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Cell-based regenerative and rejuvenation strategies for treating neurodegenerative diseases

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Abstract

Neurodegenerative diseases including Alzheimer's and Parkinson's disease are age-related disorders which severely impact quality of life and impose significant societal burdens. Cellular senescence is a critical factor in these disorders, contributing to their onset and progression by promoting permanent cell cycle arrest and reducing cellular function, affecting various types of cells in brain. Recent advancements in regenerative medicine have highlighted "R3" strategies—rejuvenation, regeneration, and replacement—as promising therapeutic approaches for neurodegeneration. This review aims to critically analyze the role of cellular senescence in neurodegenerative diseases and organizes therapeutic approaches within the R3 regenerative medicine paradigm. Specifically, we examine stem cell therapy, direct lineage reprogramming, and partial reprogramming in the context of R3, emphasizing how these interventions mitigate cellular senescence and counteracting aging-related neurodegeneration. Ultimately, this review seeks to provide insights into the complex interplay between cellular senescence and neurodegeneration while highlighting the promise of cell-based regenerative strategies to address these debilitating conditions.

Keywords Neurodegenerative diseases, Rejuvenation, Senescence, Cell-based therapy, Reprogramming

Introduction

The natural process of growing older involves a gradual deterioration of bodily functions, which significantly increases an organism's vulnerability to various age-related illnesses, particularly disorders affecting the nervous system. Neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic lateral sclerosis (ALS), among others, have a substantial impact on an individual's quality of life and pose a significant burden on society [1]. These neurodegenerative diseases share common underlying mechanisms, including protein aggregation, oxidative stress, inflammation, apoptosis, and mitochondrial dysfunction, all of which contribute to neuronal loss [2]. Cellular senescence plays a crucial role in neurodegenerative disorders and is considered a potential underlying cause. Senescent cells contribute to the onset and advancement of these diseases through various mechanisms [3]. As a key indicator of aging, cellular senescence is defined by permanent cell cycle arrest and a reduction in cellular functions [4]. This process is not limited to somatic cells, but also encompasses stem cells, including neural stem

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cells (NSCs). When these cells age, their regenerative capacity -essential for maintaining tissue homeostasis and repair- declines [5].

In regenerative medicine, there are three major therapeutic categories known collectively as the "R3" paradigm [6, 7]: (1) Rejuvenation—restoring the functional capacity of existing cells or reversing cellular aging processes; (2) Regeneration—stimulating repair or regrowth of tissues using stem cells or host repair mechanisms; and (3) Replacement—directly substituting lost or damaged cells with functional ones.

The objective of this review is twofold: (1) to critically analyze the processes of cellular senescence that contribute to neurodegenerative disorders, and (2) to discuss cell-based strategies in the R3 context. In recent years, remarkable advancements have been made in the field of regenerative medicine. By integrating R3 concepts, we distinguish how certain approaches focus on rejuvenation, some on regeneration, and others on outright replacement. These strategies aim to counteract the effects of aging and mitigate neurodegeneration by specifically targeting the underlying mechanisms of aging, such as cellular senescence.

This review comprehensively examines the mechanisms of cellular senescence and explores potential R3 strategies. Specifically, it summarizes the role of cellular senescence in neurodegenerative diseases, highlighting its contributions to disease onset, progression acceleration, and the hindrance of traditional treatment effectiveness. Additionally, various cell-based strategies, such as stem cell therapy, direct lineage reprogramming, and partial reprogramming, are explored. Their potential benefits and challenges in treating neurodegenerative diseases are evaluated, with a focus on how these strategies may target senescent cells to restore functionality (rejuvenation), enhance endogenous repair (regeneration), or replace lost neurons (replacement). By delving into these underlying mechanisms and investigating innovative therapeutic approaches, we aim to pave the way for more effective treatments that can enhance patients' quality of life and potentially delay or even reverse the aging process.

Cellular senescence and neurodegenerative diseases

The association between cellular senescence and neurodegenerative diseases

In neurodegenerative diseases such as AD, PD, and ALS, various cell types within the brain undergo aging-related changes that play a crucial role in initiating and driving disease progression. Neurons, glial cells (including microglia and astrocytes), and NSCs all exhibit senescence-like phenotypes during both physiological aging and neurodegeneration [8]. These changes contribute to the complex pathogenesis of these disorders (Fig. 1).

Neurons Neurons, which have limited regenerative capacity, are highly susceptible to aging-related damage. Interestingly, although neurons were traditionally regarded as exempt from senescence due to their post-mitotic nature, recent evidence shows that they can in fact enter senescence in response to multiple stressors such as oxidative stress and DNA damage [9, 10]. For instance, the loss of SATB1, a DNA binding protein associated with PD, has been shown to activate a cellular senescence transcriptional program in dopaminergic neurons, suggesting neuronal senescence as a contributing factor to PD pathology [11]. Senescent neuronal cells accumulate with age and exhibit characteristics such as cell cycle arrest, pro-inflammatory secretory phenotype, and altered proteostasis, which can exacerbate neuroinflammation and oxidative stress, leading to cognitive decline and neuronal degeneration [12, 13]. This neuronal senescence phenomenon has led to increased interest in senolytic therapies specifically targeting neurons. Such therapies aim to selectively eliminate senescent neurons or modulate their harmful effects on neuronal function [14, 15]. Preliminary studies have shown promising results, with senolytic treatments blocking disease progression in mouse models of tau - mediated neurodegeneration by acting on affected neurons and improving outcomes in SARS-CoV-2-induced neuropathology involving neuronal damage [14, 15]. Nonetheless, further research is needed to thoroughly investigate the occurrence of neuronal senescence and evaluate the long-term safety and efficacy of senolytic treatments in neurodegenerative diseases [16].

Glia cells Glia cells, particularly microglia and astrocytes, are crucial components of the central nervous system (CNS) that significantly contribute to the pathogenesis of neurodegenerative diseases. Microglia, the primary immune cells of the CNS, undergo age-related and senescence-driven changes that profoundly impact the onset and progression of these disorders [16]. In PD, for example, reactive microglia have been observed in the substantia nigra and striatum, accompanied by elevated levels of pro-inflammatory cytokines [17]. These changes in microglial function can lead to chronic neuroinflammation, exacerbating neuronal damage and accelerating disease progression.

