from 1.5 months-of-age (Kim et al., 2022). Another study found that the proliferation and migration of NPCs in the SVZ were reduced in APP/PS1 mice at 3 and 6 months-of-age (Esteve et al., 2022). Autopsy results revealed a significant 9-fold reduction in the immunoreactivity of progenitor cells (Musashi1) in the SVZ of AD patients when compared with controls (Ziabreva et al., 2006). In another study, SVZ neurogenesis was found to be already impaired at the pre-symptomatic stage of AD, thus representing a new biomarker for the early diagnosis of AD (Scopa et al., 2020). The number of doublecortin (DCX)-positive cells in the subgranular zone (SGZ) were shown to decrease gradually in APP/PS1 mice over a period of 4 to 6 months, while the number of SGZ $BrdU^+/DCX^+$ cells decreased significantly over a period of 6 months (Baglietto-Vargas et al., 2017). The number of hippocampal DCX^+PCNA^+ cells has been shown to be negatively correlated with the risk of mild cognitive impairment and AD (Mango et al., 2019; Tobin et al., 2019). With advancing age, SVZ and SGZ neurogenesis in patients with early AD are progressively impaired; consequently, these represent valuable markers for diagnosing the onset of AD (Demars et al., 2010; Sorrells et al., 2018; Ottoboni et al., 2020). To conclude, AHN is impaired in both early and late AD.

As the primary manifestation of neurogenesis impairment, neuronal loss is considered as the pathophysiological basis of AD (Kim et al., 2015; Zhang et al., 2019; Colom-Cadena et al., 2020; Gómez-Isla and Frosch, 2022). Some studies have detected a reduction in hippocampal neurons in SAMP8 mice at an early stage (Liu et al., 2020b; Zhao et al., 2020, 2021). In another study, patients with AD showed a reduction in hippocampal neurons and DCX^+ neuroblasts (Moreno-Jiménez et al., 2019). Neuronal loss was most obvious in the CA1 region although neuronal loss was also evident in the CA2, CA3, and DG regions (West et al., 1994). The number of new neurons has been shown to be negatively correlated with the severity of dementia (Li Puma et al., 2020; Gómez-Isla and Frosch, 2022). With an increase in AD symptoms and age, the number and maturity ratio of hippocampal neurons has been shown to decrease continuously; in addition, the maturity of DCX^+ cells was severely damaged (Moreno-Jiménez et al., 2019, 2021; Zhou et al., 2022).

Collectively, these studies suggested that neurogenesis is impaired in AD, although the exact mechanisms involved remain unclear. The intrinsic pathology of the NPC and the extrinsic pathology of the neurogenic niche are critical factors that contribute to impaired neurogenesis (Demars et al., 2010). Neuronal fate is strongly influenced by adult NPCs in the SVZ and SGZ under normal physiological conditions. These can differentiate into neurons, astrocytes, and oligodendrocytes (Gage and Temple, 2013; De Gioia et al., 2020; Navarro Negredo et al., 2020) to protect the CNS from inflammatory damage and repair damaged brain tissue (Martino and Pluchino, 2006). NPC transplantation has been shown to enhance AHN and improve cognitive impairment in patients with AD and traumatic brain injury (TBI). In pathological conditions, inflammatory damage in the CNS has been shown to reduce the number of NPCs and their ability to migrate and differentiate (Haughey et al., 2002; Kowiański et al., 2018; Xu et al., 2018). Several studies have demonstrated that the survival, proliferation, and differentiation of NPCs in AD mice are reduced, thus leading to neuronal depletion (Wu et al., 2008; Kizil and Bhattarai, 2018; Papadimitriou et al., 2018). For example, the ability of NPCs to proliferate and differentiate into neurons in APPswe/PS1DeltaE9 mice was shown to be significantly reduced (Demars et al., 2010).

BDNF is a major regulator of AHN and plays a vital role in the growth and repair of neurons. BDNF stimulates neuronal differentiation and dendrite morphogenesis in the SGZ by binding to TrkB receptors (Kowiański et al., 2018; Wu et al., 2021). Researchers have demonstrated a reduction in the expression of BDNF and TrkB in the HIPP, CTX, cerebrospinal fluid, and peripheral blood of AD patients and animal models (Blurton-Jones et al., 2009; Zhang et al., 2014b; Wang et al., 2020; Wu et al., 2021). Research has shown that high levels of BDNF can alleviate the symptoms of AD and reduce suffering in patients with AD (Gao et al., 2022).

Both clinical and preclinical studies have identified dysfunctional neurogenesis in early AD. With the aggravation of AD symptoms, the damage caused to AHN is gradually aggravated, particularly in terms of neuronal loss. This is not only related to the reduced survival, proliferation and differentiation of NPCs but is also closely associated with a reduction in the levels of BDNF and TrkB.

The Importance of Modulating Neuroplasticity

In the early stages of AD, impaired neuroplasticity is a crucial cause of learning and memory impairment (Mesulam, 1999). Recent data suggest that impaired neuroplasticity is caused by the downstream aggregation of Aβ and phosphorylated tau (p-tau) (Hu et al., 2018; Houben et al., 2019). Extracellular deposition of Aβ is a crucial cause of synaptic dysfunction (such as LTP), which leads to synaptic failure (Mesulam, 1999; Selkoe, 2002; Oddo et al., 2003; Walker and Herskowitz, 2021). The mechanism involved in this process might be related to the shape, density, and composition of synapses (Walsh et al., 2002; Hayashi et al., 2020). $A\beta_{1-42/43}$ fragments are neurotoxic and cause damage to synaptic density and connections (Walsh et al., 2002; Hayashi et al., 2020; Walker and Herskowitz, 2021). Aβ and p-tau both contribute to the loss of neurons and disease progression (Li Puma et al., 2020). $A\beta_{1-42}$ damages AHN by inhibiting the interferon-gamma and NF-kappaB pathways (Zheng et al., 2013). Extracellular Aβ induces p-tau and excessive neurofibrillary tangles by activating glycogen synthase kinase 3 beta, cyclin-dependent kinase 5, and caspases; these proteins all interfere with cytoskeletal integrity (Mesulam, 1999; Hu et al., 2018), causing synaptic failure and neuronal death. P-tau causes neuron loss by inhibiting the transmission of gamma-aminobutyric acid (GABA) (Zheng et al., 2020) and the proliferation of NPCs (Houben et al., 2019). Conversely, tau deficiency has been shown to enhance AHN in mice (Criado-Marrero et al., 2020). An anti-aggregant tau mutant was shown to exhibit enhanced neurogenesis; the mechanism involved may be related to the inhibition of Wnt5a (Joseph et al., 2017). Similarly, the genetic ablation of tau in postnatal neurons has been shown to rescue reduced AHN (Houben et al., 2019).

With the deposition of Aβ and tau, there is a further detrimental effect on neuroplasticity, thus creating a vicious circle. With increased age and cognitive impairment, the aggregation of Aβ and p-tau increases continuously (Pang et al., 2022); furthermore, in humans, neurogenesis, and the density, number and connectivity of hippocampal synapses show increased levels of impairment (Zhang et al., 2019; Mercerón-Martínez et al., 2021; Pang et al., 2022). SYP in the BLA and mPFC of 5×FAD mice was shown to be reduced in the early stages and more significantly in the later stages of AD (Apodaca et al., 2021; Montero-Crespo et al., 2021). In addition, both AD and Parkinson's disease have been shown to exert adverse effects on neuronal proliferation, differentiation, survival ability, LTP, and synaptic function (Toda et al., 2019; Liu et al., 2021; Terreros-Roncal et al., 2021).

