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Stem Cell Engineering in Alzheimer's Disease

Jiya Doshi
jiyahdoshi@gmail.com
Prabhavati Padamshi Soni International Junior College, Mumbai, Maharashtra

ABSTRACT

Alzheimer's disease (AD) is a devastating neurodegenerative disorder marked by cognitive decline, neuronal loss, and the accumulation of amyloid plaques and tau tangles. Despite decades of research, effective treatments remain limited, primarily addressing symptoms without halting disease progression. Stem cell engineering offers a novel therapeutic approach with the potential to repair damaged neurons, modulate the immune response, and clear toxic protein aggregates. This review explores advances in the use of stem cells for developing disease-modifying treatments for AD. In this paper, the challenges and barriers to stem cell engineering for AD have been discussed despite the encouraging results from the preclinical and early clinical studies. With continued research and refinement, stem cell engineering holds significant promise for transforming AD treatment. However, further studies are needed to optimize delivery methods, mitigate risks, and fully unlock the potential of this innovative approach. The future of Alzheimer's therapy may lie not only in managing symptoms but also in repairing the brain itself through advanced stem cell technologies.

Keywords: *Stem Cell Engineering, Alzheimer's Disease, Amyloid Plaque, Tau Tangles*

INTRODUCTION

Research in stem cell engineering has shown great potential in the field of neurodegenerative diseases. Alzheimer's disease, the most common form of dementia, is marked by the progressive degeneration of brain cells leading to memory loss and cognitive decline.
The current treatments for Alzheimer's only provide symptomatic relief and fail to address the root cause of the disease. Stem cell engineering offers a promising avenue for developing novel therapies by utilizing the regenerative capacity of stem cells to replace damaged or lost neurons in the brain. This approach holds the potential to not only halt the progression of Alzheimer's disease but also reverse the damage that has already occurred.
But before I talk about stem cells, what exactly is Alzheimer's?
Well, Alzheimer's disease is a neurodegenerative disorder characterized by the formation of plaques and tangles in the brain, leading to memory loss, language difficulties, and progressive disorientation.
These 'plaques' that I talk of are deposits of a protein fragment called beta-amyloid that build up in the spaces between nerve cells. Tangles are twisted fibers of another protein called tau that build up inside cells. [2]

THE DEVELOPMENT OF ALZHEIMER'S IS DUE TO GENETIC OR ENVIRONMENTAL REASONS.

Background

Recent advancements in the understanding of Alzheimer's disease have shed light on the complex mechanisms underlying this devastating condition. Alzheimer's disease is a neurodegenerative disorder characterized by the accumulation of amyloid-beta plaques and neurofibrillary tangles in the brain, leading to progressive cognitive decline and memory loss. An amyloid-beta plaque is when amyloid-beta, a peptide, is extracellularly deposited in the brain. Neurons and oligodendrocytes together produce and secrete this peptide, causing the plaque spoken about. The neurofibrillary tangles, on the other hand, are intracellular in nature. It is caused by the hyperphosphorylation of the tau protein causing it to take over a very insoluble form.
While the exact cause of Alzheimer's disease remains unknown, researchers have identified genetic, environmental, and lifestyle factors that may increase the risk of developing the condition. Studies have shown that individuals with a family history of Alzheimer's disease, as well as those with certain genetic mutations, are at a higher risk of developing the condition. Additionally, factors such as high blood pressure, diabetes, obesity, and smoking have been linked to an increased risk of Alzheimer's disease. As the global population ages, the prevalence of Alzheimer's disease is expected to rise, making it a significant public health challenge [1].

Importance of Finding a Cure

The urgent need to discover a remedy, for Alzheimers disease is a concern in healthcare today. This degenerative neurological condition not only affects those diagnosed but also places social and financial strains on families and caregivers of those affected. With the population aging the prevalence of Alzheimer's is expected to increase, underscoring the critical nature of finding a cure.

Stem cell engineering has emerged as an approach to developing therapies that could potentially slow down or even reverse the progression of Alzheimer's disease.

Researchers are optimistic about utilizing the properties of stem cells to target the root causes of the condition and create treatments. The significance of uncovering a cure for Alzheimer's cannot be emphasized enough as it holds the promise of enhancing the quality of life for millions around the globe.

STEM CELL THERAPY

Overview Of Stem Cell Engineering

Recent advancements in stem cell engineering have revolutionized the field of regenerative medicine, offering promising solutions to devastating neurodegenerative disorders like Alzheimer's disease.

Through the utilization of innovative technologies such as microfluidic devices, researchers have been able to efficiently sort neural stem cell populations, providing a deeper understanding of their behavior and differentiation mechanisms. This breakthrough in stem cell sorting not only facilitates comprehensive studies of neural stem cells but also paves the way for the development of targeted therapies.

