Histol Histopathol (2024) 39: 157-170

Histology and Histopathology
From Cell Biology to Tissue Engineering

REVIEW Open Access

Prospects of induced pluripotent stem cells in treating advancing Alzheimer's disease: A review

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Summary. The World Health Organization has identified Alzheimer's disease (AD), the leading cause of dementia globally, as a public health priority. However, the complex multifactorial pathology of AD means that its etiology remains incompletely understood. Despite being recognized a century ago, incomplete knowledge has hindered the development of effective treatments for AD. Recent scientific advancements, particularly in induced pluripotent stem cell (iPSC) technology, show great promise in elucidating the fundamental mechanisms of AD. iPSCs play a dual role in regenerating damaged cells for therapeutic purposes and creating disease models to understand AD pathology and aid in drug screening. Nevertheless, as an emerging field, iPSC technology requires further technological advancement to develop effective AD treatments in the future. Thus, this review summarizes recent advances in stem cell therapies, specifically iPSCs, aimed at understanding AD pathology and developing treatments.

Key words: Alzheimer's disease, Neurodegenerative disease, Stem cells, Induced pluripotent stem cell, Disease modeling, Regenerative cell therapy, Drug screening

Introduction

Alzheimer's disease (AD) is the most common degenerative neurological disorder, primarily affecting individuals aged ≥65 years. It severely impairs cognitive functions, such as language, memory, comprehension, and judgment. Moreover, AD presents substantial challenges to affected individuals and societal structures. A notable increase has been recently observed in AD prevalence with the demographic trend toward an aging population. Projections suggest a considerable increase, expecting a global prevalence of 131 million individuals by 2050.

This rapid increase in the number of patients with AD requires public system support, including financial aid and healthcare systems, imposing a considerable socioeconomic burden on society. Various studies have explored treatments for this disease to prevent this phenomenon. Researchers have identified specific targets and approaches based on the multifaceted pathological mechanisms underlying AD onset. However, despite extensive research, current therapies only delay or alleviate symptoms rather than offer a comprehensive cure for the disease. Researchers attribute the challenge of developing a definitive cure to the technical complexities of research, which have led to

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www.hh.um.es. DOI: 10.14670/HH-18-766

Abbreviations. AD, Alzheimer's disease; iPSCs, induced pluripotent stem cells; Aβ, amyloid-β protein; APP, amyloid precursor protein; hESCs, human embryonic stem cells; ASCs, adult stem cells; NSCs, neural stem cells; BDNF, brain-derived neurotrophic factor; BM-MSCs, bone marrow derived-mesenchymal stem cells; AD-MSCs, adipose-derived mesenchymal stem cells; UCB-MSCs, umbilical cord blood mesenchymal stem cells; IL-10, interleukin-10; TGF- β1, transforming growth factor; TNF, tumor necrosis factor; ECM, extracellular matrix; APOE, apolipoprotein E; OOC, organ-on-a-chip; CRISPR/Cas-9, Clustered Regularly Interspaced Short Palindromic Repeats/Cas9; TALEN, transcription activator-like effector nuclease

an incomplete understanding of AD.

Thus, a novel approach has emerged as a potential solution: utilizing stem cells to understand the underlying mechanisms of AD and advancing treatment strategies. Innovations in stem cell research have equipped researchers with the tools to tackle longstanding questions that hinder our understanding of the disease.

The discovery of induced pluripotent stem cells (iPSCs) in 2006 marked a groundbreaking innovation during the rapid progression of stem cell research. Since their discovery, iPSCs have demonstrated substantial potential, surpassing previous approaches and other types of stem cells. Derived from a patient's own somatic cells, iPSCs can induce regeneration and restore functionality. Consequently, they hold promise for various applications, including disease modeling to understand pathology and developing therapies for direct administration to stimulate cell regeneration as a treatment. Nevertheless, acknowledging the concerns and disadvantages associated with these approaches is essential. Therefore, this review evaluates current progress in stem cell research, particularly iPSCs, while discussing their challenges, and potential research avenues that may advance AD treatment.

Pathophysiology and societal impact of Alzheimer's disease (AD)

AD is a progressive neurodegenerative disease characterized by considerable impairment of cognitive functions, including memory, language, navigation, and learning. As the disease progresses, individuals increasingly struggle to perform everyday activities. Neuropathologically, AD is caused due to severe brain atrophy resulting from synaptic loss and neuronal death (Tzioras et al., 2023) (Fig. 1).

AD is a complex disorder with interrelated pathophysiological causes. AD onset is linked to the abnormal aggregation of amyloid-β (Aβ) protein and the accumulation of tau in neurofibrillary tangles (Holtzman et al., 2011). Aβ is cleaved from amyloid precursor protein (APP) by three protease types: α-, β-, and γ-secretase (Calabrò et al., 2021). Normally, the α- and γ-secretase cleave the APP. However, Aβ peptides are generated if β- and γ-secretase sequentially act on APP due to the disruption in homeostatic regulation that APP mutations induce (De-Paula et al., 2012). These abnormal Aβ peptides primarily consist of Aβ1-40 and Aβ1-42 (Lane et al., 2018), with Aβ1-42 playing a critical role in AD onset due to its poor solubility and strong tendency to aggregate (LeVatte et al., 2019). As the hydrophobic Aβ1-42 aggregates, it forms insoluble fibrils that deposit into amyloid plaques, which are neurotoxic and lead to synaptic dysfunction and neuronal death (Wu et al., 2022). While Aβ has traditionally been a primary target in AD treatment, recent evidence indicates that Aβ1-42-induced oligomer production causes acute neurological injury due to its neurotoxicity (Wu et al., 2022; Amano, 2023).