In conclusion, impaired neuroplasticity may be associated with the occurrence and development of AD. The restoration or promotion of hippocampal neuroplasticity may represent an attractive strategy for the prevention and treatment of AD (especially mild cognitive impairment).

Neural Stem Cells

In a previous study, Mckay proposed that NSCs can differentiate into neurons, astrocytes, and oligodendrocytes, and self-renew to provide the brain tissue with many new neurons (McKay, 1997). In humans, mammals, rodents, and non-human primates, the SVZ and SGZ are the primary source of NPCs and NSCs; these structures are responsible for generating new neurons throughout an organism's lifespan. Quiescent NSCs in the postnatal and adult CNS can generate several neurons, astrocytes, and oligodendrocytes (Navarro Negredo et al., 2020). Following the completion of CNS development, the NSCs in some brain regions cease to proliferate and enter a state of terminal differentiation or quiescence. Research has shown that quiescent NSCs located in the neurogenic niche are activated in pathological conditions to generate proliferative NSCs; in turn, these generate NPCs that differentiate into newly formed neurons, astrocytes, and oligodendrocytes (Gage and Temple, 2013; Navarro Negredo et al., 2020). Three methods can be used to isolate NSCs: (1) the extraction of tissue from the CNS, including the fetal brain, adult brain, and spinal cord tissue; (2) the differentiation of pluripotent stem cells, such as embryonic stem cells and induced pluripotent stem cells, and (3) the differentiation and transfer of somatic cells, such as skin fibroblasts and cells from the urine and blood (Tang et al., 2017; Babcock et al., 2021). It has also been found that BMSC-derived NSCs can exert significant neuroprotective effects, reverse pathological and cognitive deficits in AD, integrate donor cells into host neural circuits, and provide neurotrophic support for other neural circuits via donor cells (Tang et al., 2017). The factors that affect the activation, exhaustion, and fate of NSCs mainly include key cell cycle regulators (Gage and Temple, 2013), cytokines, growth factors (GFs), hormones, and NTs (De Gioia et al., 2020; Ottoboni et al., 2020). NSCs are essential brain development and homeostasis in both normal and aging conditions. NSCs play a vital role in the neuroprotection, repair, and replacement of damaged neurons and synapses by regulating NTs, GFs, and cytokines and possess broad prospects for the treatment of neurodegenerative diseases.

There are several stages in the effective treatment of disease by NSCs, including (1) arrival at the target site (migration), (2) survival, (3) directed proliferation and differentiation, and (4) the reversal of lost neurons and synapses. Hence, the migration and differentiation of NSCs are closely related to the repair of pathological damage in the CNS. The presence of cytokines in the brain tissue microenvironment can affect the migration, proliferation, and differentiation capacity of NSCs. Next, we outline the effects of GFs, cytokines, and stromal cell-derived factor-1 (SDF-1) on the migration, survival, and differentiation of NSCs, and discuss the mechanisms that might be involved.

Basic fibroblast growth factor promotes the proliferation and differentiation of NSCs, enhances neuronal survival, and inhibits apoptosis (Palmer et al., 1999). At lower concentrations, basic fibroblast growth factor induces the migration and differentiation of NSCs into neurons; at higher concentrations, the main effect of this growth factor is to promote the proliferation of NSCs (Carmeliet, 2003). Vascular endothelial growth factor not only promotes the proliferation of neuronal cells, but also plays a significant role in the differentiation of NSCs into neurons (Song et al., 2014). Nerve growth factor (NGF) exerts neurotrophic activity, enhances the migration and differentiation of NSCs and prevents neuronal apoptosis. In a previous study, Pencea et al. imported BDNF into the lateral ventricle and observed a significant increase in the levels of positive markers for NSCs (Pencea et al., 2001). BDNF promotes the proliferation and differentiation of NSCs by activating the Wnt/β-catenin pathway (Chen et al., 2013). The binding of BDNF to TrkB enhances TrkB phosphorylation; in turn, this activates the cAMP response element-binding protein (CREB) via the phosphatidylinositol 3-kinase and mitogen-activated protein kinase pathways; this process is known to regulate the migration of NSCs into the SVZ (Ortega-Martínez, 2015). Granulocyte colony-stimulating factor (G-CSF) is an important GF that regulates neurons and NSCs and can also exert significant neuroprotective effects. G-CSF enhances the levels of signal transducer and activator of transcription 3 (STAT3) phosphorylation, thereby regulating the proliferation and migration of NSCs (Liu et al., 2009). G-CSF also regulates the differentiation of NSCs through a basic helix-loop-helix and promotes the differentiation of NSCs into glial cells (Piao et al., 2012). In addition, NSCs that overexpress neurotrophic factors (BDNF, NT-3, and NGF) are known to exhibit higher rates of survival and migration while also providing neuroprotective properties (De Gioia et al., 2020; Gao et al., 2022). The overexpression of BDNF by NSCs has been shown to significantly promote the survival and migration of NSCs while also increasing synaptic plasticity (Ma et al., 2012).

Cytokines exert significant influence on the migration and differentiation of NSCs. Interleukin-1β promotes the differentiation of NSCs into glial cells by activating the STAT-3 pathway; this process can be reversed effectively by STAT-3 inhibitors (Chen et al., 2013). Similarly, interleukin-6 promotes the differentiation of NSCs to astrocytes and inhibits the differentiation of NSCs into other neuronal cells in embryonic mice via STAT-3 and basic helix-loop-helix pathways (Wang et al., 2011). Low concentrations of interferon-beta1b have been shown to promote the differentiation of NSCs toward neuronal and astrocytes, while high concentrations of interferon-beta1b enhance the differentiation of NSCs toward oligodendrocytes (Arscott et al., 2011). Interferon-γ can promote the differentiation of NSCs in a very effective manner; the mechanism involved may be related to the activation of the c-Jun N-terminal kinase pathway (Kim et al., 2007). In addition, SDF-1 plays an important role in the regulation of migration, differentiation, and proliferation in NSCs. The receptor for SDF-1, C-X-C motif chemokine receptor 7, also mediates the differentiation and migration of NSCs via the activation of extracellular signal-regulated kinase 1/2 and Ras-related C3 botulinum toxin substrate 1 in C-X-C motif chemokine receptor 4 knockout mice (Chen et al., 2015). In one study, SDF-1 was injected into the brains of TBI mice in slow-release formulations (SDF-1 microspheres and SDF-1 nanoparticles); analysis showed that SDF-1 nanoparticles effectively induced the migration of NSCs to areas of brain damage (Zamproni et al., 2017).

Finally, the ability of transplanted human NSCs (hNSCs) to migrate and integrate into pathological brain regions may depend on the stage of donor cell differentiation; this has significant implications for the role of transplanted hNSCs in the treatment of AD. The transplantation of dopaminergic neurons during the mid-differentiation phase is more suitable in a model of Parkinson's disease and was shown to increase the survival of dopaminergic neurons and significantly reverse the reduction in movement when compared with cells during early or late differentiation (Ganat et al., 2012).

In conclusion, the capacity of NSCs to migrate, differentiate, and proliferate is mainly determined by a variety of factors, including the levels of GFs and cytokines and the differentiation status of donor cells. Therefore, regulating the levels of GFs and cytokines and the stage of differentiation in donor cells will help to facilitate the capacity of NSCs to migrate, survive, and proliferate.