Astrocytes, once considered merely supportive cells, are now recognized as active participants in various complex CNS functions. Like microglia, astrocytes also experience age-related changes that can influence the development and progression of neurodegenerative diseases [17]. These changes may include alterations in astrocyte morphology, reactivity, and their ability to provide metabolic support to neurons. Astrocytes are also integral to maintaining the integrity and function of the blood-brain barrier (BBB), forming part of the neurovascular unit along

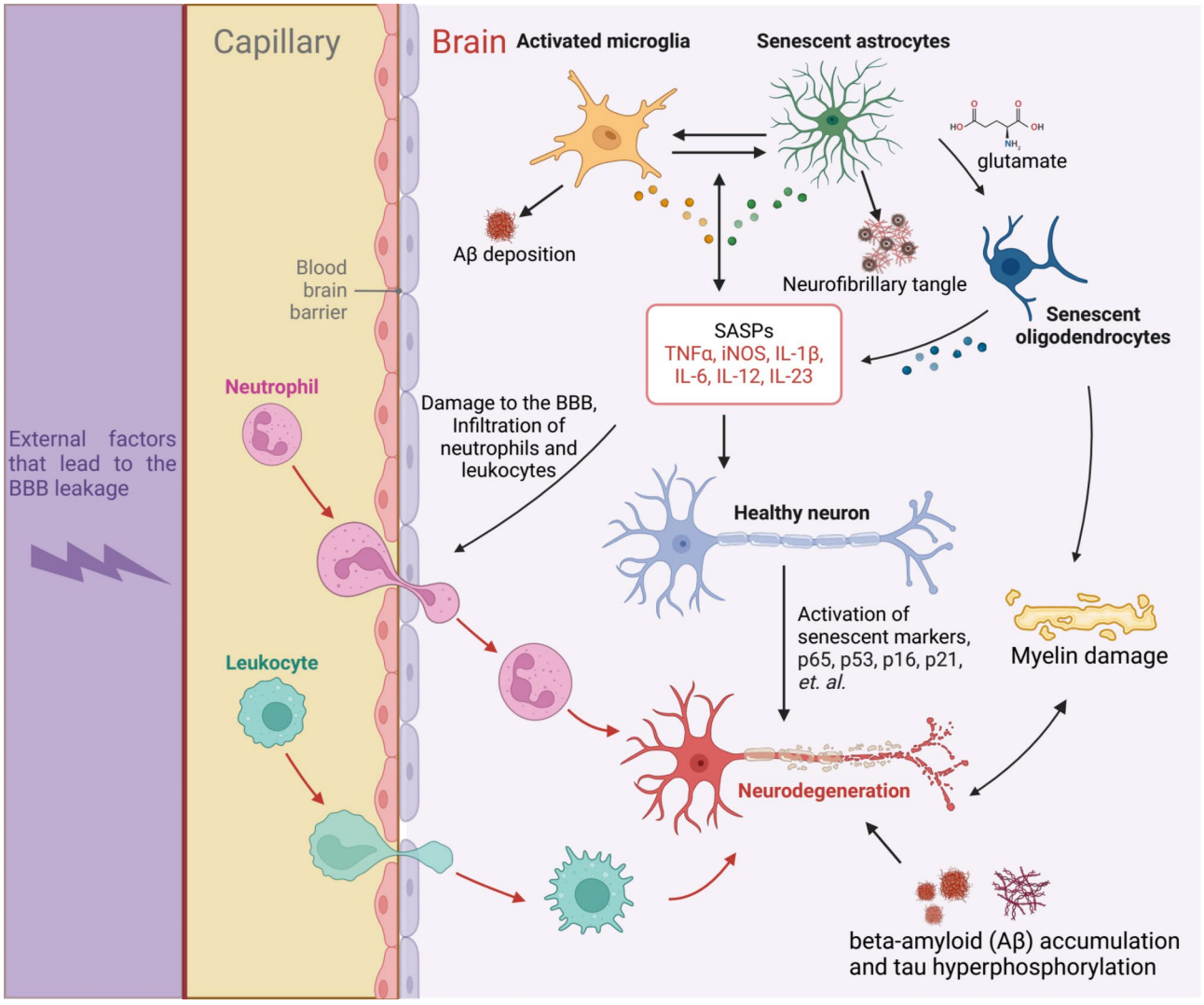

Fig. 1 Impact of cellular senescence and inflammation on neurodegeneration. This figure depicts the progression of neurodegenerative diseases driven by cellular senescence. Key processes include the activation of senescent markers (p65, p53, p16, p21) in astrocytes, which release senescence-associated secretory phenotype (SASP) factors (TNFα, iNOS, IL-1β, IL-6, IL-12, IL-23) that intensify neuroinflammation. Blood-brain barrier (BBB) breakdown leads to neutrophil and leukocyte infiltration, further contributing to inflammation. Microglia activation and the presence of senescent oligodendrocytes result in additional neuronal damage, characterized by Aβ plaque deposition, tau hyperphosphorylation, and myelin degradation, all of which are hallmarks of neurodegeneration

with brain microvascular endothelial cells (BMVECs), pericytes, and neurons [18]. Senescent astrocytes significantly contribute to neurodegenerative processes and linked to cognitive decline [19, 20]. The accumulation of senescent astrocytes in the aging brain, characterized by lamin-B1 reduction and nuclear deformations, may lead to astrocyte dysfunctions and subsequent neurodegeneration [21]. Their ability to support neuronal survival, clear neurotransmitters, and remove toxic protein aggregates, which are essential for maintaining a healthy CNS environment, is reduced [19]. Interestingly, senescent astrocytes display a unique transcriptome distinct from reactive astrocytes, with dysregulated pathways and downregulation of brain-expressed genes involved in neuronal development and differentiation [22, 23]. Contradictory to their normal protective role, senescent astrocytes exhibit impaired astrocytic responses to injury and decreased expression of genes involved in antigen processing and presentation [22]. Targeting senescent astrocytes and their associated pathways presents a promising approach for developing therapies to counter age-related neurodegeneration and improve brain health [24, 25].

The accumulation of senescent cells in the brain, including oligodendrocytes, contributes to age-related pathologies and neurodegeneration [9]. Oligodendrocytes, specialized glial cells in the CNS, are crucial for maintaining neuronal health and function, not just for

myelination. Recent evidence shows that oligodendrocyte dysfunction, such as senescence, significantly contributes to neurodegenerative processes. Senescent oligodendrocytes can produce SASPs, fostering chronic inflammation and oxidative stress, which lead to progressive CNS demyelination, microglial inflammation, and further neurodegeneration [26]. Importantly, the finding that deletion of the $p21^{CIP1}$ pathway ameliorated the disease, while blocking microglial inflammation did not prevent neurodegeneration in demyelinating disorders suggests that senescence, particularly of oligodendrocytes, is a key factor in driving neurodegeneration. This contradicts the traditional view that microglial inflammation is the sole primary driver and highlights the significance of directly targeting senescent oligodendrocytes as potential therapeutic targets [26].

Pericytes Senescent pericytes also play a significant role in neurodegenerative processes, contributing to brain aging and neurological disorders. Pericytes, located within the neurovascular unit, are crucial for maintaining BBB integrity, regulating cerebral blood flow, and supporting overall brain health [27, 28]. As pericytes become senescent, they exhibit characteristic features such as increased β-galactosidase activity, cell cycle arrest, and enhanced expression of SASP factors [29]. These changes can lead to BBB dysfunction, reduced cerebral blood flow, and impaired clearance of toxic cellular by-products [30]. Understanding the molecular mechanisms of pericyte senescence and its impact on the neurovascular unit is essential for developing targeted therapies to combat neurodegenerative disorders and enhance brain health during aging.

Neural stem cells (NSCs) NSCs are pivotal for brain function and maintenance, yet their senescence is closely linked to neurodegenerative processes. Amyloid-β (Aβ), a pathogenic protein associated with AD, has been shown to accelerate cellular senescence in human NSCs [31]. This process involves enhanced expression of senescence-related genes, increased senescence-associated-β-galactosidase (SA-β-gal) activity, and activation of the DNA damage response [31]. Interestingly, reprogramming of human fibroblasts into induced NSCs (iNSCs) using miR-302a has demonstrated promising results in combating cellular aging and improving cognitive performance in AD models [32]. These miR-302a-hiNSCs showed delayed aging, increased resistance to oxidative stress, and improved cognitive function when implanted into senescence-accelerated mice [32]. This contradicts the notion that all NSCs are susceptible to senescence and suggests that certain reprogramming techniques may offer therapeutic potential.