In addition to Aβ, tau proteins contribute to AD development. Normally, microtubules facilitate intracellular transport, supporting neuronal function. Tau proteins bind to phosphate molecules and interact with microtubules, stabilizing and assisting in their assembly (Medeiros et al., 2011). However, in AD, Aβ aggregation induces tau protein hyperphosphorylation, causing them to dissociate from microtubules and aggregate with other tau proteins. This aggregation forms insoluble neurofibrillary tangles within neurons, severely disrupting their communication (Kumar et al., 2024). Current AD therapies focus on clearing

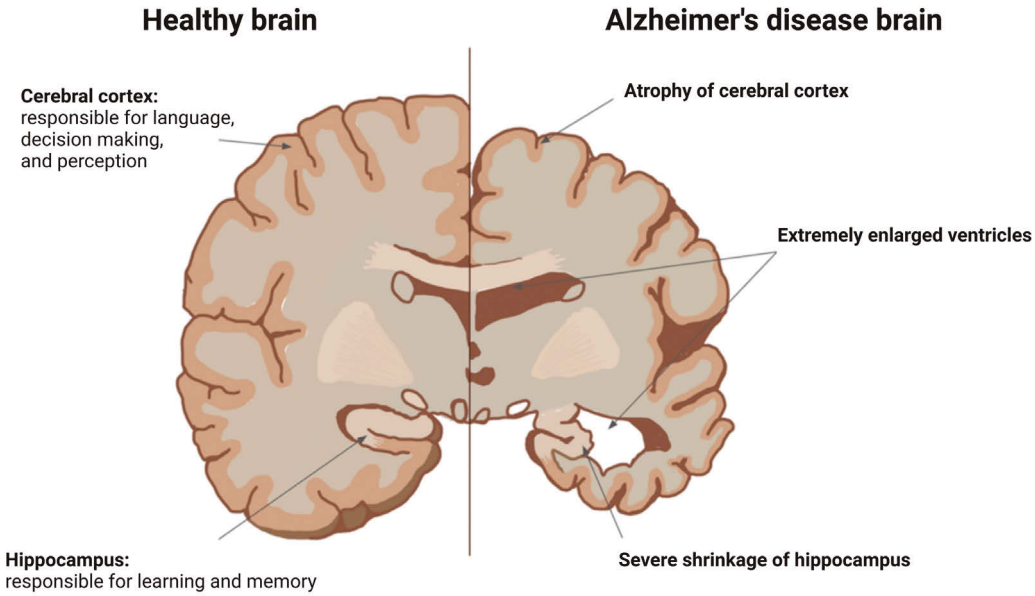

Fig. 1. Coronal plane diagram: Comparison of a healthy brain (left) and brain with Alzheimer's disease (right). AD progression is characterized by extreme changes in the brain. The cerebral cortex, the brain's outermost layer responsible for key cognitive functions like language, decision making, and perception, undergoes substantial deterioration, leading to a decline in these cognitive abilities (Cadwell et al., 2019). Additionally, the hippocampus, which is crucial for memory formation and learning, experiences severe shrinkage, leading to considerable memory and learning difficulties (Fig. 1) (Anand and Dhikav, 2012). The ventricles and fluid-filled spaces expand when the volume of the brain's critical regions decrease.

intracellular tau and inhibiting its phosphorylation.

Recent studies have identified alternative pathological mechanisms in AD, including mitochondrial dysfunction, abnormal oxidative stress, epigenetic alterations, and neuroinflammation (Marques et al., 2010; Yang, 2016). While various theories on AD pathology exist, definitive conclusions have yet to be reached. Uncertainty and limited understanding of the disease's fundamental mechanisms have stalled the development of effective AD treatments. Therefore, gaining a comprehensive understanding of the pathological mechanisms underlying the disease is crucial. This will enable the identification of specific disease targets, laying the groundwork for potential therapeutic strategies.

In fact, addressing AD, recognized as a public health concern by the World Health Organization, is urgently required (Lane et al., 2018). This condition poses a substantial societal challenge, with its epidemiological impact growing daily. Over 90% of cases manifest AD symptoms in individuals aged ≥65 years (Kumar et al., 2024). Advancements in science and technology have increased life expectancy, which in turn raises the susceptibility to AD. In 2019, AD was the sixth leading cause of death in the United States, marking an approximate 150% increase since 2000 (2022 alzheimer's disease facts and figures, 2022). As of 2022, approximately 6.5 million Americans aged ≥65 years exhibited AD; projections indicate this number will rise to 13.8 million by 2060 (Skaria, 2022), and globally to 131 million by 2050 (Tiwari et al., 2019). This rising number of patients with AD will impose considerable social, economic, and medical burdens. The strain on healthcare systems, rising costs, and resultant indirect impacts such as workforce reduction and increasing dependency ratio will substantially affect society (Skaria, 2022). Therefore, further research is required to develop effective AD therapies and alleviate these challenges.

Stem cell innovations and challenges in Alzheimer's disease therapeutics

To date, promising efforts have been made to identify effective therapeutic agents for AD. Multiple targets including amyloid, secretases, tau proteins, and neuroinflammation have been identified, (Athar et al., 2021) with various approaches like the use of microRNAs, cytokines, exosomes, and chemical inhibitors being explored (Qin et al., 2022). These studies, conducted using animal models, faced substantial ethical and technical challenges, including interspecies differences. Differences in disease mechanisms and therapeutic responses between human and animal models often led to failures in translating research findings into effective treatments.

To address these issues, stem cell technologies are increasingly being used as an alternative approach in research. Stem cells, known for their unspecialized and self-renewing capabilities, can differentiate into various somatic cell types (Zakrzewski et al., 2019) (Fig. 2). These attributes hold promise for future advancements in cell therapies for several diseases.

Human embryonic stem cells (hESCs)

James Thomson in the USA in 1998 first discovered hESCs, which are pluripotent stem cells. With their pluripotent capabilities, hESCs can differentiate into any cell type, making them highly versatile for use in stem cell therapies across various diseases (Yamanaka, 2020; Hwang, 2021). Despite their potential clinical applications, the broader use of hESCs in research is limited by ethical concerns and immunogenic challenges. Derived from blastocysts during the embryonic stage, the use of hESCs sparks ethical debate about the initiation of human life and the acceptability of harvesting cells from blastocysts. Moreover, hESC transplantation may trigger immunological rejection in recipients, posing further challenges (Kim et al., 2022). Consequently, these obstacles have spurred efforts to find alternative stem cell sources.