Alzheimer's Disease can Cause Changes to Neural Stem Cells

Previous research showed that the abilities of NSCs to proliferate and differentiate were reduced in aging mice and a mouse model of AD (Gage and Temple, 2013; Kizil and Bhattarai, 2018; Papadimitriou et al., 2018; Navarro Negredo et al., 2020). Moreover, with the aggravation of AD symptoms, the number of NSCs in the HIPP fell significantly, as did their capacity to proliferate and differentiate (Haughey et al., 2002; Gage and Temple, 2013; Navarro Negredo et al., 2020). The proliferation of NSCs was shown to be reduced by 63% in 4-month-old 3×Tg mice and no neurons were formed at 12 months-of-age (Scopa et al., 2020). Another study showed that the proliferation and differentiation of NSCs in the SVZ of 1.5-month-old Tg2576 mice were insufficient (Toda et al., 2019). In addition, the number of $BrdU^+$ cells and the number and volume of primary neurospheres were reduced in Tg2576 mice

(Scopa et al., 2020). Furthermore, the proliferation of NSCs in the SGZ was shown to be reduced in 6-month-old APP/PS1 mice (Hu et al., 2018).

The accumulation of Aβ and p-tau can cause a decline in the ability of NSCs to proliferate and differentiate. Aβ and p-tau can both inhibit neurogenesis and network formation (Papadimitriou et al., 2018; Toda et al., 2019; Li Puma et al., 2020). A previous study identified a large amount of Aβ42 in SVZ neurospheres in 1.5-month-old Tg2576 mice; this was related to the reduced proliferation and differentiation ability of NSCs. Interfering with intracellular Aβ oligomer has been shown to restore the insufficient proliferation and differentiation of NSCs in Tg2576 mice (Toda et al., 2019). The proliferation of NSCs in the HIPP was found to occur faster in 2-month-old Bi-Tg mice containing pPDGF-APPSw,Ind and pNes-LacZ transgenes without Aβ plaques. In contrast, there was significantly fewer Aβ plaques in 8-month-old mice and significantly more Aβ plaques in 12-month-old mice (Gan et al., 2008). These findings might be related to the induction of kynuric acid by $A\beta_{42}$ (Papadimitriou et al., 2018). In addition, extracellular tau does not affect the migration of NSCs, although the intracellular phosphorylation/dephosphorylation of tau has been shown to inhibit the migration of NSCs (Qi et al., 2016).

As mentioned earlier, the number and function of endogenous NSCs is reduced in AD. Endogenous repair functionality is insufficient to compensate for the damage incurred by NSCs in the CNS; this might be related to the classical pathology of AD. Therefore, it is imperative that we investigate therapeutic methods that can reduce Aβ and (or) tau expression to regulate and maintain the normal homeostatic and regenerative potential of endogenous NSCs in the brain tissues of patients with AD.

Neural Stem Cell Treatments for Alzheimer's Disease

Mouse models of AD play a key role in exploring therapeutic approaches for AD. Because of their strong correlation with human physiopathology, these mouse models can effectively mimic the disease features and clinical manifestations of human AD. There are several mouse models of AD, including 5×FAD mice, 3×Tg mice, APP/PS1 mice, Tg2576 mice, SAMP8 mice, and tetracycline-off inducible transgenic (CaM/Tet-DTA) mice. Previous research has shown that 5×FAD mice harbor three mutations in APP and PS2 (M146V and L286V) and show the most rapid onset of disease (Chen and Zhang, 2022). Levels of $A\beta_{42}$ in this model were found to be much higher than those in Tg2576 mice; furthermore, more $A\beta_{42}$ had accumulated in the brain than $A\beta_{40}$ (Nakai et al., 2021). A previous study reported that 5×FAD mice displayed cognitive impairment and early hippocampal dysfunction, mainly in the form of reduced basal synaptic transmission and LTP (Crouzin et al., 2013). This suggests that the mouse model may be a valuable model for reproducing the pathology of human AD. 3×Tg mice overexpress human APPswe and tau MAPTP301L and encode a knock-in of PS1M146V. These mice exhibit intracellular and extracellular aggregation of Aβ and tau, respectively, along with impaired LTP and neurogenesis (Oddo et al., 2003). Excessive Aβ and tau deposition and insufficient neuroplasticity were observed in patients with AD (Mesulam, 1999).This model is well represented and the pathology developed by Aβ and tau is more similar that experienced by humans (Mango et al., 2019). Therefore, this is one of the most widely used AD models for studying the development of tau and amyloid pathology. APP/PS1 double mutant mice facilitate the accelerated accumulation of Aβ and plaque in the brain (Mango et al., 2019). This model is associated with the significant loss of synapses, dendritic density and neurons (Nakai et al., 2021). Due to their stable genetic background, these mice are well suited for the investigation of new therapeutic strategies for AD. Tg2576 mice overexpress the 695–amino acid isoform of human APP protein and exhibit impaired neurogenesis in the HIPP and CTX. These aged mice are known to exhibit concentrations of $A\beta_{40}$ and $A\beta_{42/43}$ that are 5-fold and 14-fold higher, respectively, than younger mice (Nakai et al., 2021). The SAMP model was identified by Professor Toshio Takedaare and is now widely used and recognized (Liu et al., 2020b). This model features large numbers of amyloid plaques and tau protein deposits in the HIPP (Zhao et al., 2020). The SAMP8 mouse is an ideal model for studying AD and exhibits age-related learning and memory deficits. CaM/Tet-DTA mice represent a transgenic model of hippocampal cell loss and exhibit upregulated endogenous neurogenesis, although this enhanced level of neurogenesis does not alleviate cognitive deficits (Yeung et al., 2014).

In conclusion, the AD mouse model provides significant insights into the drug development and neurobiological basis of AD. It will be necessary to conduct preclinical experiments in multiple animal models in the future until a more complete animal model of AD is available to ensure that preclinical results can improve the efficiency of AD treatment.

Targeted drug delivery to key brain regions in AD remains a major unresolved challenge; very few studies have investigated delivery modalities for NSCs. The route of administration has a significant impact on the biodistribution and therapeutic efficacy of NSCs; the main modes of drug delivery in AD include intranasal, intracerebral, intravenous, and oral administration; each of these methods has its own advantages and disadvantages in terms of clinical application.

Intranasal administration is mainly based on the clear nasal-brain pathway to achieve non-invasive brain-targeted delivery; however, only a small number of NSCs can be delivered by this method. This method has the advantages of being non-invasive with good targeting ability and rapid action (Gratpain et al., 2021). However, the limited surface area of the olfactory epithelium and the short residence time for drug absorption may have an impact on the therapeutic effect. A previous study found that the intranasal transplantation of hNSCs alleviated cognitive deficits by enhancing neuroplasticity and by alleviating neuroinflammation and cholinergic dysfunction in the HIPP of APP/PS1 mice, with no significant adverse effects. This indicates the significant potential of the intranasal delivery of stem cells as a non-invasive therapeutic strategy for AD (Lu et al., 2021). Thus, the intranasal delivery of NSCs can reach pathological brain regions in AD and this non-invasive route of administration renders this method particularly suitable for translation into clinical practice.

In severe cases and emergencies, direct and topical drug injection (intracerebral administration) is the simplest and most common delivery method. The intracerebral administration of NSCs was shown to significantly reduce Aβ protein levels and increase synaptic density in both 3×Tg-AD and Thy1-APP transgenic mice, thereby alleviating cognitive and learning deficits (Blurton-Jones et al., 2009; Zhang et al., 2022). Compared with systemic administration, the intracerebral administration of NSCs significantly increases their duration and concentration of action locally, and also prevents NSCs from entering the circulation, thus avoiding hepatic and splenic clearance (Xu et al., 2021). The intracerebral administration of hNSCs also promotes cell survival and extensive migration and differentiation into new neurons (Hayashi et al., 2020). This not only solves the problem of poor stability but also allows for better peri-lesion accumulation and thus long-term effects. However, this method has some shortcomings that need to be considered; for example, this technique is invasive, requires complex equipment and advanced operating skills, and also relies upon imaging to locate to define the exact point of administration; if this procedure is not carried out correctly, it may cause complications such as pain and infection (Gratpain et al., 2021).