Endothelial cells Senescent endothelial cells significantly influence neurodegenerative processes by contributing to age-related vascular and neurological disorders. The accumulation of these cells can lead to endothelial dysfunction, which is associated with conditions such as atherosclerosis, diabetes mellitus, hypertension, and ischemic injury [33]. Senescent endothelial cells display a distinct SASP, characterized by the release of pro-inflammatory cytokines, chemokines, and proteases that disrupt the local microenvironment. Unlike in normal, healthy endothelial cells, the SASP in senescent ones initiates a cascade of events that can lead to tissue dysfunction and further exacerbate the aging process at the local level. This unique secretory behavior of senescent endothelial cells thus becomes a crucial focus when studying the mechanisms underlying age-related pathologies and potential therapeutic interventions [34]. For example, exposure to neurotoxic amyloid β (Aβ1–42) oligomers can induce a senescence phenotype in human brain microvascular endothelial cells (HBMECs) [35]. This finding suggests a direct link between endothelial cell senescence and neurodegenerative diseases such as AD. Furthermore, senescent endothelial cells show alterations in morphological and nanomechanical properties, including increased membrane stiffness and changes in adhesion properties, which may contribute to cerebrovascular dysfunction [35].

The challenges and limitations of traditional treatments for neurodegenerative diseases in the context of cellular senescence

Cellular senescence poses significant challenges to traditional treatments for neurodegenerative diseases. It involves multiple aspects that complicate the treatment process.

Senescent cell accumulation, apoptosis resistance, and SASP

The accumulation of senescent cells, their resistance to apoptosis, and the SASP are major issues. The SASP exacerbates neurodegeneration by creating a pro-inflammatory milieu that affects neighboring healthy cells. This not only leads to chronic inflammation and tissue dysfunction but also interferes with treatment efficacy. Senescent cells may respond differently to medications, impair neurogenesis, disrupt the BBB, and exhibit mitochondrial dysfunction. Moreover, senescence-associated epigenetic changes, cellular heterogeneity in affected brain regions, and reduced regenerative capacity of NSCs further compound the challenges in targeted treatment.

Drug delivery and uptake

In terms of drug delivery and uptake, cellular senescence causes changes in membrane permeability and the function of transport proteins. These cells have reduced membrane permeability, affecting drug uptake and efficacy.

Altered endocytic activity in these cells, as seen in the blockage of clathrin-dependent receptor-mediated endocytosis in senescent human diploid fibroblasts, impacts their ability to internalize drugs [36]. However, this reduced permeability can also be exploited for targeted drug delivery. Muñoz-Espín et al. describes an innovative approach that takes advantage of the high lysosomal β-galactosidase activity in senescent cells to design a drug delivery system using galacto-oligosaccharides [37]. This method allows for preferential release of encapsulated drugs within senescent cells, improving efficacy and reducing side effects in non-senescent cells [37]. Additionally, changes in transport proteins can lead to altered drug distribution within the cell, resulting in suboptimal drug concentrations at the target sites [38]. Studies have shown that replicative senescence in renal proximal tubular epithelial cells (RPTECs) leads to changes in the expression of various transporters. Notably, the mRNA level of organic cation transporter 2 decreased rapidly with increasing passage numbers, indicating a significant impact of senescence on transporter expression [39]. Furthermore, the uptake of fluorescent cationic substrates was reduced in SA-β-gal-positive RPTECs compared to SA-β-gal-negative cells, suggesting altered transporter function in senescent cells [39]. Besides, the regulation of drug transporter expression and activity can occur at various levels, including transcription, mRNA stability, translation, and post-translational modification, which may be influenced by the senescence process [40].

Drug-target interaction

Regarding drug-target interaction, the SASP can modify the expression or function of target proteins, interfere with intended drug-target interactions, and contribute to chronic inflammation and tissue dysfunction, potentially reducing the effectiveness of conventional treatments. Inflammatory cytokines and chemokines released as part of the SASP can alter signaling pathways, gene expression programs, and even cause conformational changes in drug targets like receptors or enzymes, making it difficult for drugs to bind effectively (41,42, 43). Traditional treatment approaches for neurodegenerative diseases have limitations. These treatments often focus on alleviating symptoms or targeting specific aspects of the disease mechanism rather than addressing cellular senescence, the root cause. For instance, neurotransmitter-enhancing drugs for AD patients only provide symptomatic relief without tackling neuronal senescence issues [3, 44].

Disease heterogeneity

Disease heterogeneity is another challenge. Neurodegenerative diseases are highly heterogeneous in affected cell types and underlying molecular mechanisms, and cellular senescence exacerbates this. Different cell types in the brain, such as glial cells, endothelial cells, neural stem cells, and neurons, can exhibit various senescence-like phenotypes and respond differently to treatments and interventions [8]. This heterogeneity is further complicated by the fact that senescent cells may respond differently to genetic and pharmacological interventions, known as senolytics or senomorphics [45]. Recent advancements, such as the machine learning program SenCID, have enabled the identification of six major senescence identities (SIDs) with different baselines, stemness, gene functions, and responses to senolytics [46]. This improved understanding of senescent cell heterogeneity may contribute to the effective treatments.

Lack of long-term efficacy

There is a lack of long-term efficacy in traditional treatments. Many traditional therapies, like those for ALS, have limited long-term benefits. For example, Riluzole, approved in the 1990s, remains one of the few FDA-approved treatments for ALS, offering only modest survival benefits. More recently, edaravone has been approved, but the search for effective therapies targeting disease progression is still desperately needed [47]. This lack of long-term efficacy highlights the need for more innovative treatment strategies that can address the underlying causes of cellular senescence and disease progression.

Cell-based R3 strategies for treating neurodegenerative disease

In this section, we discuss how "R3" approaches (Rejuvenation, Regeneration, and Replacement) can be applied to mitigate cellular senescence and aid in treating neurodegenerative disorders [48–50]. Specifically, we highlight stem cell therapy and cellular reprogramming (direct lineage reprogramming and partial reprogramming) as representative R3 modalities. These strategies aim to mitigate the effects of cellular senescence by (1) rejuvenating existing cells to restore youthful function, (2) regenerating neural tissues through stimulating or transplanting stem cells, or (3) replacing entirely lost neuronal populations with new, functional cells (Fig. 2).