Adult stem cells (ASCs)

ASCs are undifferentiated cells found in all adult tissues. Their proliferation and differentiation abilities can be used to replace malfunctioning cells, thereby treating diseases or injuries (Cable et al., 2020). Among various ASC types, mesenchymal stem cells (MSCs) and brain-derived neural stem cells (NSCs) are the most commonly used sources in stem cell therapy in AD. MSCs are multipotent stem cells typically derived from mesodermal germ layers like bone marrow, umbilical cord blood, and Wharton's jelly (Duncan and Valenzuela, 2017). NSCs are multipotent stem cells that generate various neural cell types. While ASCs offer multipotency and broad applicability, there are concerns about their invasive extraction methods, safety, and clinical efficacy (Liu, 2020; Hwang, 2021; Qin et al., 2022). Notably, their limited production has promoted interest in alternative stem cell sources.

Induced pluripotent stem cells (iPSCs)

Shinya Yamanaka, in 2006, first developed iPSCs, which are pluripotent cells (Poetsch et al., 2022). Adult somatic cells were artificially reprogrammed to regain pluripotency by combining four reprogramming factors to generate iPSCs (Yamanaka factors/OSKM factors): octamer-binding transcription factor 3/4, sex-determining region Y-box 2 (Sox2), Krüppel-like factor 4 (Klf4), and c-Myc (Yamanaka, 2020). Like embryonic stem cells (ESCs), iPSCs can indefinitely regenerate and differentiate into any cell type. However, iPSCs provide several advantages over the earlier cell types, making them a promising alternative stem cell source. iPSCs are derived from somatic cells, typically obtained from

easily accessible sources like blood, skin, and urine. This abundance of sources resolves the concerns about cell availability in other stem cell types (Ebert, 2012; Poetsch et al., 2022). Additionally, iPSC derivation minimizes patient burden by not raising ethical questions or involving invasive harvest procedures. Additionally, the direct collection of somatic cells from patients makes them a valuable resource for various biomedical applications, including disease modeling, drug screening, and regenerative cell therapy (Marotta et al., 2022) (Fig. 3). iPSC technology facilitates the generation of three-dimensional (3D) models that effectively overcome challenges found in animal models, making them highly valuable for *in vitro* studies (Spitalieri et al., 2018). Furthermore, iPSC technology provides autologous stem cells that carry the donor's genetic information, reducing the risk of immunological rejection after transplantation (Moradi et al., 2019). Overall, these advantages have positioned iPSCs as a revolutionary resource in developing novel therapeutics for currently untreatable diseases.

The emergence of novel iPSC technologies has overcome the limitations of previous research and introduced a groundbreaking strategy for future research. Nevertheless, further research is required to validate the safety and reliability of this technology given its novelty.

Previous applications of stem cell therapy in Alzheimer's disease: Past endeavors and insights

Recently, stem cells have gained traction for providing new insights into therapeutic avenues for AD. Their ability to differentiate into various neuronal cells and regenerate damaged cells has become key to developing stem cell therapies for AD.

ESCs

One potential approach involves using ESCs, which can differentiate into neural progenitor cells (NPCs). Tang et al. transplanted NPCs into an AD rodent model and compared the escape latency in the Morris water maze test between the AD-induced control and two-week post-NPC-transplanted groups. An improvement in impaired cognitive abilities was observed in the NPC-transplanted groups (Tang et al., 2008; Zhang, 2020). Furthermore, hESCs can be differentiated into basal forebrain cholinergic neurons and γ-aminobutyric acid neurons, both substantially affected in patients with AD (Liu et al., 2020). In a study by Liu et al., these differentiated cells were transplanted into the hippocampus of mice with impaired neurons, successfully restoring cognitive skills like learning and