The intravenous injection of NSCs has become a widely used method. The current clinical trials of stem cell treatment for neurodegenerative diseases predominantly involve intravenous injection. This method of transplantation is simple and convenient to perform, causes less damage to the patient; has a rapid effect and results in high bioavailability (Xu et al., 2021). However, the operational requirements are relatively high, and only very few cells may end up in the brain. In a recent study, the retro-orbital vein injection of NSC-derived small extracellular vesicles (NSC-EVs) attenuated Aβ in the HIPP of 5×FAD mice, prevented synaptic loss and suppressed neuroinflammation, and subsequently improved cognitive impairment without any significant side effects (Apodaca et al., 2021).

The oral administration of NSCs is also a crucial route of administration in clinical practice. In this strategy, NSCs are absorbed into the circulation via the mucosa of the gastrointestinal tract to reach the systemic or local level and are less costly to produce and less invasive. Furthermore, patient compliance and acceptability are good. However, this method has limited applicability and is not recommended for patients with severe AD. Cellular absorption is slow and irregular, and efficacy is easily influenced by gastrointestinal function and the intestinal flora (Gratpain et al., 2021). Different routes of administration have their own advantages and disadvantages; future research should focus on identifying and developing the best method of administration.

Neural Stem Cells Can Alleviate the Pathology of Alzheimer's Disease

The main pathological features of AD are extracellular Aβ plaques and intracellular tau-containing neurofibrillary tangles in the brain. Changes in Aβ accelerate the disease process and initiate a deleterious cascade involving tau pathology and neurodegeneration.

Numerous studies have found that exogenous NSCs can effectively improve learning and memory and reduce the levels of Aβ and tau protein in the brain. For example, the administration of NSCs significantly reduced tau and p-tau in the CA1 region of 12-week-old regulatable mutant P301L human tau transgene mice (rTg(TauP301L)4510) (Zhang et al., 2022) and decreased the levels of Aβ in the HIPP and CTX, and p-tau/tau in the CTX, of 12-month-old Tg2576 mice (Kim et al., 2015). Furthermore, hNSC-EVs reduced the levels of Aβ in the infralimbic and prelimbic areas of the mPFC in 2-month-old (early) 5×FAD mice, reduced the levels of Aβ in the BLA, and reduced the levels of $A\beta_{1-40}$ in the mPFC of 6-month-old (late) 5×FAD mice (Martin et al., 2014). *In vitro*, neprilysin (NEP)-NSCs have been shown to maintain pluripotency and reduce the levels of Aβ and resistance to Aβ neurotoxicity (Blurton-Jones et al., 2014). Nanopagent-mediated therapies for NSCs have confirmed that they can improve cognitive deficits by clearing Aβ (Huang et al., 2021).

Further mechanistic studies relating to the use of NSCs to reduce Aβ and tau showed that hNSCs activated the protein kinase B (Akt)/glycogen synthase kinase 3 beta pathway in NSE/APP mice to inhibit p-tau protein and activate the Aβ precursor protein cleaving enzyme 1 mediated by this pathway to reduce the production of Aβ and inhibit neuroinflammation (Lee et al., 2015). In this previous study, hNSCs were shown to inhibit the accumulation of Aβ by up-regulating Aβ degrading enzymes, insulin-degrading enzymes, and NEP, thus relieving neuroinflammation, cholinergic dysfunction, and pericytic and synaptic loss, thus contributing to AHN (Lu et al., 2021). In addition, some studies have found that the transplantation of NSCs did not improve the pathology of AD pathology but did lead to improvements in learning and memory (Zhang et al., 2014b; Ager et al., 2015). For instance, NSCs were shown to enhance endogenous synaptogenesis by secreting BDNF and

subsequently improved cognitive function but did not alter the levels of Aβ and tau (Blurton-Jones et al., 2009; Ager et al., 2015). A similar study found that NSCs enhanced LTP in APP/PS1 mice and reduced the duration of escape latency; however NSC treatment had no significant effect on Aβ (Zhang et al., 2014b). This may be due to the fact that not all patients have Aβ and tau, and the correlation between the amount and distribution of Aβ plaques in these patients and the degree of cognitive impairment is not clear (Gómez-Isla and Frosch, 2022).

Two main strategies are used for NSC-based therapies: transplanting exogenous NSCs and promoting the self-repair of endogenous NSCs. The findings generated by the studies described in this section of our review indicate that endogenous repair is not sufficient to compensate for damaged NSCs in the CNS. Exogenous NSCs have been shown to alleviate some classic pathological and cognitive defects in AD mice, thus exhibiting strong potential for clinical application. Hence, exogenous NSCs might represent an effective strategy to repair damage in the CNS.

Neural Stem Cells Promote Neuroplasticity

NSCs have beneficial effects not only in regulating the levels of pathological proteins but also in increasing neuroplasticity, thus reversing the loss of neurons and synapses, and/or increasing the levels of NTs.

NSCs enhance synaptic plasticity

Synaptic plasticity is induced by NSCs in the host brain and is essential to brain plasticity. The application of exogenous NSCs was shown to increase LTP in the CA1 region of AD mice (Zhang et al., 2014b; Liu et al., 2020b; Zhao et al., 2021). In another study, induced NPCs enhanced synaptic connections between LTP and neurons in HIPP of AD mice (Zhang et al., 2019). It has been demonstrated that Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) is a crucial mediator of LTP and that CaMKII expression is enhanced following NSC transplantation (Zhang et al., 2022). Some studies found that hNSCs increased the levels of SYP and GAP-43 proteins in the CA3 region of APP/PS1 mice (Zhang et al., 2014a; Lu et al., 2021; Shu et al., 2021). Other studies indicated that hNSCs upregulated the expression levels of SYP and PSD-95 protein in CTX and HIPP (Lee et al., 2015; Xiong et al., 2018). Similarly, hNSCs increased the levels of SYP protein in the stratum radiatum of the hippocampal CA1region of 3×Tg-AD and CaM/Tet-DTA mice, and raised the expression levels of GAP-43 protein in the HIPP of CaM/Tet-DTA mice (Ager et al., 2015). HNSCs also augmented the levels of PSD-95 and microtubule-associated protein 2 protein in the HIPP and CTX of Tg2576 mice (Kim et al., 2015). Moreover, hNSCs increased stratum radiatum synaptic density in the CA1, and increased the expression levels of SYP and BDNF proteins in the HIPP of 18-month-old 3×Tg-AD mice (Zhang et al., 2019). HNSC-EVs augmented the expression levels of SYP protein in the BLA and mPFC of 5×FAD mice during the early stages of disease, and the levels of SYP protein in the BLA during the late stage of disease (Apodaca et al., 2021).