Stem cell therapy

Stem cells are characterized by two key features: self-renewal, which allows them to divide repeatedly; potency, which enables them to differentiate into various specialized cell types 5152, 53. Based on these properties, stem cells are categorized into totipotent, pluripotent, multipotent, or unipotent [51, 54]. Most mature human cells are highly differentiated, unable to divide, and are known as "post-mitotic cells" [55]. When these differentiated post-mitotic cells become senescent or die due to natural aging, injury, or disease, their regeneration depends on

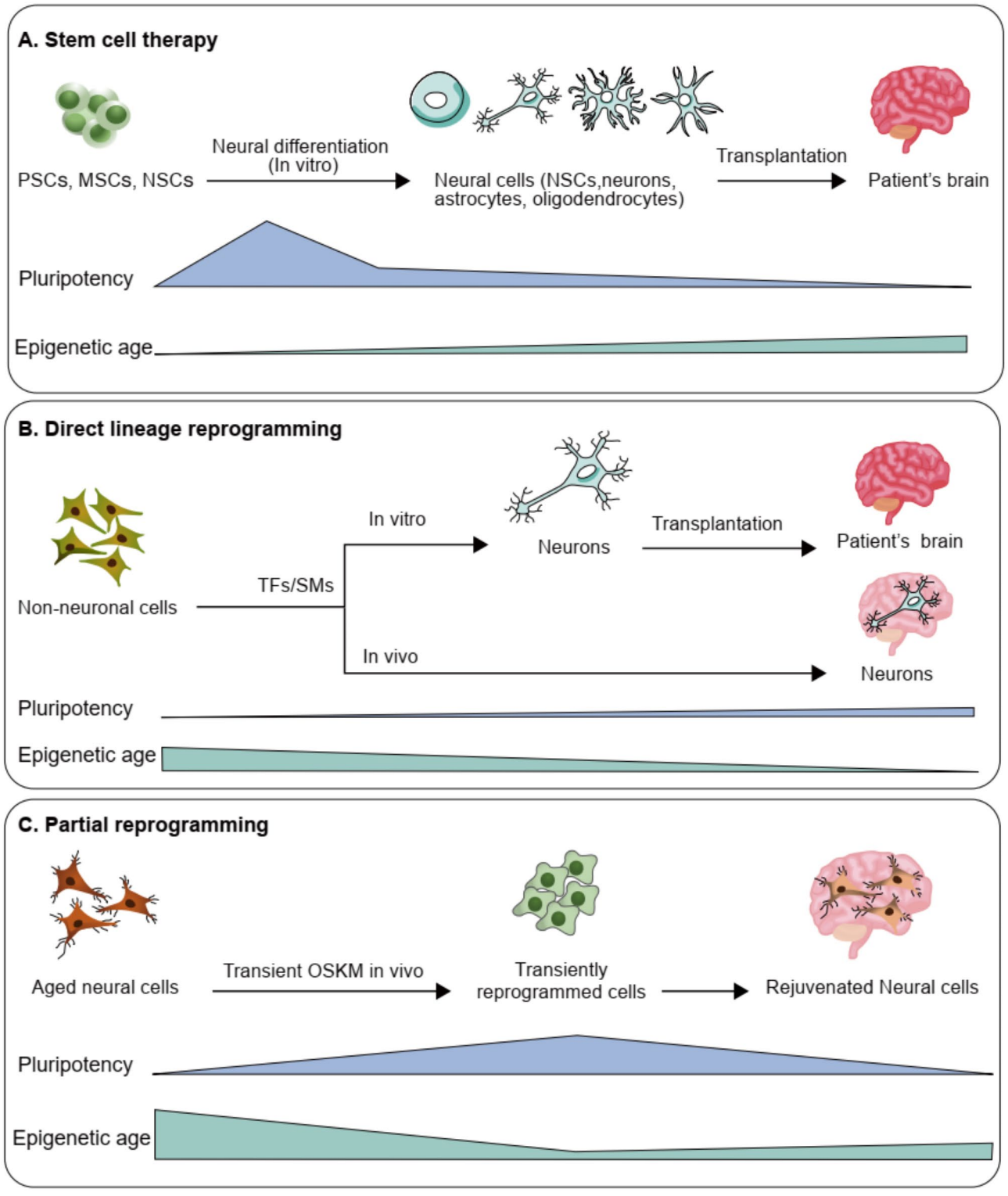

Fig. 2 Overview of cell-based strategies for treating neurodegenerative diseases. This diagram summarizes cell-based strategies to treat neurodegenerative diseases. Stem cells, including pluripotent stem cells (PSCs), mesenchymal stem cells (MSCs), and NSCs, may rejuvenate existing cells and regenerate or replace damaged ones by serving as sources for generating neural cell types like neurons, astrocytes, and oligodendrocytes. Non-neuronal cells can also be directly reprogrammed into neurons, bypassing the stem cell stage. Additionally, aged neural cells undergo transient reprogramming to a stem-like state, promoting rejuvenation and potentially reversing age-related damage. These methods aim to produce functional neural cells that could replace or repair damaged cells in neurodegenerative conditions, helping to restore brain function and slow disease progression

the activation of local stem cells, which replenishes the tissue with younger, healthy cells [56]. However, in the aging brain or neurodegenerative conditions, local stem cells often lose their regenerative potential [57]. Consequently, stem cell therapy has emerged as a promising R3 approach for treating neurodegenerative conditions [58–61], by using stem cells or stem cell-derived neurons/NSCs to repair or replace damaged and senescent neurons, thereby supporting neural function, regeneration, and rejuvenation (Table 1).

Pluripotent stem cells (PSCs)

Cell sources PSCs are a type of stem cell capable of differentiating into any cell type in the body, making them highly valuable for therapeutic applications. PSCs can be derived from various sources, including embryonic

Table 1 Summary of stem cell therapy for treating neurodegenerative disease

Therapy type	Cell type transplanted	Disease type	Effect	Therapy stage	Potential rejuvenation mechanism	References
PSCs-based	mDA neurons, mDA progenitor cells	PD	Restores motor function, reinnervates host brain	Preclinical	Neuronal replacement	75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85
PSCs-based	mDA neurons, mDA progenitor cells	PD	Symptom stabilized or improved after implantation	Clinical	Neuronal replacement	84, 85, 86, 87, 88, 89, 90
PSCs-based	forebrain cholinergic neurons	AD	Reduced pathology, improved cognitive function	Preclinical	Neuronal replacement	99, 100
PSCs-based	NSCs or NPCs	AD	Increased synaptic strength, improved memory	Preclinical	Neuronal replacement, Neurogenesis	96, 97, 98
PSCs-based	NSCs	ALS	Life extension, improved neuromuscular function and survival, neuroprotection	Preclinical	Neuronal replacement, Neurotrophic Support	104, 105, 106, 107, 108
MSCs-based	MSCs	AD	Aβ degrading and anti-inflammatory, increase in hippocampal synaptic density, enhances endogenous neurogenesis	Preclinical	Neurogenesis, Anti-Neuroinflammation	128, 129, 131, 132
MSCs-based	MSCs	AD	Feasible, safe, and well tolerated	Clinical	NA	129, 133, 134
MSCs-based	BM-MSCs	PD	Enhance motor function	Preclinical	Neuronal replacement, Neurotrophic Support	135
MSCs-based	UC-MSCs	PD, HD, CA	Decrease in the severity of motor and non-motor symptoms	Clinical/ Preclinical	NA	137, 182
MSCs-based	MSCs	MS	Decrease inflammation and enhance remyelination, leading to improved neurological function	Preclinical	Anti-Neuroinflammation	138, 140, 141
MSCs-based	MSCs	ALS	A slower progression of disease symptoms, improvements in motor abilities	Clinical	NA	142, 143, 144, 145
NSCs-based	NSCs	ALS	Delay disease onset and progression and extend overall survival	Preclinical	Anti-Neuroinflammation, Neurotrophic Support	158, 159, 160
NSCs-based	NSCs	ALS	No serious adverse reactions or accelerated disease progression	Clinical	NA	161, 162, 163, 164, 165
NSCs-based	NSCs	MS	Well-tolerated, feasible, and safe, and it helped slow the disease's progression	Clinical	NA	166, 167
NSCs-based	NSCs	PD	Improved motor and non-motor functions and preserved dopaminergic neurons	Preclinical	Neurotrophic Support, Neurogenesis	169, 170, 171, 175
NSCs-based	NSCs	PD	No immune or adverse reactions, and most patients showed varying degrees of motor improvement	Clinical	NA	176, 177, 178
NSCs-based	NSCs	AD	Enhance neuronal connectivity and metabolic activity	Preclinical	Neurogenesis	179, 180, 181

stem cells (ESCs) [62] and induced pluripotent stem cells (iPSCs)[63, 64 65, 66]. ESCs originate from the inner cell mass of blastocysts but raise ethical concerns due to embryos destruction [62]. iPSCs are generated by reprogramming adult somatic cells (e.g., skin fibroblasts) through transcription factors (OCT4, SOX2, KLF4, and c-MYC) [63, 64] or chemical compounds [65, 66] that reset the cells' developmental clock, sharing many ESC-like properties while avoiding ethical issues. They allow for patient-specific therapies, as they can be created from the patient's own cells, reducing the risk of immune rejection.