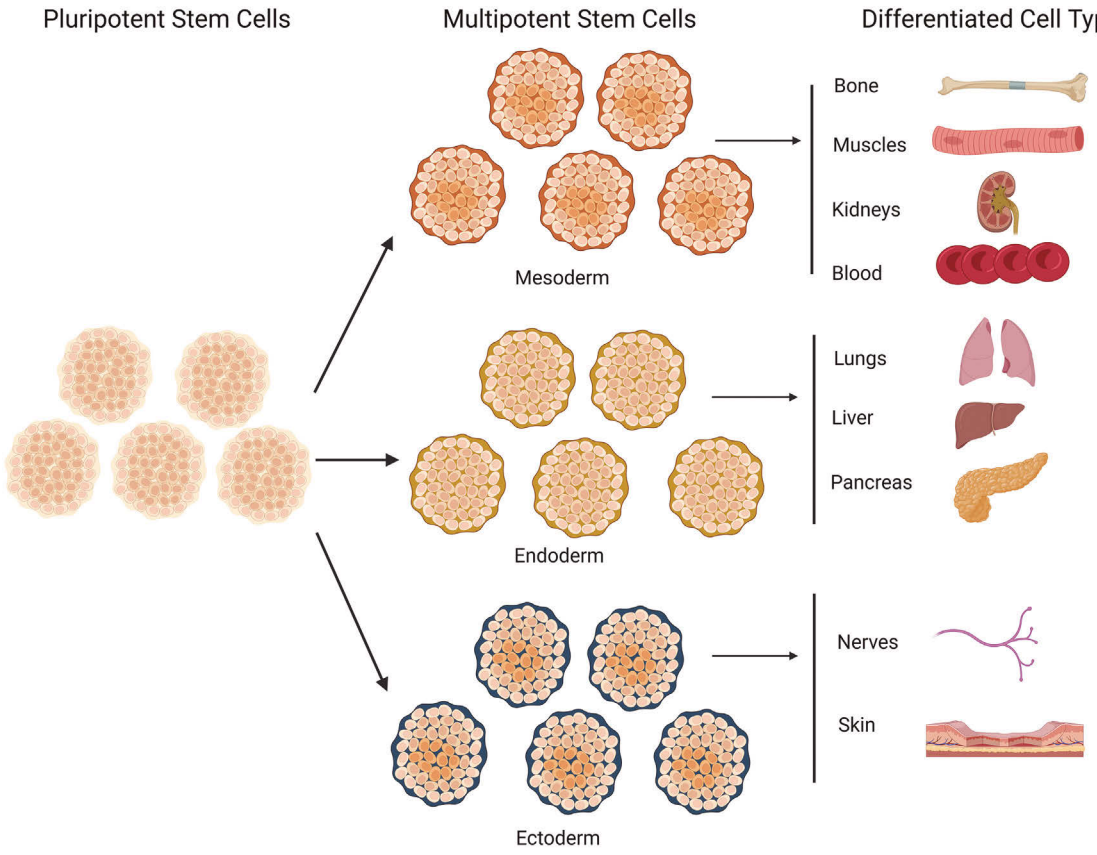

Fig. 2. Hierarchy of the stem cells. The pluripotent stem cells can indefinitely proliferate and differentiate into cells of all three germ layers. Contrastingly, multipotent stem cells can only differentiate into specific cell types depending on the germ layer type. These cells, once differentiated, lose their multipotency and are unable to self-renew (Ratajczak et al., 2012).

memory (Liu et al., 2013). The clinical use of hESCs remains controversial due to challenges in translating results from animal models to humans, despite the success seen in animal models. Additionally, the pluripotency of ESCs poses a risk of uncontrolled teratoma formation, complicating direct transplantation and necessitating measures to control tumorigenicity (Bulic-Jakus et al., 2016). Moreover, immunogenic reactions and ethical concerns have limited the use of ESCs in AD treatment.

NSCs

Brain-derived NSCs have emerged as another potential option for treating AD, alongside ESCs. NSCs are multipotent stem cells that can differentiate into various neural cells, including neurons, oligodendrocytes, and astrocytes (Vasic et al., 2019). This versatility enables neurogenesis, synaptic restoration, and neurotrophic factor secretion, offering promising prospects for AD treatment.

Neurogenesis

One way for NSCs to treat AD is by differentiating into and replacing damaged or lost neurons. However, a major challenge of stem cell transplantation into the brain is the blood-brain barrier, which selectively restricts the passage of compounds from the blood into the brain (Ballabh et al., 2004). This barrier often prevents most stem cells from reaching their target cells for replacement. However, some studies suggest that intranasal delivery allows stem cells to bypass the blood-brain barrier and noninvasively reach their target destination (Jiang, 2011; Li et al., 2015). In the study by Lu et al., researchers successfully transported human NSCs into the brain of AD-induced mice via intranasal injection, minimizing system damage. Once in the brain, these transplanted cells differentiated into various cell types, replacing malfunctioning neurons, improving AD pathology, and restoring cognitive abilities in AD-induced mice. Additionally, Chen et al. found that NSCs could replace degraded cholinergic neurons and enhance synaptic connections in the brain, demonstrating their potential as an AD treatment (Zhu, 2020; Chen et al., 2023).

Synaptic restoration

NSCs can also aid in AD treatment by differentiating into various glial cells, such as astrocytes and oligodendrocytes (Nicaise et al., 2022), which support neuronal activity, synaptic function, and neurotransmission (Fields et al., 2014). This cell replacement repairs the synaptic dysfunction caused by AD and improves neural connectivity in the brain. For example, Ager et al. demonstrated that NSC transplantation improved memory and promoted endogenous synaptogenesis through the differentiation of glial cells (Ager et al., 2015). Another approach uses NSC transplantation to prevent tau phosphorylation, Aβ plaque formation, microgliosis, and astrogliosis by regulating associated enzymes (Lee et al., 2015). This application of NSCs induces synaptic restoration,

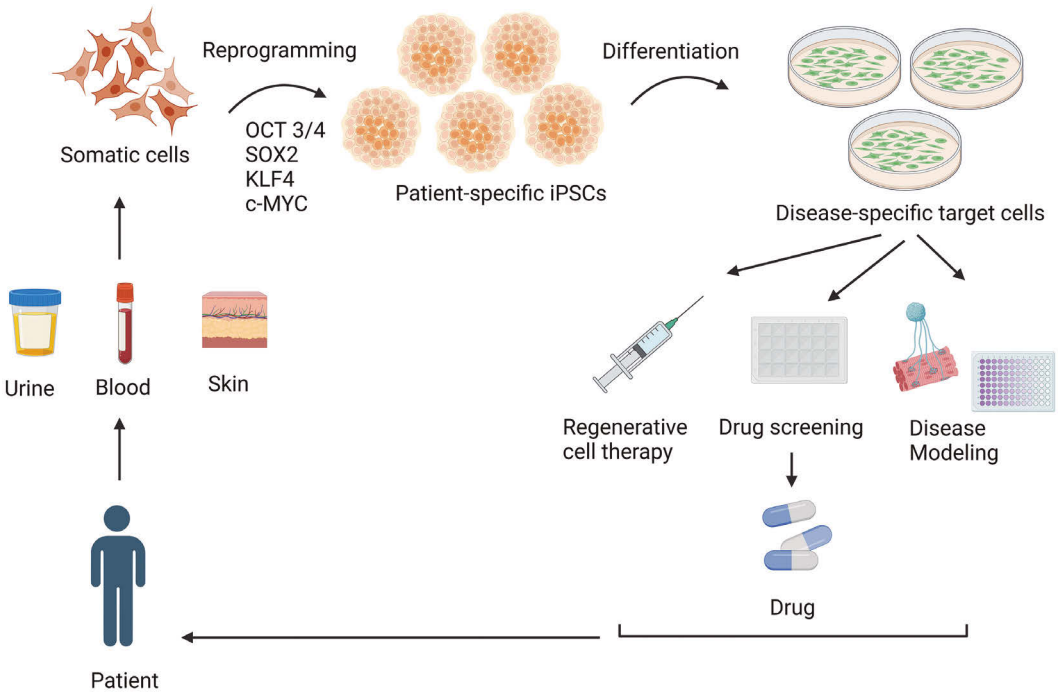

Fig. 3. Key steps in producing induced pluripotent stem cells (iPSC) and their application in regenerative cell therapy, drug screening, and disease modeling. Somatic cells collected from patient's urine, blood, or skin are reprogrammed into the iPSCs, which are subsequently differentiated into various cell types such as adipocytes, chondrocytes, neurons, and hepatocytes, depending on the target disease. The iPSC-derived cells have diverse applications such as direct injection into patients for regenerative stem cell therapy, drug screening for drug development, and disease modeling to understand complex disease mechanisms.

resulting in increased neuronal and synaptic densities (Li et al., 2016).