The Human Genome Project has further catalyzed progress in stem cell research by unraveling the genetic aspects influencing cell behavior and function, enhancing the precision of interventions. By combining the insights gained from genetic research with the advancements in stem cell engineering, a synergistic approach emerges, holding tremendous potential for unlocking treatments and ultimately combating complex neurological diseases.

Mechanisms Of Stem Cell Therapy

A. Neurogenesis

Stem cells can differentiate into neuronal and glial cell types, potentially replacing lost neurons and restoring synaptic connections.

In simple terms, Neurogenesis is the formation of new neurons in the brain, particularly in the hippocampus, a region in the brain associated with memory and spatial processing. However, the number of neurons generated throughout your lifespan is limited.

What regulates this neurogenesis?

Growth factors, neurotrophins, cytokines, and hormones are the major intrinsic regulators of adult neurogenesis; extrinsic regulators include lifestyle, environmental, and pharmaceutical factors. [3]

Stem cell neurogenesis progresses through three phases: neural induction, patterning, and terminal differentiation. In 2D cultures, dual SMAD inhibition has been widely adopted to enhance neural fate choice and closely mimic signalling conditions in the early embryo. (Arber et al., 2017)

The earliest step in neurogenesis (and gliogenesis) begins with the specification of neural progenitors, followed by proliferative cell divisions that amplify the progenitor pool, cell fate specification and determination, exit from the cell cycle, and finally terminal differentiation. Each of these steps is precisely orchestrated to generate multiple cell-types that ultimately will populate the mature central nervous system (CNS). ("The Zebrafish: Cellular and Developmental Biology, Part A," 2010) [8]

Neuronal Replacement

Loss of neurons is at the core of cognitive and functional failures in various neurological conditions spanning from acute injuries, such as traumatic brain injury and stroke, to a multitude of neurodegenerative diseases, such as Alzheimer disease, Huntington disease, and Parkinson disease (PD). Pioneering transplantation approaches in patients with PD showed an amelioration of symptoms by ectopic transplants of dopaminergic neurons into the basal ganglia, the target region of the lost neurons in the substantia nigra pars compacta (SNpc). The target site of SNpc dopaminergic neurons (i.e. basal ganglia) was chosen owing to the uncertainty that axons of transplanted neurons would have grown properly in an adult brain. Now we know that young neurons can readily extend axons in an adult brain and even find their correct target regions— a crucial and promising prerequisite for achieving adequate functional repair of neural network activity. This and the knowledge gained in the last decades on transplanted neuron differentiation and integration in adult brains set the stage toward successful neuronal replacement therapies, by replacing the lost neuronal subtypes at their appropriate sites. This would encompass not only the generation of the exact lost neuronal subtype (either from exogenous or endogenous sources) but also the appropriate integration into the pre-existing network, including correct input and output connectivity. (Götz & Bocchi, 2021) [9]

Neuroprotection

Stem cells secrete neurotrophic factors that support neuron survival, reduce apoptosis, and promote endogenous repair mechanisms.

By definition, neuroprotection is an effect that may result in salvage, recovery or regeneration of the nervous system, its cells, structure and function.[1] It is thought that there are many neurochemical modulators of nervous system damage. In epilepsy, excessive glutamate-mediated neurotransmission, impaired voltage sensitive sodium and calcium channel functioning, impaired GABA-mediated inhibition and alterations in acid base balance, when set in motion, may trigger a cascade of events leading to neuronal damage and cell death. Acute and chronic nervous system damage in response to an insult may lead to acute or delayed neuronal death, apoptotic cell death, neuronal degeneration, injury and loss, and gliosis. Cell death in the CNS following injury can occur in the manner of apoptosis, necrosis or hybrid forms.[2] In general, NMDA receptor and non-NMDA receptor mediated excitotoxic injury results in *neurodegeneration* along an apoptosis-necrosis continuum. The effects of neuronal injury depend on factors including the degree of brain maturity or site of the lesion. [10]

Immunomodulation

Immunomodulation is the process of modifying an immune response in a positive or negative manner by administration of a drug or compound. [11]

Immunomodulation encompasses all therapeutic interventions aimed at modifying the immune response.