Neural cell differentiation from PSCs Efficient differentiation from PSCs into neurons is critical for stem cell replacement therapy against neurodegenerative diseases. In this process, PSCs are induced into neuronal progenitors and further specified into specific neuronal subtypes using factors like brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), and others, tailored to produce dopaminergic (DA) neurons for PD treatment [67–69], cholinergic neurons for AD treatment [70, 71], or motor neurons for ALS treatment [72, 73].

PSCs-based therapy PSC-based therapies can function within the replacement dimension of the R3 paradigm by transplanting PSC-derived specialized neurons that restore lost neural functions and counteract disease progression [74]. In some cases, they may also promote rejuvenation or regeneration via paracrine signaling and local microenvironment modulation.

PD In 2011 and 2017, pre-clinical studies established proof of concept for dopamine (DA) neurons derived from human ESCs (hESCs) and human induced PSCs (hiPSCs) [75, 76]. Later then, more pre-clinical studies reported that PSC-based therapy can contribute to the treatment of PD [77–85]. In 2018, a clinical trial commenced involving the surgical transplantation of allogeneic hiPSC-derived DAergic neuron precursors into the putamen of individuals with PD [86, 87]. In 2020, a study documented the clinical implantation of patient-derived midbrain dopaminergic (mDA) progenitor cells, differentiated in vitro from autologous iPSCs, in a patient with idiopathic PD [88]. Ongoing clinical trials involving PSCs for PD have shown promise in terms of safety and efficacy [84, 85, 89, 90].

AD Recent animal model studies have shown potential for PSC-based therapies to reduce pathology and enhance cognitive function [91–95]. Transplanting NSCs derived from mouse adult brains or PSCs into AD rodent models led to the generation of cholinergic neurons, increased synaptic strength, and improved memory performance [96, 97]. Additionally, hiPSC-derived NPCs and cholinergic neurons successfully survived and differentiated into cholinergic and GABAergic neurons in the host brain, leading to improved spatial memory [98–100].

ALS Although iPCS is increasingly used in ALS research, the studies published so far have mainly focused on iPSC-based ALS cellular models for disease mechanisms or drug screening [101–103]. Some studies utilizing iPSC-derived NSC transplants in ALS mouse models have demonstrated positive therapeutic effects, including extended lifespan, enhanced neuromuscular function, and neuroprotection [104–108].

Despite the promise, PSC-based therapies face hurdles in aging-related contexts. One significant concern is that aberrant DNA methylation patterns and histone modifications, which may be exacerbated by senescent cellular environments, can lead to improper differentiation of PSCs into desired neuronal subtypes or reduce the functionality of the resulting cells [109]. Furthermore, tumorigenicity remains a critical risk, as PSCs can form teratomas if not carefully monitored. Advanced imaging techniques and biomarkers are being developed to detect early signs of teratoma formation, but the risk persists during pre-clinical and clinical trials [110]. Immune rejection is another hurdle, as PSCs may elicit an immune response. Researchers are exploring modifications to the epigenetic and genetic profiles of PSCs during reprogramming to reduce this risk [111, 112]. Moreover, functional integration into existing neural networks is challenging in an aged or degenerating brain. Studies suggest that applying specific electrical fields can enhance synapse formation between transplanted neurons and native cells [113, 114], but achieving consistent and effective integration remains a challenge within the context of neurodegenerative diseases.

Mesenchymal stem cells (MSCs)

Cell sources MSCs are multipotent stromal cells derived from various tissues, including bone marrow, adipose tissue, and umbilical cord blood [115], and more recently, dental pulp. Bone marrow is the original and most extensively studied source [116], known for its well-characterized MSCs. Adipose tissue provides a more accessible and abundant source [117], with less invasive extraction procedures compared to bone marrow. The umbilical cord is a non-invasive source that yields MSCs with high proliferative capacity and immunomodulatory properties [118], while the placenta and amniotic fluid are rich in MSCs and offer potent regenerative properties in an ethically favorable context [119]. Dental pulp-derived MSCs have shown unique properties and promising results in pre-clinical studies for neurodegenerative diseases [120], demonstrat-

ing enhanced neuroprotective and regenerative capabilities compared to MSCs from traditional sources.

MSCs-based therapy MSCs have the capacity to differentiate into a variety of cell types such as osteoblasts, chondrocytes, adipocytes, and even neurons [121]. They show potential for mitigating senescence and promoting rejuvenation through the secretion of anti-inflammatory and neurotrophic factors, as well as exosomes [122–125]. Recent studies have underscored MSCs' potential to enhance cognitive function and neuronal health in age-related neurodegenerative diseases [126, 127].

AD In AD models, MSCs have demonstrated the ability to reduce amyloid-beta plaques, accompanied by improvements in cognitive functions, as observed in pre-clinical studies [128–132]. A Phase I clinical trial led by Kim et al. involved nine patients with mild-to-moderate AD, resulting in stabilization of cognitive decline and enhancement of cognitive function [129, 133, 134].

PD In the context of PD, MSCs have been utilized to protect and preserve DA neurons. Pre-clinical studies have demonstrated that MSC transplantation can enhance motor function [135], attributed to their neuroprotective properties and their potential to differentiate into neuron-like cells that can assimilate into existing neural pathways [136]. Moreover, a 2021 Phase I clinical trial studied intravenous infusion of umbilical cord MSCs (UC-MSCs) for PD treatment [137].

ALS and MS MSC therapy may also help mitigate inflammation and demyelination in ALS and MS [138, 139]. In ALS animal models, MSCs have decreased inflammation and promoted remyelination, improving neurological function [140, 141]. These promising animal study results have catalyzed clinical trials assessing MSC therapy's effects in ALS patients, with early studies indicating safety and therapeutic benefits, including symptom stabilization and improvements in motor abilities and quality of life [142–145].

Despite their promise in aging-related neurodegenerative diseases, several challenges remain. In an aging body, ensuring the long-term safety and consistent efficacy of MSC therapies is of utmost importance. For instance, as cells age, there may be an increased risk of abnormal cellular behaviors, and potential risks such as tumor formation associated with MSC therapies must be carefully addressed [146, 147]. Developing standardized protocols for the isolation, expansion, and administration of MSCs is highly necessary in the context of aging. The aging process can affect the characteristics of MSCs, making it essential to have consistent procedures to ensure reproducibility and efficacy across studies [148, 149]. Moreover, extensive clinical trials designed to meet regulatory standards are needed before MSC-based therapies gain wide clinical acceptance, particularly in complex aging condition like neurodegeneration.