Neurotrophic factor production

The paracrine effects of NSCs offer promising therapeutic potential. NSCs differentiate into neurons and glial cells that produce paracrine cytokines, indirectly promoting neuron formation and restoring cognitive abilities (Hayashi, 2020; Qin et al., 2022). For example, NSC transplantation results in the secretion of neurotrophic factor, a nerve growth factor, which induces differentiation into various neuronal types. This promotes neuron survival, restores learning and memory, and enhances synaptic plasticity (Marsh and Blurton-Jones, 2017). Moreover, NSCs secrete brain-derived neurotrophic factor (BDNF), which mitigates cognitive deficits and boosts cell viability and synaptic density in the hippocampus (Blurton-Jones et al., 2009; Wu et al., 2016; Zhang, 2020). This secretion of neurotrophic factors by NSCs is a promising therapeutic strategy for AD, enhancing cognitive performance. Additionally, NSCs overexpress neprilysin, an Aβ degrading enzyme (Blurton-Jones et al., 2014; Devi, 2015), and induce anti-inflammatory effects to reduce neuronal damage (Zhang et al., 2016).

Given these mechanisms by which NSCs mitigate AD's deteriorating impact, they hold considerable potential for AD therapeutics. Nonetheless, further studies are required to address the remaining challenges. For example, establishing regulatory processes is crucial, as neurotrophin production or non-neuronal glia transdifferentiation by the NSCs could harm the brain (Marsh, 2017; Qin et al., 2022). Furthermore, like the other stem cell types, issues such as immune rejections and rodent-to-human translation must be addressed. If these challenges are addressed through research, NSCs could offer new therapeutics for AD.

Mesenchymal stem cells

MSCs have been widely used for studying AD treatment. They are isolated from various body sites, with the primary sources being bone marrow (BM-MSCs), adipose tissue (AD-MSCs), and umbilical cord blood (UCB-MSCs), due to their accessibility (Guo et al., 2020). MSCs are multipotent stem cells that can differentiate into neuronal cells *in vitro*, primarily exerting therapeutic effects through their secretory properties (Kaminska et al., 2022). MSCs bypass the blood-brain barrier and target damaged regions, suggesting their potential effectiveness in treatment (Conaty et al., 2018). Their primary therapeutic effects are outlined below.

Neurogenesis

MSCs promote neurogenesis in the hippocampus and neuronal maturation by enhancing the Wnt signaling pathway (Oh et al., 2015; Hayat, 2022). Supporting this, Doshmanziari et al. showed that transplanting hUCB- and hAD-MSCs significantly reduces neuronal cell apoptosis in the hippocampus of AD-induced mouse models, thereby facilitating neurogenesis and synaptic enhancement (Doshmanziari et al., 2021). Therefore, these results suggest that MSC transplantation could mitigate cognitive impairments associated with AD.

Aβ plaque reduction

Alternatively, MSC transplantation alleviates AD pathology by reducing Aβ deposits and tau-phosphorylation. Matchynski-Franks et al. reported that transplanting BM- and hUCB-MSCs into the lateral ventricles or/and hippocampi of AD-induced 5xFAD mouse models enhanced cognitive skills such as memory and learning by reducing Aβ deposits (Matchynski-Franks et al., 2016). Ceccariglia et al. similarly found that MSCs can modulate autophagy, leading to considerable Aβ aggregate degradation (Ceccariglia et al., 2020).

Immunomodulation

The immune system of the human central nervous system primarily consists of glial cells (Gilhus and Deuschl, 2019), which can induce neuroinflammation to protect the body (Lyman et al., 2014); however, excessive and prolonged inflammation can exacerbate brain damage (Zhang et al., 2020). Neuroinflammation induces apoptosis of the brain cells, thereby contributing to AD onset (Jain et al., 2020). In healthy individuals, a balance between anti- and pro-inflammation is maintained through neuroinflammation homeostasis, which is disrupted in patients with AD. A proposed solution is to alleviate neuroinflammation by inhibiting glial cells and modulating immune responses to minimize damage. Boza-Serrano et al. showed that removing the Gal3 gene, which induces pro-inflammatory microglial activation, from an AD-induced 5xFAD mouse model reduced Aβ aggregates and improved cognitive skills (Boza-Serrano et al., 2019). Similarly, Yang et al. transplanted UBC-MSCs into transgenic mice overexpressing APP to increase the population of regulatory T-cells. T-cells helped maintain neuroinflammation homeostasis by secreting anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor (TGF-β1) while suppressing pro-inflammatory cytokines like interferon-γ (Zhang et al., 2020; Song, 2020; Yang, 2013).

Trophic factor production

MSCs produce and overexpress numerous trophic factors that promote neurogenesis, synaptogenesis, astrogliosis, and cell survival (Lykhmus et al., 2019). When hUBC-MSC-derived cholinergic-like neurons overexpressing BDNF were transplanted into an AD-

induced mouse model, improvements were observed in spatial learning and memory, increased acetylcholine release, glial cell functions, and reduced neuronal apoptosis (Hu et al., 2019). These findings highlight the importance of BDNF and other neurotrophic factors produced by MSCs, confirming their potential as a therapeutic strategy for AD.