In conclusion, NSC transplantation reverses the synaptic loss of CTX and HIPP in AD mice and increases synapse-related molecules (**Table 1**); however, the specific mechanisms underlying this process remain unclear. BDNF knockdown combined with NSC transplantation was shown to reduce the levels of SYP, while the combination of BDNF antibodies and NSC transplantation also significantly reduced the levels of both SYP and β-synuclein (Xiong et al., 2018). The depletion of NSC-derived BDNF failed to improve cognition or restore synaptic density in the HIPP of 3×Tg-AD mice (Blurton-Jones et al., 2009). It has been suggested that the mechanism by which NSCs promote synaptic plasticity may be closely related to the regulation of BDNF. BDNF-overexpressing NSCs were shown to enhance LTP and synaptic density (De Gioia et al., 2020). Furthermore, the overexpression of BDNF increased the levels of PSD-95, SYP, and BDNF protein in the HIPP of Tg2576 mice, as well as the density of dendritic spines. More mature granular cells entered the granular cell layer, thus extending the highly refined dendritic structure to the molecular layer, thus suggesting that exogenous NSCs form novel synaptic connections with endogenous cells (Wu et al., 2016). In conclusion, BDNF plays a crucial role in enhancing hippocampal synaptic plasticity in NSCs.

NSCs promote neurogenesis

The primary goals of regenerative therapy include the replacement of missing neurons, increasing the generation of functional neurons, and facilitating the integration of newly generated neurons into functional neural loops. Research has shown that exogenous NSCs survived and differentiated into neurons and astrocytes in the HIPP of AD mice, migrated to the lesion site, repaired and replaced the lost neurons, eventually formed functional neurons and integrated into the neural circuit, and secreted NTs to protect existing neurons against damage *in situ* (**Table 1**).

Some studies previously demonstrated that exogenous NSCs could survive, proliferate, and differentiate into neurons and astrocytes in the HIPP of SAMP8 mice (Zhang et al., 2014a; Zhou et al., 2018; Zhao et al., 2020). Furthermore, the NSCs of NSE/APP mice migrated to the SVZ, CTX, hypothalamus, and striatum, and subsequently transformed into immature neurons and glial cells (Lee et al., 2015). NSCs in the HIPP of 3×Tg-AD and CaM/Tet-DTA mice also successfully differentiated into immature neurons and astrocytes and migrated to the CA1 region and corpus callosum (Ager et al., 2015). After 12 days of suspension culture, hNSCs propagated and formed neurospheres and then differentiated into neurons, astrocytes, and oligodendrocytes two weeks later (Lu et al., 2021). Following the intranasal transplantation of hNSCs in APP/PS1 mice for three months, a large number of $stem121^+$ cells were observed in the olfactory bulb, HIPP, ventral and dorsal CTX, thalamus, and cerebellum; most of these were $stem121^+NeuN^+$ cells. In contrast, a small number of these cells were $stem121^+GFAP^+$ and $stem121^+NG2^+$ cells. Previous research showed that hNSCs in the CTX, HIPP, and pontine differentiated into cholinergic neurons and increased the levels of choline acetyltransferase (ChAT) in the HIPP (Lu et al., 2021). NSCs transplanted into the HIPP in manganese-induced mice survived for two weeks and migrated to the CTX, ependyma, and corpus callosum, thus increasing the number of DCX^+ cells. Most of these cells migrated to the granular cell layer and differentiated into functional neurons and glial cells, thus suggesting that the NSCs had integrated functionally into the impaired local circuits (Shu et al., 2021). In another study, hNSCs increased the number of DCX^+ cells in the DG by 2- to 3-fold in APP/PS1 mice, with more and longer dendritic branches extending into the molecular layer (Lu et al., 2021).

In other studies, exogenous NSCs successfully migrated to damaged brain tissue and repaired the damaged tissue by releasing NTs (Martino and Pluchino, 2006; Zhang et al., 2014a). After NSCs treatment, AD mice have been shown to possess increased numbers of $NeuN^+$ cells, and increased protein expression levels of BDNF, TrkB, N-methyl-D-aspartic acid, and protein kinase C zeta in the HIPP and CTX (Blurton-Jones et al., 2009; Zhang et al., 2014a; Liu et al., 2020a; Zhao et al., 2021). Furthermore, NSC transplantation augmented the number of DCX^+ and $BrdU^+$ neurons, as well as the levels of polysialic-acid neural-cell adhesion molecule and vascular endothelial-derived growth factor in the HIPP of Tg2576 mice (Kim et al., 2015).

BDNF is a potent activator of neurogenesis and the intraventricular administration of BDNF has been shown to improve the number of newborn neurons in the SVZ (Cosacak et al., 2020). BDNF is known to promote neuronal survival, proliferation, and migration to damaged tissues (Schäbitz et al., 2007). The overexpression of BDNF was shown to improve the survival and proliferation of NSCs, encouraged endogenous tissue repair, and promoted the expression of NTs in TBI (Ma et al., 2012; Navarro Negredo et al., 2020).

Overall, when transplanted into AD mice, NSCs can survive for a long period of time. These cells can enhance migration, proliferation, and differentiation, can replace or repair damaged neurons, and can promote the integration of new neurons into functional neural circuits. NSCs also play a crucial role in reversing impaired neurogenesis; this process is related to NSC-mediated NTs that promote AHN.

Optimizing Neural Stem Cells Promotes Neuroplasticity

NSCs have shown remarkable potential for improving cognitive memory by regulating neuroplasticity. However, there is some resistance to clinical translation as the method needs to be further optimized to improve the safety and efficacy of NSCs for the treatment of AD.

NSC-EVs

EVs are crucial effectors of NSCs in the treatment of AD. NSCs communicate with other cells via EVs to promote the activation of regeneration processes (Li et al., 2020). EVs represent a cell-free therapy that is not associated with immunogenicity or tumorigenicity (Spinelli et al., 2020), can reduce the risk of thrombosis, and possesses the capacity to readily cross the blood-brain barrier (Zhang et al., 2021) and act directly on target organs. NSC-EVs represent a potential treatment for various neurodegenerative disorders due to their anti-inflammatory, neurogenic, and neurotrophic properties.

In previous studies, NSC-EVs increased the protein levels of p-CREBSer133, BDNF, p-TrkBTyr816, neuronal nitric oxide synthase, early growth response 3, and sirtuin 1, in the HIPP of mice fed a high-fat diet (Spinelli et al., 2020) and increased the expression levels of SYP, PSD-95, GAP-43, and microtubule-associated protein 2 proteins in the cortex of APP/PS1 mice (Li et al., 2020). NSC-EVs also improved incomplete synaptic structures and unclear synaptic gaps while reducing the rate of synaptic damage and the levels of pro-inflammatory cytokines and ionized calcium binding adapter molecule-1 in the CTX (Li et al., 2020). Similar studies have found that NSC-EVs augment the levels of SYP in the BLA and mPFC of young 5×FAD mice, decreased the levels of Aβ in the mPFC and BLA, and reduced the levels of CD68 in the mPFC (Apodaca et al., 2021). In addition, NSC-EVs eliminated the LTP abnormalities and memory defects induced by Aβ oligomers, reduced the binding of Aβ oligomers to the synapse, and increased the phosphorylation of CaMKII. Instead, ablating NSCs from the HIPP of Nestin-δ-HSV-TK-eGFP transgenic mice and combining this with the administration of valganciclovir in mouse chow reversed these negative effects (Micci et al., 2019). In conclusion, NSC-EVs can alleviate the pathological features of AD, including the accumulation of Aβ and neuroinflammation, and can promote neuroplasticity.

Regulating NTs

The simple transplantation of NSCs is associated with some limitations, including a low cell survival rate and only limited differentiation into neurons. NTs promote the differentiation of cholinergic neurons and can exert neuroprotective effects. The combined transplantation of NTs and NSCs can promote the survival and differentiation of neurons and the activation of endogenous NSCs in both APP/PS1 and Tg2576 mice. Moreover, NTs play a critical role in facilitating NSCs to promote neuroplasticity to alleviate AD/ Furthermore, the regulation of NTs is essential if we are to enhance the role of NSCs in treating AD.