Neural stem cells (NSCs)

Cell sources NSCs has gained significant attention over the past few decades as a potential treatment for neurodegenerative disease [150]. They are multipotent cells capable of differentiating into neurons, astrocytes, and oligodendrocytes. NSCs can be obtained for therapeutic purposes through several methods: isolation from fetal or adult brain tissue where NSCs naturally reside [151], differentiation from PSC [152], and direct reprogramming of somatic cells into NSCs by introducing specific TFs or chemical compounds [153].

NSCs-based therapy In the R3 paradigm, NSC-based therapy primarily fosters regeneration and replacement by generating new neurons and glial cells, which helps rejuvenate the brain. Specifically, NSCs replace aged or damaged cells, promote a healthy neural environment, and enhance neurogenesis to counteract the decline linked with aging and neurodegeneration [154–157]. Pre-clinical studies of NSCs-based therapy in animal models have shown promising results, with NSCs promoting neural repair, reducing inflammation, and improving function in conditions like ALS, PD and AD [150].

ALS&MS In mouse models of ALS, implanted human NSCs have been effective in delaying disease onset and progression and increasing survival by producing neurotrophic factors and reducing neural inflammation [158–160]. The FDA approved the first Phase I clinical trial in 2009 for transplanting human spinal cord-derived NSCs into ALS patients, followed by a Phase II trial [161–163]. These trials, which involved transplanting NSCs into the spinal cords of 6 and 18 ALS patients, respectively, did not show serious adverse reactions or accelerated disease progression [164, 165]. Clinical trials have also explored allogeneic NSC transplantation in patients with progressive MS, demonstrating that the procedure is well-tolerated, feasible, and safe, and it helped slow disease progression [162, 166, 167]. However, other trials have noted potential side effects, such as acute neurological deterioration and central pain syndrome [168].

PD Recent studies reveal NSC secretions can protect PD neurons, improving both motor and non-motor functions and preserved dopaminergic neurons in PD rats [169–171]. In PD animal models, NSC or neural progenitor cell transplants have consistently shown positive therapeutic outcomes [172–174]. In PD mice, NSCs that express dopamine-related markers increased astrocyte and

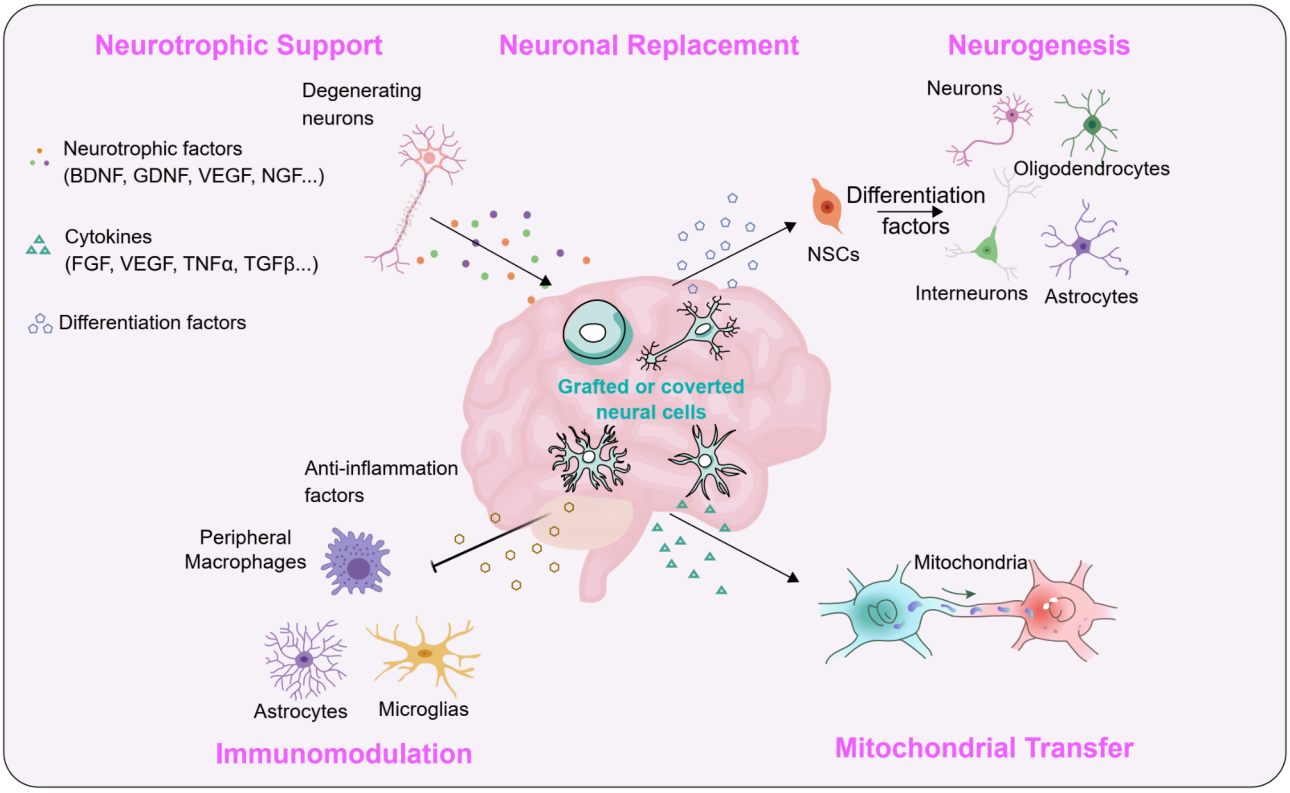

Fig. 3 Potential mechanisms underlying the stem cell therapies. This schematic illustrates how stem cell–based therapies combat neurodegeneration through multiple mechanisms in one integrated approach. Newly grafted or converted neural cells (center) replace or supplement degenerating neurons (upper left), while transplanted stem cells or induced cells also bolster neurogenesis (upper right) by differentiating into neurons, astrocytes, oligodendrocytes, or interneurons. Moreover, these cells secrete neurotrophic factors (left) that enhance cell survival and plasticity, and release anti-inflammatory mediators (lower left) to modulate immune responses involving peripheral macrophages, microglia, and astrocytes. Finally, healthy mitochondria can be transferred to damaged neurons (lower right), improving energy production and reducing oxidative stress

microglia presence and enhanced non-phosphorylated neurofilaments in the motor cortex, improving hyperactivity and gait [175]. In clinical trials, human neural progenitor cells/NSCs were transplanted into the dorsal putamen of eight patients with moderate PD, proving safe without immune or adverse reactions, and most patients showed motor improvements [176, 177]. Another trial involving NSC transplants into the striatum of 21 PD patients showed significant symptom improvement with no side effects, such as tumor formation or immune rejection [178].

AD NSC transplantation is a promising therapeutic approach for AD, as NSCs can differentiate into cholinergic neurons, thus replacing and improving lost neurons [179]. They also enhance neuronal connectivity and metabolic activity in AD through compensatory mechanisms, preserving cognitive function [180, 181]. NSCs have also been shown to reduce amyloid-beta plaques, either through direct interaction or by modulating the immune response [179].