Exosomes

Exosomes are being studied as alternative cell-free therapies due to their non-tumorigenic nature and ability to cross the blood-brain barrier. Studies have shown that exosomes contain large amounts of neprilysin, an enzyme that breaks down the Aβ peptide. A related study showed that exosomes from BM-MSCs reduce brain Aβ levels by upregulating anti-inflammatory cytokines (IL-4 and IL-10) and downregulating proinflammatory cytokines (TNF-α and IL-1β). These findings highlight the diverse ways in which exosomes interact with the brain and function as treatments for AD (Yin et al., 2019; Wang, 2023).

Nevertheless, the applications are primarily in the pre-clinical stage due to unresolved challenges. One major obstacle is the short-term viability of injected cells, as MSCs are short-lived. Additionally, as MSCs as therapeutic agents are relatively new, established standards for research in this field are absent. Achieving optimal results requires standardization of various aspects, including the optimal route for stem cell administration, source of MSCs, and amount of stem cells used. Like other cell types, MSCs are multipotent and can be tumorigenic. Although MSCs directly affect synaptic function and neuronal activity via neurogenesis and AD pathology attenuation, the greater potential may lie in cell-free approaches that utilize secreted factors and exosomes. These cell-free approaches can indirectly alleviate AD-related pathology while avoiding issues like tumorigenicity, ethical concerns, and stem cell administration through the blood-brain barrier. However, current assessments are limited to a few *in vitro* studies or animal models; therefore, a more comprehensive understanding is needed (Li et al., 2021b). Given the promising potential of MSCs, extensive research is crucial for developing MSC-derived therapies for AD.

Current advances in AD research using induced pluripotent stem cells: Unveiling new frontiers in stem cell therapy

In recent decades, researchers have increasingly used stem cell technologies to explore the complexities of AD. Initially, they explored ESCs, NSCs, and MSCs as stem cell sources; however, they encountered various limitations that hindered advancements. A significant challenge is the lack of physiologically appropriate *in vitro* models that accurately represent the cell and organ types of interest (Arber et al., 2017). Much of the research has relied on rodent models, which often fail to effectively translate to human applications. Additional hurdles, such as ethical debates, limited supply, and immune rejections, have prompted the exploration of alternative resources (Zakrzewski et al., 2019). Consequently, stem cell technologies are evolving with the introduction of novel iPSC technology. iPSCs can limitlessly differentiate into two-dimensional (2D) and 3D neuronal cells that closely resemble the human brain, thereby overcoming previous limitations. Their capacity enables diverse applications that surpass conventional methods, increasingly allowing researchers to uncover disease mechanisms and test novel therapeutics in a more human-relevant model (Poetsch et al., 2022). Therefore, iPSC technology holds promise for advancing future stem cell research, particularly in developing treatments for AD.

Direct reprogramming and differentiation of autologous cells

In 2007, Takahashi et al. first successfully generated iPSCs from human somatic cells isolated from dermal fibroblasts (Takahashi et al., 2007). Since then, the derivation of iPSCs has been widely used to develop new models of human diseases and novel therapeutics. Generally, human somatic cells are procured from patients, typically from blood, skin fibroblasts, or urine, due to their noninvasive and highly applicable nature (Poetsch et al., 2022). Selecting the appropriate somatic cell source is crucial as it substantially influences reprogramming efficiency, kinetics, and quality of the iPSC products (Ray et al., 2021). After collection, somatic cells are isolated and reprogrammed into a pluripotent state by overexpressing OSKM factors (OCT3/4, SOX2, KLF4, and C-MYC) (Baliña-Sánchez et al., 2023). Pluripotent cells can differentiate into any cell type, making them suitable for personalized therapies for various diseases. The ability to generate patient- and disease-specific iPSCs has substantially impacted regenerative medicine, disease modeling, and drug screening/discovery.

Regenerative cell therapy

One application of iPSCs is regenerative cell therapy, which aims to restore cellular function by replacing dysfunctional cells with healthy ones. This approach involves two main strategies: cell transplantation and a cell-free paracrine approach. In cell transplantation, iPSCs are differentiated into specific cell types and transplanted into the patient's brain to enhance synaptic and neuronal functions (Fujiwara et al., 2013). This method is autologous, reducing the risk of immune rejection. Alternatively, extracellular vesicles of iPSCs can be applied (Taheri et al., 2019). During cell culture, cells release extracellular vesicles like exosomes into the media. These bioactive molecules can be delivered to the brain with the cell culture media, leveraging their anti-inflammatory, immunomodulatory effects, and tissue

regeneration properties, similar to those of other stem cell types. This approach is more efficient and manageable than cell transplantation, as these molecules are highly stable and carry no risk of aneuploidy or tumorigenicity (Basu, 2016; Paik et al., 2020). Given these advantages, numerous studies have applied regenerative cell therapy to develop AD treatments (Table 1).

Disease modeling

The *in vitro* use of iPSCs also offers an effective method for investigating AD pathology through realistic, human-relevant disease modeling. Previously, studies relied on animal models or 2D cultured cells, which failed to replicate the complex 3D body systems or the adult cell phenotype, limiting disease understanding (Liu et al., 2018). Disease progression occurs at the multicellular level, making 3D models that closely mimic the brain necessary for a comprehensive understanding of their interactions and subsequent effects (Penney et al., 2020).

To date, three types of 3D modeling systems have been established: engineered scaffolds, organoids, and organ-on-a-chip (OOC) (Liu et al., 2018). Engineered scaffolds are made from materials like hydrogels, decellularized extracellular matrix (ECM) extracts, and synthetic polymers that mimic the human ECM (Varzideh, 2022; Rouleau et al., 2023). The attributes of engineered scaffolds, such as porosity and interconnectivity, depend on their composition, necessitating careful material selection to achieve the desired properties of the final product (Varzideh, 2022; Lomoio, 2023; Rouleau et al., 2023). The resultant tissue product closely resembles human tissue, making it an effective source for disease modeling. Organoids are 3D cell aggregates that replicate the organ structure and functionality. They are promising for disease modeling as they can overcome challenges associated with animal testing and organ scarcity for research. Organoids exhibit longevity and self-organization, maintaining their original phenotypes and genotypes over time (Xu et al., 2023). Organoids are invaluable for understanding disease mechanisms, organ function, and cellular interactions, making previously impractical *in vitro* tests feasible and facilitating real-time monitoring. Additionally, OOC is a microfluidic system that allows direct control over various device parameters, such as media concentration gradient, fluid shear stress, nutrient supply, and waste removal (Palasantzas et al., 2023). These controllable factors enable OOCs to simulate diverse body environments, accurately replicating specific organ features and dynamics. Compared with other 3D models, OOCs closely mimic *in vivo* conditions, providing a system for conducting *in vitro* experiments that reflect *in vivo* scenarios.