Augmentation of the immune response is desirable to prevent infection in states of immunodeficiency, to fight established infections and to fight cancer.
In immunodeficiencies, treatment of the cause is most important (e.g., malnutrition, HIV).
Specific immune defects can seldom be corrected, and the establishment of a new immune system by allogeneic stem cell transplantation should be considered. [12]

Reduction Of Amyloid And Tau Pathology
Stem cells may influence the processing and clearance of Aβ and tau proteins, potentially mitigating the formation of plaques and tangles.
In a recent study, facts related to the amyloid hypothesis is observed. By generating human neural stem cell lines carrying multiple mutations in APP together with PS1, high levels of pathogenic Aβ42 comparable to those in brains of AD patients were achieved. [13][14]

RESEARCH PROGRESS IN THE PATHOGENESIS OF ALZHEIMER'S
Genetics Of Ad Pathogenesis
Research indicates that two common misfolded proteins accumulate in the brains of Alzheimer's Disease (AD) patients:
Amyloid-beta (Aβ) is a pathological cleavage product of the amyloid precursor protein (APP). The build-up of Aβ into plaques and smaller oligomers is a key pathological feature of AD. Mutations in APP are linked to hereditary familial AD, an early-onset autosomal dominant genetic disorder with onset typically before 65 years of age, though it constitutes only 2% of all AD cases. Many clinical trials targeting this pathway, either directly or indirectly through small-molecule or antibody therapies, aimed to reduce Aβ production or enhance its clearance, have been unsuccessful.

Tau Protein, a microtubule-associated protein that forms neurofibrillary tangles within cells, closely related to cognitive decline in AD. However, over 98% of AD cases are sporadic, with onset generally after 65 years, and do not involve mutations in APP processing pathways. For these cases, age and the genetic risk factor apolipoprotein (APO) E4 are the main predictors of AD. APOE4 carriers represent 60%–75% of AD cases and tend to develop the disease at a younger age compared to non-carriers. [5]

Tau Protein and Ad Pathogenesis
In Alzheimer's Disease (AD) neurons, there is an imbalance in the protein kinase/protein phosphatase system, leading to abnormal and hyperphosphorylated tau protein. The human tau protein is encoded by a single gene on chromosome 17, consisting of 16 exons. This gene expresses six isoforms in the brain, featuring amino acid sequences at both the carboxyl and amino ends, with the carboxyl end containing a repeated microtubule-binding region.
Tau protein stabilizes microtubules in axons. Mitogen-activated protein kinases, including extracellular signal-related kinases activated by various stimuli such as growth factors, c-Jun N-terminal kinases, and p38 mitogen-activated protein kinases, phosphorylate neuronal tau protein and are closely linked to AD progression.
In AD, tau protein becomes over phosphorylated and accumulates inside cells as double-helix filaments, straight filaments, and tangled structures, correlating with dementia severity. Abnormal tau protein is also found in hereditary Parkinson-like frontotemporal dementia associated with chromosome 17, contributing to neurodegenerative diseases and dementia.
Measuring levels of hyperphosphorylated tau protein in the cerebrospinal fluid can be done through its composition. Reduced activity of phosphatases, particularly protein phosphatase-2A, plays a significant role in the abnormal hyperphosphorylation of tau. PET brain imaging shows that tau protein accumulation more accurately predicts future neurodegenerative changes in AD patients.
The progression of tau pathology and regional brain atrophy may indicate different phases of the disease, with local increases in tau levels preceding atrophy. Consequently, tau is a potential target for early AD clinical treatment.

β-amyloid protein and ad pathogenesis
The Aβ is an important hypothesis for the pathogenesis of AD. The relationship between APP and Aβ explains the pathogenesis of the lesion. APP is first cleaved at beta-secretase (BACE) by β-secretase to produce soluble amylase precursor protein and released outside the cell. Then, C99 remaining in the cell is cleaved by γ-secretase to produce Aβ polypeptide and APP intracellular domain. Aβ peptides, mainly Aβ1–40 and Aβ1–42, are released outside the cell, while APP intracellular domain remains inside the cell.

The accumulation of the toxic Aβ in the brain can cause damage or death, because it causes senile plaques in cells. Aβ1-40 in the brain has the highest content of Aβ, but Aβ1-42 is more likely to form fibers and oligomers. It is the highly toxic Aβ1-42 oligomers that are an important cause of AD.

The accumulation of Aβ in the brain and subsequent plaque formation are pathological features of AD. The impaired ability of the central nervous system to export Aβ to the periphery through the barrier is considered to be the cause of Aβ accumulation in AD and eventual plaque formation. [5]

According to previous studies, with age and the development of AD, the expression levels of the blood-brain barrier endothelial receptors change. It is the expression level of the efflux receptors that decrease, and that of the influx receptors increase. These changes and dysfunctions is the root cause of the accumulation of Aβ.

The revolutionary discovery of stem cells has cast a new hope for the development of disease-modifying treatments for AD, in terms of their potency in the replenishment of lost cells *via* differentiating towards specific lineages, stimulating *in situ* neurogenesis, and delivering the therapeutic agents to the brain. Indeed, researchers have effectively treated AD in transgenic mouse models in more than 50 different ways [6]

A recently completed open-label phase I clinical trial evaluated the safety and tolerability of intracranially injected allogeneic human umbilical cord blood-derived mesenchymal stem cells (MSCs) (Trial identifier: NCT01297218, NCT01696591) [7]
Alternatively, due to the complex nature of AD pathophysiology, a multimodal approach may be required, incorporating pharmacological targeting of pathology, stimulation of endogenous neurogenesis and synaptogenesis, as well as exogenous neuroreplacement. [5]
Endogenous And Exogenous Repair
Stem cell therapies for Alzheimer's disease (AD) focus on two primary strategies: endogenous and exogenous repair. Each approach aims to harness the regenerative potential of stem cells to mitigate the effects of AD, but they differ in methodology and mechanisms.