Despite these promising aspects, several challenges remain. Key issues include ensuring the long-term survival and integration of transplanted cells, preventing tumorigenesis, and understanding the complex interactions between NSCs and host brain tissue [150]. Ongoing advancements in NSC differentiation protocols, delivery methods, and safety measures aim to address these challenges. Overall, NSC therapy provides a comprehensive approach to treating neurodegenerative diseases by supporting rejuvenation and combating senescence.

Potential mechanisms of stem cell therapies

The underlying mechanisms of stem cell therapy are complex and multifaceted, encompassing neuronal replacement, paracrine mechanisms, immune modulation, neurotrophic support, mitochondrial transfer [183, 184] (Fig. 3).

Neuronal replacement One of the primary mechanisms by which stem cell therapy operates is through neuronal replacement (the "replacement" aim of the R3 paradigm) [185–187], thereby addressing the fundamental problem of neuronal loss and aging. In PD, for instance, stem cells can become dopaminergic neurons, integrating into existing neural circuits to restore functions [75, 188–191].

Similarly, hESC-derived neurons can improve motor function in Huntington's disease models [192].

Neurogenesis Stem cell therapies offer regeneration potential by promoting neurogenesis, which is the generation of new neurons from neural stem cells. During neurogenesis, transplanted stem cells migrate to areas like the hippocampus, vital for memory and learning, where they replenish the neuronal population by generating new neurons [193]. Interestingly, stem cell therapy can support the activity of endogenous NSCs, enhancing neurogenesis by creating a favorable environment and secreting factors that promote neural differentiation and growth [132, 193].

Neurotrophic support Stem cells contribute significantly to neurotrophic support by producing and releasing factors like BDNF and GDNF [108, 182, 194, 195] and other neurotrophic factors [196, 197]. Administration of MSC-overexpressing neurotrophic factors such as GDNF, vascular endothelial growth factor (VEGF), BDNF into mouse model of PD [198], AD [199, 200] and ALS [201] resulted in promising in vivo outcomes. This neurotrophic support aligns with the rejuvenation aspect of R3, preserving neurons and delay senescence of both neurons and glial cells, thereby enhancing overall brain health and longevity [202, 203].

Anti-neuroinflammation Neuroinflammation involves various chronic, pro-inflammatory, immune system-mediated processes, mostly allied with neurodegeneration [204–206]. Stem cells modulate immune responses by dampening neuroinflammation [207]. In a transgenic mouse model of ALS, administration of MSCs could hinder disease progress by downregulating inflammatory inducible nitric oxide synthase (iNOS) activation [208] and suppressing expression of pro-inflammatory cytokines in vivo [208, 209]. This immunomodulatory effect is critical for rejuvenation, as it reduces the burden of the SASP, which is associated with chronic inflammation and contributes to the perpetuation of neurodegenerative processes [210].

Mitochondrial transfer Mitochondrial dysfunction is a key factor in the progression of many neurodegenerative diseases, and the ability of stem cells to enhance mitochondrial function in damaged neurons represents a significant therapeutic advantage [211–213]. For instance, restoring mitochondrial function in aged NSCs with Piracetam can improve hippocampal neurogenesis in vivo in old mice [214]. In some studies, MSCs have been shown to transfer healthy mitochondria to damaged neurons, which is crucial for restoring cellular energy production and reducing oxidative stress [215, 216]. By improving mitochondrial function, stem cells support the rejuvenation dimension of the R3 paradigm, helping delay cellular senescence and maintain the functional integrity of neurons, thus supporting the overall goal of brain rejuvenation [217, 218].

Cellular reprogramming

Direct lineage reprogramming

Direct lineage reprogramming, also known as transdifferentiation, is a transformative process that converts one differentiated cell type directly into another without passing through a pluripotent stem cell stage [219, 220]. In the context of neuroscience, this method involves converting non-neuronal cells directly into neurons [221], offering promising research and therapeutic applications, particularly as regenerative strategies for neurodegenerative diseases [222].

Genetic and chemical reprogramming Genetic methods typically involve overexpressing specific TFs or microRNAs to induce neuronal identity. For example, a combination of Ascl1, Brn2, and Myt1l can convert fibroblasts or hepatocytes into functional neurons, known as induced neurons (iNs) [223, 224]. Similarly, Other TF combinations can reprogram fibroblasts and astrocytes into neurons or neural stem cells (NSCs) [225–228]. As for chemical methods, chemical cocktails consisting of Forskolin, CHIR99021, I-BET151, and Wnt/β-catenin agonists efficiently convert mouse fibroblasts to neurons [229]. A cocktail of CHIR99021 and other molecules has been demonstrated to reprogram fibroblasts into NSCs [230, 231]. Human fibroblasts were converted to vGLUT1-positive glutamatergic neurons using a combination of specific chemical compounds [232]. Astrocytes could also be converted to neurons through chemical reprogramming [233–235].

In vitro and in vivo reprogramming In vitro reprogramming involves converting non-neuronal cells, such as fibroblasts or glial cells, into neurons within a controlled laboratory environment. Different neuronal subtypes, including dopaminergic neurons [226, 236, 237], glutamatergic neurons [238–240] and motor neurons [241], have been generated in vitro. This capability is useful for creating patient-specific neurons for cell replacement therapies. In vivo reprogramming bypass the need for cell delivery by converting local glial cells to neurons within the brain [242, 243]. This process employs TFs or chemical compounds to reprogram cells at the target site. Commonly used TFs for neural reprogramming include NeuroD1, Ascl1, Brn2, and Myt1l, which together convert glial cells into functional neurons [244, 245]. Chemical reprogramming in vivo leverages small molecules that can modulate signaling pathways, epigenetic states, and transcriptional networks to induce cellular reprogramming, especially astrocytes to neurons [246]. A cocktail

named FICBY has demonstrated success in transforming astrocytes into neurons in vivo [235].

Mechanism of action n line with the R3 paradigm, direct lineage reprogramming supports "Regeneration" or "Replacement" by converting non-neural cells (e.g., glial cells or fibroblasts) into functional neurons. This process allows for neuron regeneration directly at injury sites, promoting repair and restoring function in neurodegenerative diseases while avoiding challenges associated with stem cell transplantation, like cell delivery and integration.

Advantages Direct lineage reprogramming avoids the risks of tumorigenesis associated with pluripotency in iPSCs or ESCs [219, 220]. In vivo reprogramming allows conversion within the brain's intrinsic environment, supporting better integration and functionality [247]. It also reduces the need for cell transplantation, lowering the risk of immune rejection. Additionally, since patient-specific cells can be directly reprogrammed into neurons, this technique holds great potential for creating personalized models of neurological diseases.

Challenges Reprogramming can result in incomplete transformation and integration into neural networks, with potential off-target effects [248]. Ensuring the functionality and maturity of reprogrammed neurons in vitro, is challenging, as is their survival post-transplantation. In vivo methods require precise control to avoid aberrant reprogramming, which could lead to tumorigenesis or other adverse effects [222]. Additionally, the efficiency of reprogramming and long-term survival of newly generated neurons are critical issues that need addressing.

Partial reprogramming

Partial reprogramming, which aligns with the rejuvenation aspect of the R3 paradigm, involves the temporary activation of OSKM factors (OCT4, SOX2, KLF4, and c-MYC) to reverse cellular aging effects, such as telomere shortening, mitochondrial dysfunction, and altered gene expression [207, 249, 250]. This rejuvenation effect is achieved without pushing the cells into a fully pluripotent state, which would erase their identity and lead to potential risks such as tumorigenesis.