With their ability to replicate human organ architecture and functionality, 3D models are poised to replace several animal models in the near future. When using iPSC-derived brain models to study AD, 3D modeling systems offer better insights than 2D systems, providing a more comprehensive understanding of AD pathology by facilitating cortical organization, regional specification, cellular interactions, and neuronal migration (Rowe and Daley, 2019). Nevertheless, iPSC-derived models cannot completely replace animal models as, while 3D modeling resembles organ structure, it does not fully replicate all cell types and functions. However, as research progresses, integrating 3D modeling with animal testing can help overcome limitations and advance our understanding and treatment of AD (Palasantzas et al., 2023).

Drug screening

iPSC disease modeling enhances the understanding of disease pathology and improves the efficiency of drug discovery systems. Compared with animal models, iPSC-derived human models offer an accurate organ representation, enhancing translational outcomes when evaluating newly designed drugs (Liu et al., 2018). Several studies have used iPSCs for drug screening to develop treatments for AD (Table 1). Nevertheless, establishing a standardized protocol for organ modeling is urgently required to address major challenges like organ reproducibility, scalability, maturity, and heterogeneity (Costamagna et al., 2021).

iPSC technology has diverse applications, including regenerative cell therapy, disease modeling, and drug development. iPSC technology offers a novel avenue for studying AD and developing new therapeutics by promoting neurogenesis and creating patient-specific platforms that resemble human organs.

Future perspectives in iPSC research for AD: Overcoming challenges and exploring new avenues

With its diverse applications, advancing iPSC technology presents a compelling strategy to combat AD (Singh et al., 2015). However, despite the ground-breaking preclinical results observed in several previous studies, numerous challenges remain that hinder the successful clinical application of this technology.

One such challenge is verifying the safety of iPSC technology, as iPSCs are tumorigenic and may differentiate into undesired cell lineages or develop tumors *in vivo* (Wu et al., 2018). The main factors driving this transformation include incomplete iPSC differentiation, active iPSC reprogramming, and genetic mutations (Wuputra et al., 2020; Yamanaka, 2020).

Several strategies have been developed to mitigate this risk. One attempt involves avoiding the use of tumor-related transcription factors during reprogramming. For instance, efforts have been made to reprogram cells without using c-Myc, a transcription factor closely linked to tumorigenicity. Moreover, the use of doxorubicin has been proposed to selectively induce apoptosis in undifferentiated cells (Chour et al.,

Table 1. Summary of the recent studies that use induced pluripotent stem cells (iPSCs) for Alzheimer's disease (AD) research.

Approach	Source	Cell type	Model	Results	Reference
Cell transplantation	Mouse tail-tip fibroblasts	iPSC-derived neural precursorsStereotaxic surgery (hippocampus)	Transgenic 3xTg-AD mice	Improved memory and synaptic plasticity Reduced AD pathology: reduced amyloid deposits amyloid deposits	Armijo et al., 2021
	Mouse skin fibroblasts	Protein iPSC-derived glial cells Stereotaxic surgery (bilateral injections/ subiculum)	Transgenic 5xFAD mice	Mitigation of cognitive dysfunction (memory impairment) Upregulation of oligodendrocyte-related genes Decrease in Aβ plaque depositions	Cha et al., 2017
Cell-free approach	Cord blood cells	iPSC-derived cortical neuron stem cell secretome Nasal cavity (5 µg/g, once a week, 4 weeks)	Transgenic 5xFAD mice	Increased neuronal proliferation and dendritic structure formation Memory restoration and reduced Aβ plaque aggregation Enhanced electrical network activity of the neurons	Mo et al., 2023
	Human iPSCs (Stem Cell Bank)	iPSC- neural progenitor cells–derived exosomes	*in vitro* oxygen-glucose deprived-primary rat cortex neurons	Improved brain-derived neurotrophic factor level Enhanced neuronal survival Overexpression of NF200, synapsin, GAP43, and PSD95 proteins that are crucial for synaptic plasticity	Li et al., 2021
Disease modeling	Human iPSCs of patients with AD		Hippocampal spheroids	Models exhibited AD features, including synaptic protein loss, increased Aβ42 peptide levels and tau phosphorylation	Pomeshchik et al., 2020
	Mouse iPSC and AD mutant genes (amyloid precursor protein (APP) and presenilin genes)		AD cerebral organoids	Models exhibited AD pathological alterations, including reduced neurite length, increase in Aβ and p-Tau levels Substantial increase in the number of GFAP-positive astrocytes and glutamatergic excitatory neurons but a decrease in the number of GABAergic interneurons	Fan et al., 2019
	Triple MAPT-mutant hiPSCs		*In vitro* tauopathy model	Mutant neurons exhibited aggregation of tau, deficiencies in neurite outgrowth and neuronal differentiation, and upregulation of neurodegenerative pathways	García-León et al., 2018
	Peripheral blood from a patient with AD and presenilin-1 mutation		*In vitro* cortical neurons	Models exhibited an increase in the intra/extracellular Aβ and p-Tau levels Impaired axonal transport of the mitochondria was detected AD features such as defective autophagy were identified	2020 alzheimer's disease facts and figures, 2020
	iPSCs of a patient with AD		Neurons derived from the iPSCs of patients with AD	Cholesterol esters are the upstream regulators of Tau during the early period of AD CE regulates Aβ and p-Tau through various pathways	van der Kant et al., 2019
	hiPSCs		three-dimensional cerebral organoid	Mutations in presenilin-1 in patients with familial AD induce premature neurogenesis, accelerating neurodegeneration	Arber et al., 2021
	hiPSC-derived neural stem cells		Neuron-astrocyte coculture model, iPSC-derived microglia culture	Models reveal signs of Aβ plaques, dystrophic neurite formation, axon fragmentation, neuronal cell death, and synapse loss	Bassil et al., 2021
	hiPSC-derived neural progenitor cells, genetically engineered ReNcell VM human neural stem cells		Neurospheroids	Models exhibited Aβ and phosphorylated tau accumulation	Jorfi et al., 2018
	CRISPR/Cas 9 gene editing of the APOE3 cells derived from an unaffected participant		iPSC-derived organoids, iPSC-derived neural and glial cells	Deduced APO4 impairs astrocyte- and microglia-mediated Aß clearance Potential therapeutic applications include targeting glia-mediated Aβ clearance and lipid biogenesis	Jackson et al., 2022