Table 1 | **Changes in neuroplasticity-related indicators after NSC treatment for AD**

	Before NSC treatment	After NSC treatment
Symptoms	Cognition, learning, memory↓ (Berger et al., 2020; Moreno-Jiménez et al., 2021; Mecca et al., 2022)	Cognition, learning, memory↑ (Zhang et al., 2014b, 2019; Hayashi et al., 2020)
Pathological features	Aβ↑ (Apodaca et al., 2021; Gómez-Isla and Frosch, 2022)	Aβ↓ (Zhang et al., 2014b; Apodaca et al., 2021)
	$Aβ_{42}$↑ (Toda et al., 2019; Lu et al., 2021)	$Aβ_{40}$↓ (Apodaca et al., 2021)
	$Aβ_{1–40}$↑ (Zhang et al., 2014b; Apodaca et al., 2021)	$Aβ_{42}$↓ (Lu et al., 2021)
	tau, p-tau↑ (Kim et al., 2015; Zhang et al., 2022)	$Aβ_{1–40}$↓ (Apodaca et al., 2021)
		tau, p-tau↓ (Kim et al., 2015; Zhang et al., 2022)
Synaptic plasticity	LTD↑ (Zhang et al., 2014b; Mango et al., 2019)	LTD↓ (Mango et al., 2019)
	LTP↓ (Zhang et al., 2014b; Wang et al., 2020)	LTP↑ (Zhang et al., 2019; De Gioia et al., 2020; Liu et al., 2020b; Zhao et al., 2021)
	Synaptic connection↓ (Yamasaki et al., 2007; Wu et al., 2016; Babcock et al., 2021; Mecca et al., 2022)	Synaptic connection↑ (Wu et al., 2016)
	Synaptic density↓ (De Gioia et al., 2020; Montero-Crespo et al., 2021; Mecca et al., 2022)	Synaptic density↑ (Wu et al., 2016; Zhang et al., 2019; De Gioia et al., 2020)
	Number of synapses↓ (Zhang et al., 2014a)	Number of synapses↑ (Zhang et al., 2014a)
	Dendritic branches↓ (Lu et al., 2021)	Dendritic branches↑ (Wu et al., 2016; Lu et al., 2021)
	Dendritic spine density↓ (Montero-Crespo et al., 2021; Walker and Herskowitz, 2021)	Dendritic spine density↑ (Wu et al., 2016; Zhao et al., 2020)
NSCs	Proliferation↓ (Zhao et al., 2017; Hu et al., 2018; Toda et al., 2019; Scopa et al., 2020)	Proliferation↑ (Scopa et al., 2020; Lu et al., 2021; Shu et al., 2021)
	Survival↓ (Zhao et al., 2017)	Survival↑ (Duncan and Valenzuela, 2017; Shu et al., 2021; Zhao et al., 2021)
	Migration↓ (Ager et al., 2015; Shu et al., 2021)	Migration↑ (Ager et al., 2015; Shu et al., 2021)
	Differentiation↓ (Wu et al., 2008; Lu et al., 2011; Kizil and Bhattarai, 2018)	Differentiation↑ (Ager et al., 2015; Zhao et al., 2017; Shu et al., 2021)
Cell marker	Tuj1+↓ (Lu et al., 2021)	$Tuj1^+$↑ (Lu et al., 2021)
	$Sox2^+$↓ (Boldrini et al., 2018; Scopa et al., 2020)	$Sox2^+$↑ (Boldrini et al., 2018; Scopa et al., 2020)
	$Stem121^+$↓(Lu et al., 2021)	$Stem121^+$↑(Lu et al., 2021)
	$BrdU^+$↓ (Yan et al., 2016; Baglietto-Vargas et al., 2017; Scopa et al., 2020)	$BrdU^+$↑ (Kim et al., 2015; Yan et al., 2016; Scopa et al., 2020)
	$NeuN^+$↓ (Yang et al., 2014; Yan et al., 2016; Shu et al., 2021)	$NeuN^+$↑ (Yan et al., 2016; Lu et al., 2021; Shu et al., 2021)
	DCX^+↓ (Moreno-Jiménez et al., 2019; Tobin et al., 2019; Li Puma et al., 2020; Zhou et al., 2022)	DCX^+↑ (Kim et al., 2015; Baglietto-Vargas et al., 2017; Lu et al., 2021; Shu et al., 2021)
	$Stem121^+NeuN^+$↓ (Scopa et al., 2020)	$Stem121^+NeuN^+$↑ (Lu et al., 2021)
	$GFAP^+$↓ (Yang et al., 2014; Shu et al., 2021)	$GFAP^+$↑ (Yang et al., 2014; Shu et al., 2021)
	$Stem121^+GFAP^+$↓ (Lu et al., 2021)	$Stem121^+GFAP^+$↑ (Lu et al., 2021)
	$O4^+$↓ (Lu et al., 2021)	$O4^+$↑ (Lu et al., 2021)
	$NG2^+$↓ (Yang et al., 2014; Yan et al., 2016)	$NG2^+$↑(Yang et al., 2014; Yan et al., 2016)
	$Stem121^+NG2^+$↓(Lu et al., 2021)	$Stem121^+NG2^+$↑(Lu et al., 2021)
Molecular	PSD-95↓ (Masliah et al., 2001; Martin et al., 2014; Zhang et al., 2014a; Bustos et al., 2017)	PSD-95↑ (Zhang et al., 2014a; Kim et al., 2015; Wu et al., 2016)
	SYP↓ (Martin et al., 2014; Zhao et al., 2020; Apodaca et al., 2021)	SYP↑ (Zhang et al., 2014a; Ager et al., 2015; Wu et al., 2016; Apodaca et al., 2021)
	NT-3↓ (Park et al., 2020)	NT-3↑ (Park et al., 2020)
	VEGF↓ (Kim et al., 2015; McGinley et al., 2016)	VEGF↑ (Kim et al., 2015; McGinley et al., 2016)
	NGF↓ (Park et al., 2012; Park et al., 2013)	NGF↑ (Park et al., 2012; Park et al., 2013)
	BDNF, TrkB↓ (Zhang et al., 2014b; Wang et al., 2020; Wu et al., 2021; Gao et al., 2022)	BDNF, TrkB↑ (Blurton-Jones et al., 2009; Wu et al., 2016; Xiong et al., 2018; Shu et al., 2021)
	GAP-43↓ (Ma et al., 2012; Li et al., 2020)	GAP-43↑ (Ma et al., 2012; Li et al., 2020)
	ChAT↓ (Park et al., 2012, 2020; Yan et al., 2016; Lu et al., 2021)	ChAT↑ (Park et al., 2012, 2020; Yan et al., 2016; Lu et al., 2021)
	Ach, Hes1↓ (Yan et al., 2016)	Ach, Hes1↑ (Yan et al., 2016)
	MAP2↓ (Li et al., 2020)	MAP2↑ (Li et al., 2020)
	p-ERK↓ (Zhang et al., 2022)	p-ERK↑ (Zhang et al., 2022)
	CREB↓ (Li et al., 2020)	CREB↑ (Li et al., 2020)
	p-CREB↓ (Zhang et al., 2022)	p-CREB↑ (Zhang et al., 2022)
	NF-κB, p-NF-κB↑ (Zhang et al., 2022)	NF-κB↓ (Zhang et al., 2022)
	CaMKII↓ (Zhang et al., 2022)	CaMKII↑ (Zhang et al., 2022)
	Mash1, Ngn1↑ (Yan et al., 2016)	Mash1, Ngn1↓ (Yan et al., 2016)
	Akt, p-Akt↓ (Park et al., 2020; Zhang et al., 2022)	Akt, p-Akt↑ (Park et al., 2020; Zhang et al., 2022)
	NMDA, PKCζ↓ (Park et al., 2020)	NMDA, PKCζ↑ (Park et al., 2020)