Therapeutic potential Several studies have demonstrated the potential of partial reprogramming to induce rejuvenation across a variety of tissues in mice including pancreas and muscle [251, 252], to different extents depending on the cell type [253–255]. In a study, mice subjected to periodic activation of OSKM factors exhibited reduced signs of aging, improved tissue regeneration, and better overall health, suggesting that partial reprogramming can be an effective strategy for promoting rejuvenation [256]. Another study demonstrated that partial reprogramming increased the lifespan of older mice by 109% compared to controls [257].

Partial reprogramming has also emerged as a promising approach for treating neurodegenerative diseases [258, 259], with effects observed in the spinal cord [260] and brain regions such as the optic nerve, hippocampus, and striatum [261–264]. Improvements have been noted in neuroblast populations in aged neurogenic niches with whole-body partial reprogramming [265]. Another promising application of partial cell reprogramming in brain is restoration of visual function [262]. When inducible OSK-containing AAV9 was delivered to the retinal ganglion cells of old mice via intravenous delivery, continuous expression of OSK factors led to a partially restored vision [262].

Mechanism of action Partially reprogrammed mice apparently exhibited rejuvenation of certain cellular phenotypes, including the reduction of mitochondrial ROS and restoration of H3K9me levels [249]. Cyclic cell partial reprogramming was shown to return the transcriptome, lipidome, and metabolome of multiple tissues to a younger state [253]. Interestingly, targeting partial reprogramming specifically to the neurogenic niche also boosts the proportion of neuroblasts and their precursors in old mice and improves several molecular signatures of aging, suggesting that the beneficial effects of reprogramming are niche intrinsic [265]. Additionally, in cellular models, partial reprogramming has been shown to rejuvenate aged human cells, making them function more like their younger counterparts [252]. This includes improvements in cellular metabolism, reduced oxidative stress, and enhanced DNA repair mechanisms, all of which contribute to a more youthful cellular phenotype [252].

Benefits and risks The benefits of partial reprogramming using OSKM factors include potential neuronal regeneration and neuroprotection from degenerative diseases like AD and PD, along with reduced secondary degeneration from neuroinflammation and oxidative stress [252]. However, risks include potential tumorigenesis from improper regulation of pluripotency activation that increase proliferation and suppress somatic cell identity [252, 266, 267], leading to unwanted cell proliferation [268, 269]. Issues such as incomplete reprogramming, coding mutations, and cell heterogeneity pose complications for therapeutic applications [270, 271]. Additionally, unintended differentiation pathways could form non-functional or maladaptive cells, with examples of liver and intestinal failure noted from continuous Yamanaka factor expression in mice [272, 273]. Therefore, robust pre-clinical and clinical evaluations are critical to determine the safety and efficacy of partial reprogramming before its clinical adoption.

Challenges and future directions in treating neurodegenerative diseases

Cell-based strategies rooted in the R3 paradigm (rejuvenation, regeneration, and replacement) hold great promise in regenerative medicine for neurodegenerative diseases. However, several challenges specific to this context need to be overcome.

Limited survival and engraftment in aging context In the aging population, mechanical stress during implantation, loss of extracellular matrix, and nutrient and oxygen deprivation are exacerbated, along with host inflammatory responses, often leading to significant cell death post-transplantation [274]. This issue is compounded by the age-related decline in adult stem cell functionality, reducing the efficacy of regenerative therapies [275]. The disparity between results in animal models and aged human patients emphasizes the need for more relevant pre-clinical models and a better understanding of age-related stem cell changes [275]. Furthermore, the translation of cellular therapies from "bench to bedside" remains challenging due to various intrinsic and extrinsic barriers, including manufacturing, regulatory, reimbursement, and clinical adoption issues [276].

Safety and efficacy evaluation in neurodegenerative diseases Comprehensive assessment of safety and efficacy is crucial. While pre-clinical data are promising, clinical trials must determine the true safety and effectiveness in humans with neurodegenerative diseases. Rigorous trial protocols and appropriate outcome measures are required. Long-term follow-up is essential to detect potential late-emerging adverse effects, such as in partial reprogramming, where long-term consequences like tumorigenesis or epigenetic instability need to be ruled out.

Personalized medicine for heterogeneous neurodegenerative diseases Given the heterogeneity of neurodegenerative diseases, personalized medicine is vital. Biomarkers are needed to predict patient responses. For stem cell therapy, these could be based on genetic profiles, disease stages, and cellular damage levels to select suitable candidates [277]. Similar considerations apply to direct lineage and partial reprogramming to identify patients likely to benefit and those at risk [278–281].

Regulatory and ethical challenges in aging-related therapies The development and application of these R3-based strategies raise regulatory and ethical questions [282]. Regulatory requirements for different applications, especially involving stem cell-derived tissue constructs in neurodegenerative disease treatment, are complex and lack clear guidance [283]. Ethical issues include implications for donors, risks related to iPSCs like unwanted differentiation or malignancy, and concerns about MSCs promoting tumor growth, especially in the context of an aging population seeking these therapies [284].

Conclusion

Remarkable progress has been made in R3-focused cell-based strategies for treating neurodegenerative diseases. Advances in stem cell therapy, direct lineage reprogramming, and partial reprogramming offer promising solutions for addressing cellular deficits. Emerging technologies like gene editing and combinatorial therapies provide additional opportunities. However, challenges such as cell and factor delivery and integration, safety and efficacy evaluation, personalized medicine, and regulatory and ethical considerations still exist. Overcoming these challenges requires continued research, collaboration, and innovation. With further progress, R3-based therapies have the potential to transform the treatment of neurodegenerative diseases and bring new hope to patients.

Abbreviations

AD	Alzheimer's Disease
PD	Parkinson's disease
ALS	Amyotrophic lateral sclerosis
RPE	Retinal pigment epithelium
ASO	Antisense oligonucleotide
CNS	Central nervous system
BBB	Blood brain barrier
BMVECs	Brain microvascular endothelial cells
SASP	Senescence-associated secretory phenotype
RPTECs	Renal proximal tubular epithelial cells
SA-β-gal	Senescence-associated-β-galactosidase
NSCs	Neural stem cells
iNSCs	Induced neural stem cells
iPSCs	Induced pluripotent stem cells
ESCs	Embryonic stem cells
PSCs	Pluripotent stem cells
DA	Dopaminergic
mDA	Midbrain dopaminergic
NPCs	Neural progenitor cells
MSCs	Mesenchymal stem cells
UC-MSCs	Umbilical cord mesenchymal stem cells
BM-MSCs	Bone marrow mesenchymal stem cells
hESCs	Human embryonic stem cells
hiPSCs	Human induced pluripotent stem cells
BDNF	Brain-derived neurotrophic factor
GDNF	Glial cell line-derived neurotrophic factor
iNs	Induced neurons
OSKM	OCT4, SOX2, KLF4, and cMYC
TFs	Transcription factors
FGF	Fibroblast growth factor
SHH	Sonic hedgehog
VEGF	Vascular endothelial growth factor
iNOS	Inducible nitric oxide synthase
HBMECs	Human brain microvascular endothelial cells
Aβ	Amyloid-β

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Data availability
All additional files are included in the manuscript.

Declarations

Conflicts of interest
The authors declare no conflicts of interest.

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