2021). Additionally, chemically induced reprogramming has been introduced (Zhong et al., 2022). Traditionally, karyotyping has been used to detect the genetic abnormalities caused by mutations; however, this method cannot detect single-nucleotide variations (Ito et al., 2019). Recent advances in next-generation sequencing technologies have improved the accuracy of detecting small genetic mutations.

Another challenge is ensuring the consistency and reproducibility of research using iPSCs (Hayashi et al., 2019). iPSCs are often heterogeneous, producing cells with varying attributes, such as maturation properties and epigenetic states. Consequently, experiments using identical cell lines may yield inconsistent results across trials. This lack of reproducibility hampers technological progress in the field (Hayashi et al., 2019).

A fundamental challenge is addressing the lack of standards and regulations in iPSC research. Establishing standardized protocols as standard operating procedures for all iPSC applications is crucial to overcoming this obstacle (Pandey et al., 2022). Once regulations for iPSC-based research are established, it will be possible to resolve issues like tumorigenicity risk, cell production and delivery optimizations, and immune rejection, thus enabling the clinical use of iPSCs. Furthermore, strict guidelines on the preferred iPSC lines and cell culture methods for various clinical uses are essential due to the variability in outcomes among different cell lineages. Subsequently, rigorous quality control measures should be implemented to assess iPSC quality before clinical use. This approach enhances research reproducibility, thereby minimizing disparities and ambiguities in outcomes.

Alternatively, emerging technologies like Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)/Cas9 and transcription activator-like effector nuclease provide precise genetic control, facilitating the genetic engineering of iPSCs (Gaj et al., 2016). This enables the optimal design of cells for disease modeling or transplantation purposes. If these challenges are successfully addressed, iPSC technology could be widely used to treat incurable diseases in the near future.

Conclusion

The iPSC technology represents a transformative strategy for addressing AD, which is a global health crisis. By generating patient-specific cells and

Table 1. (Continued).

Approach	Source	Cell type	Model	Results	Reference
Drug screening	Peripheral blood from a patient with AD and presenilin-1 mutation	Cortical neurons	*In vitro* cell culture *Treated with* LY-2886721 (β-site APP cleaving enzyme 1 (BACE1) inhibitor)	A substantial decrease in the Aβ42/ Aβ40 ratio and p-Tau level was detected No significant improvement was observed related to the mitochondria and autophagy dysfunction	2020 alzheimer's disease facts and figures, 2020
	hiPSCs	Cholinergic neurons treated with Aβ1–42	*In vitro* cell culture *Treated with* natural antioxidant Thymoquinone (TQ)	TQ treatment alleviated the synaptic toxicity and apoptosis caused by Aβ TQ treatment exhibited the inhibition of reactive oxygen species and restoration of the decrease in the levels of intracellular antioxidant enzyme glutathione	Alhibshi et al., 2019
	Fibroblasts of patients with AD	iPSC-derived neurons	*In vitro* cell culture, C57Bl/6J mice *Treated with* BACEi, GSM, GSI	GSM has the potential as an effective AD treatment All three compounds reduced Aβ production in varying ways Comparable results were obtained *in vitro* and *in vivo*	Cusulin et al., 2019
	hiPSC-derived neural stem cells	Neuron-astrocyte, iPSC-derived microglia	Neuron-astrocyte co-culture model, iPSC-derived microglia culture *Treated with* anti-Aβ antibodies	Deduced the mechanism of anti-Aβ antibody protection and neuroprotection	Bassil et al., 2021
	Patients with APP mutation (D678H)	hiPSC-derived neurons	AD-iPSCs model *Treated with* NC009-1	Demonstrated Aβ42 and Aβ40 accumulation, impaired neurite outgrowth, increased caspase 1 activity, and synaptophysin downregulation Treatment exhibited normalized Aβ level and tau phosphorylation, reduced caspase 1 activity, and enhanced neurite outgrowth of the model	Chang et al., 2021

developing advanced 3D modeling systems, such as engineered scaffolds, organoids, and OOC, iPSCs enhance cell regeneration therapy, disease modeling, and drug screening. This offers great potential for deepening our understanding of AD pathology and discovering effective treatments. Nevertheless, substantial challenges remain such as controlling tumorigenicity, establishing standardized protocols and regulations, and ensuring research reproducibility. Encouragingly, advancements in genetic engineering techniques like CRISPR/Cas9 offer potential solutions to these challenges. As research progresses and these challenges are addressed, iPSCs hold considerable potential for advancing personalized medicine for AD.

Ethics approval and consent to participate. Not applicable

Consent for publication. Not applicable

Availability of data and material. All data generated or analyzed during this study are included in this published article.

Competing interests. The authors declare that they have no competing interests.

Funding. This research was supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI22C1314). This work was supported by grants from the Basic Science Research Program through the National Research Foundation of Korea, funded by the Ministry of Science, ICT, and Future Planning (NRF-2021R1C1C2004688).

Author contributions. JJP designed the study and wrote the manuscript. YAR, YS, and YN edited the manuscript. YN and JHJ approved the final manuscript. All the authors have read and approved the final draft of this manuscript.

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Accepted May 21, 2024