Aβ: Amyloid-β; Ach: acetylcholine; AD: Alzheimer's disease; Akt: protein kinase B; CaMKII: Calcium-calmodulin-dependent protein kinase II; ChAT: choline acetyltransferase; CREB: cAMP response element binding protein; ERK: extracellular regulated protein kinase; GAP-43: growth-associated protein-43; GFAP: glial fibrillary acidic protein; Hes1: hairy and enhancer of split homolog-1; LTP: long-term potentiation; LTD: long-term depression; MAP2: microtubule-associated protein 2; Mash1: mammalian achaete-scute homolog 1; NF-κB: nuclear factor kappa beta; NGF: nerve growth factor; Ngn1: neurogenin 1; NMDA: N-methyl-d-aspartic acid; NT-3: neurotrophin-3; p-CREB: phosphorylated CREB; p-ERK: phosphorylated ERK; p-NF-κB: phosphorylated NF-κB; p-tau: phosphorylated tau; PKCζ: protein kinase C zeta; PSD-95: postsynaptic density-95; Sox2: SRY-box transcription factor 2; SYP: synaptophysin; Tuj1: neuron-specific class III beta-tubulin; VEGF: vascular endothelial-derived growth factor.

BDNF was shown to enhance the survival, migration, and differentiation capacity of NSCs in 16-month-old Tg2576 mice; the application of BDNF increased the protein levels of PSD-95, SYP, and BDNF, and the number of dendritic spines in the HIPP while promoting more mature granule cells into the granular cell layer. The dendritic structure extended to the molecular layer, thus indicating that exogenous NSCs formed a novel synaptic junction with hippocampal endogenous cells (Wu et al., 2016). The transplantation of BDNF-overexpressing NSCs into the CTX of TBI rats resulted in more NSCs surviving after eight weeks, as well as an increase in the proportion of βIII-tubulin-positive neurons and GAP-43 protein levels. After 2 weeks, NSCs had migrated to the HIPP and CTX and increased the levels of BDNF mRNA and SYP protein in the CTX (Ma et al., 2012).

NT-3 was shown to boost the survival, renewal, proliferation, and differentiation of NSCs into tubulin beta-III $(TUBB3)^+$ neurons (Lu et al., 2011) while increasing the numbers of $NeuN^+$, $GFAP^+$, $BrdU^+$, $ChAT^+$, and neuron-glial

antigen 2 (NG2)$^+$ cells in bone marrow-derived NSCs (BM-NSCs). In another study, the transfection of BM-NSCs with NT-3 augmented levels of ChAT mRNA and acetylcholine, along with the protein levels of hairy and enhancer of split homolog-1. This strategy also reduced the mRNA and protein levels of mammalian achaete-scute homolog 1 and neurogenin 1 during the proliferation of BM-NSCs, increased the levels of mammalian achaete-scute homolog 1 and neurogenin 1 mRNA and protein, and reduced the mRNA and protein levels of hairy and enhancer of split homolog-1 (Yan et al., 2016). Furthermore, NT-3 was shown to increase the number of BrdU$^+$ and Nestin$^+$ cells in BM-NSCs and induce the production of interleukin-10 and glial cell line-derived neurotrophic factor (Yang et al., 2014).

In another study, insulin-like growth factor-1 (IGF-1) was shown to enhance the proliferation and differentiation of NSCs (De Gioia et al., 2020). On day 3, there was an increase in primary neurite and neurite growth from the hNSCs; this was followed by an obvious increase in neurite growth on day 7. Upon the addition of an Akt inhibitor, IGF-1 failed to stimulate neurite growth on day 1. On days 3 and 7, there was an increase in the death rate of hNSCs, thus indicating that Akt is essential for IGF-1 to promote the growth of neurites, and the proliferation and differentiation of hNSCs (Lunn et al., 2010). A previous study found that IGF-1 promoted the survival of NSCs in the HIPP of APP/PS1 mice, promoted differentiation into GABAergic neurons, increased the level of vascular endothelial-derived growth factor in the HIPP, and had a long-term therapeutic effect without notable adverse effects (McGinley et al., 2016). After exposure to Aβ *in vitro*, IGF-1 reduced the levels of apoptosis in HK532 cells; when an IGF-1R inhibitor was added, the level of apoptosis in HK532 cells was increased.

Collectively, these findings indicate that NTs can promote the survival, proliferation, and differentiation of NSCs, enhance synaptic and dendritic spine density and plasticity-related molecular levels, inhibit neuroinflammation, and promote the endogenous repair of damaged tissues without causing significant side effects.

The genetic modification of NSCs

NEP-NSCs have been shown to promote Aβ degradation, enhance the survival and differentiation of NSCs into neurons and astrocytes, increase synaptic density in the HIPP of both 3×Tg-AD and Thy1-APP mice, reduce the levels of Aβ in the HIPP and BLA, and protect NSCs from Aβ toxicity (Blurton-Jones et al., 2014).

In aged Institute of Cancer Research (ICR) mice, ChAT has been shown to promote the survival and differentiation of NSCs into neurons, astrocytes, and cholinergic neuron while increasing the levels of microtubule-associated protein 2, acetylcholine, BDNF, NGF, and Trkβ in the HIPP (Park et al., 2013). A further study showed that ChAT improved acetylcholine levels in cerebrospinal fluid induced by the ethylcholine aziridinium ion in AD rats and promoted the survival and migration of NSCs, of which 66% migrated to the CTX, 21% to the HIPP, and 10% to the striatum (Park et al., 2012). ChAT also boosted the differentiation of NSCs into neurons and astrocytes (Park et al., 2012). Another study discovered that NSC encoding ChAT improved the differentiation of NSCs into neurons in the HIPP and CTX of APPswe/PS1dE9 mice, as well as the protein levels of ChAT, choline transporter, vesicular acetylcholine transporter, and acetylcholine receptor (m1 muscarinic acetylcholine receptor, nicotinic acetylcholine receptor α5 and nicotinic acetylcholine receptor β2) in the HIPP and CTX. In addition, ChAT enhanced the protein levels of NGF, protein kinase C, phosphorylated extracellular signal-regulated kinase, phosphorylated Akt (p-Akt), BDNF, NT-3, TrkB, and CaMKII in the HIPP while inhibiting the deposition of Aβ and the activation of microglia in the HIPP and CTX, respectively (Park et al., 2020).

Collectively, these data show that NSCs over-expressing ChAT or NEP promotes survival, differentiation and migration of NSCs, enhances the expression of NTs and reduces Aβ and neuroinflammation in the HIPP and CTX.

Clinic Trials Relating to Neural Stem Cell Therapy in Alzheimer's Disease

Most studies focusing on the application of NSC transplantation for the treatment of AD have remained at the animal experimental stage and have not progressed to clinical studies. A preclinical clinical study performed by Lu et al. found that the intranasal transplantation of hNSCs alleviated cognitive deficits in APP/PS1 mice with no significant adverse effects (Lu et al., 2021). This suggests that the intranasal administration of hNSCs represents a non-invasive treatment strategy for AD. In 2020, this research team further demonstrated the safety and efficacy of hNSCs in the clinical setting by preforming the intranasal transplantation of different doses of hNSCs into the upper nasal tract via cavernosal drops into the olfactory mucosal region in ten subjects with moderate-to-severe AD; however, these results have not yet to be published (further details can be found on the Chinese Clinical Trial Register: ChiCTR2000028744).

From the results of published studies, it is evident that the clinical efficacy of NSCs for the treatment of AD is limited. This limitation may be related to a number of factors. Firstly, the choice of the optimal transplantation route appears to be crucial. Different transplantation routes, such as intranasal, intracerebral, intravenous and oral routes, can have notable effects on the migration and differentiation capacity of NSCs in the brain (Mango et al., 2019). Secondly, despite the feasibility of NSCs for the treatment of AD, their safety profile needs to be validated and refined; safe strategies still need to be developed before these methods can be translated into clinical trials. Finally, the quality of NSC preparation also needs to be studied in greater depth; this needs to be carried out at the enzymic, protein, and molecular levels.

Conclusion

Impaired neuroplasticity becomes increasingly impaired with age and cognitive impairment, and is a valid marker for the early prediction and diagnosis of AD (**Figure 1**). Early diagnosis is essential if we are to prevent the development of AD. Neuroplasticity is already impaired in early AD; therefore testing the level of neuroplastic impairment in aging and AD is beneficial and could enhance the early diagnosis rate of AD. NSCs have several advantages: for example, they exhibit self-renewal, multi-directional differentiation, low immunogenicity, strong homing ability, and can perform immunomodulatory and paracrine functions. In addition, NSCs secrete molecules related to neuroplasticity via paracrine action to promote neurogenesis, synaptogenesis, and microenvironmental recovery at the injured site. Importantly, the transplantation of NSCs can fundamentally address AD neurons and synaptic loss. BDNF-mediated neuroplasticity underlies the mechanism of NSC transplantation for AD treatment in mice. Moreover, NSCs can alleviate the classical pathologies of AD, such as the aggregation of Aβ and tau, and neuroinflammation. NSCs can be easily applied in the clinic and represent a safe and efficient method with significant potential for development. Accordingly, the regulation of neuroplasticity by NSCs represents a promising regenerative therapy for AD.

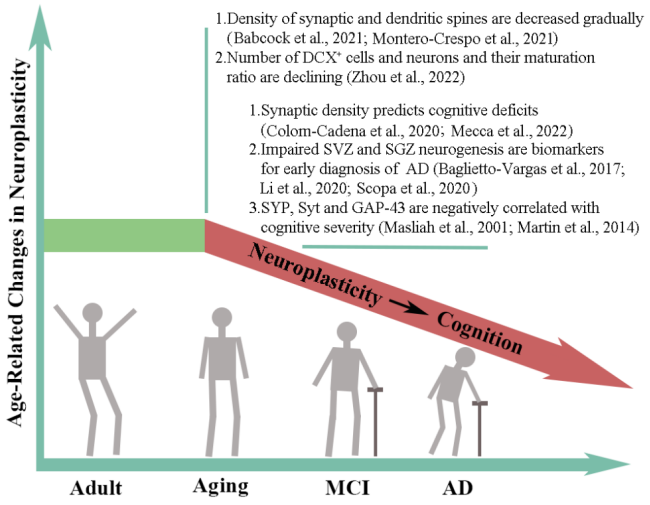

Figure 1 | **Age-related changes in neuroplasticity.**
Neuroplasticity in the adult hippocampus (HIPP) is normal, but declines sharply in aging, and patients with MCI and AD, thus increasing the occurrence and development of disease. Synaptic and dendritic spine density, along with neuronal numbers gradually decline. Neurogenesis and some plasticity-related proteins are also associated with the development of AD. Created using Adobe Photoshop (version 21.0.1). AD: Alzheimer's disease; DCX: doublecortin X; GAP-43: growth-associated protein 43; MCI: mild cognitive impairment; SGZ: subgranular zone; SVZ: subventricular zone; SYP: synaptophysin; Syt: synaptotagmin.

Preclinical studies have revealed that NSC therapy is safe and efficacious and associated with a broad range of prospects. Nonetheless, numerous clinical trials have failed thus far. This indicates that there are still many obstacles to overcome before basic experiments can be implemented in clinical settings; these experiments need to be focused on safety, cell sources, and optimized treatment duration. Tumorigenic risk and adverse reactions both represent significant safety concerns (Zhang et al., 2014a; Hunsberger et al., 2016) and need to be addressed. Previous work has shown that transplanted NSCs are safe and do not lead to the generation of tumors (Ottoboni et al., 2020), ectopic cell clusters (Zhang et al., 2019), or adverse reactions (infection, bleeding, tumor, mental abnormalities) (Zhang et al., 2014a). Furthermore, NSCs integrate into the host's neural circuit (Liu et al., 2021). Cell sources and dosage play a key role in determining the efficacy of treatment; hNSCs are a reliable source of cells. When transplanted into the CNS, these cells can integrate into the host's damaged tissues and exhibit high rates of survival, differentiation, and proliferation. Clinical prognosis is closely related to the optimal time window for NSC treatment. However, the optimal treatment window has only been reported in a small number of preclinical studies. The optimal time to transplant NSCs in order to alleviate cognitive deficits in Tg2576 mice is early in the course of disease (12 months); whereas late transplantation (15 months) had no therapeutic effect (Kim et al., 2022). However, some studies have demonstrated that NSCs improved cognitive deficits in both 16-month-old Tg2576 mice (Wu et al., 2016) and 18-month-old 3×Tg-AD mice (Blurton-Jones et al., 2009). Consequently, the optimal time window for transplantation may change as models of AD evolve and a comprehensive and efficient standardization scheme is established. Neuroplasticity is known to be already impaired in early AD; we believe that

the optimal intervention time is early in life (mild cognitive impairment). The long-term benefits of NSC transplantation need to be clarified, and cognitive improvement appears to be misunderstood as a permanent improvement or a means of slowing AD progression. Nonetheless, the boundaries of temporary remission and complete curation of cognitive impairment need to be further investigated. In addition, the limited migration and integration of transplanted hNSCs in the recipient's brain may depend on the stage of differentiation in the donor cells; this is a crucial factor underlying the success of transplantation. In future, it will be necessary to establish effective directional differentiation *in vitro* and to employ rigorous purification techniques to eliminate undifferentiated and non-target cells. As personalized therapy becomes a significant trend in contemporary medicine, it is necessary to develop individualized transplantation strategies for different patients.

Despite these obstacles, we advocate accelerating translational research on hNSCs to investigate the etiology and potential treatments for AD and develop more effective anti-AD therapies. NSC-EVs, the regulation of NTs, the genetic modification of NSCs, and other combination therapies that have no notable side effects, can all reverse the loss of neurons and synapses, alleviate the classic pathology and neuroinflammation of AD, provide neurotrophic effects for neurons and synapses, and offer a safe and clinically transformative therapy for patients with AD. We believe that in the not-too-distant future, and with the continued advancement of science and technology, NSCs will become a genuinely beneficial clinical therapy and bring exciting prospects to patients worldwide. This study has some limitations which need to be considered. First, the role of NSCs in the different stages of AD pathogenesis has not been fully discussed in this review and needs to be further explored. Second, some studies lack the analysis of the characteristic pathological indicators of AD such as Aβ and tau. Meanwhile, the treatment of NSCs for AD is still in the experimental stage. Therefore, further studies are needed to improve the therapeutic potential of NSCs for AD.

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