Endogenous Repair
Endogenous repair involves stimulating the body's own neural stem cells (NSCs) to repair and regenerate damaged brain tissues. This strategy capitalizes on the brain's inherent regenerative capabilities.
Activation of Resident Stem Cells: Endogenous NSCs, primarily located in the subventricular zone (SVZ) and the hippocampus, can be activated to proliferate, differentiate into neurons and glial cells, and integrate into existing neural circuits. This activation can be achieved through pharmacological agents, growth factors, and environmental modifications [19] [24]
Gene Therapy and Small Molecules: Gene therapy can introduce genes encoding neurotrophic factors like brain-derived neurotrophic factor (BDNF) to stimulate NSC proliferation and differentiation. Similarly, small molecules that target signaling pathways such as Wnt, Notch, and Sonic hedgehog can enhance NSC activity [19].
Modulation of the Microenvironment: Creating a supportive environment for NSCs involves reducing inflammation and providing neurotrophic support. This can be achieved through the administration of anti-inflammatory drugs and neuroprotective agents [22].

Exogenous Repair
Exogenous repair involves the transplantation of stem cells derived from external sources into the patient's brain.
Types of Stem Cells
Mesenchymal Stem Cells (MSCs): These cells can differentiate into various neural cell types and secrete neuroprotective factors. MSCs have shown potential in reducing amyloid-beta plaques and improving cognitive functions in AD models. [15]
Induced Pluripotent Stem Cells (iPSCs): iPSCs are reprogrammed from adult cells and can differentiate into neurons. They offer a personalized treatment approach, reducing the risk of immune rejection. iPSC-derived neurons have shown promise in preclinical studies by improving neurological functions and reducing inflammation in AD models [18].
Cell Transplantation: Stem cells are cultured and differentiated into neural cells before being transplanted into the brain. Techniques include direct injection into affected regions like the hippocampus or cortex [25].
Grafting and Integration: The success of exogenous repair depends on the survival, integration, and functional contribution of the transplanted cells to the existing neural network. This often involves addressing the hostile AD brain environment, which includes chronic inflammation and the presence of amyloid-beta plaques [28].
Immune Modulation: To enhance the survival of transplanted cells, immune-modulating therapies are employed to prevent rejection. This is particularly important for non-autologous transplants [20].
Classification Based on Cell Type [Nscs]

Neural stem cells
Neural stem cells (NSCs) are a group of ectodermal progenitor cells, which can differentiate into committed neural sub-types, such as neurons, astrocytes, or oligodendrocytes. [21]

The paracrine effect of NSCs has significant therapeutic potential. In rodent AD models[39] and senile primate brains[40], transplantation of growth factor-secreting NSCs can improve neurogenesis and cognitive function, while transplantation of human NSCs with high expression of choline acetyltransferase can reverse spatial memory and learning deficits in rodent models of alkaline neurotoxicity[41] NSC transplantation may reduce neuroinflammation in AD rodent models through the paracrine release of neuroprotective or immunomodulatory factors and also mediate neuronal differentiation[42]. These cells reduce tau and Aβ expression levels[43], promote neurogenesis and synapse formation[44,45], and reverse cognitive deficits[42,44,45].

However, non-glial cells widely produced from transplanted NSCs are the main limiting factor for neural replacement strategies[46]. Studies on rodent AD models have shown that human NSCs **(**hNSCs) from the embryonic telomere, when transplanted into the lateral ventricle of the brain of mice with AD, can migrate and differentiate into neurons and glial cells in the lateral ventricle. This phenomenon reduces tau phosphorylation and Aβ–42 levels, decreases glial and astrocyte hyperplasia[43], enhances endogenous synapse formation[45], and increases neuronal, synaptic, and nerve fiber density[47], ultimately improving spatial memory in mice with AD.

CURRENT RESEARCH AND TRIALS
Animal Studies
Preclinical research using animal models has demonstrated the potential benefits of MSC-based therapies for neurodegenerative diseases like Alzheimer's Disease (AD). Key studies include:
- Bone Marrow MSCs: A study investigated the effects of bone marrow-derived MSCs in an AD mouse model, showing significant improvements in cognitive function and reduction in amyloid-beta plaques. These MSCs helped in enhancing neuronal survival and reducing neuroinflammation.
- Adipose-Derived MSCs: Research focused on MSCs obtained from adipose tissue demonstrated their potential in alleviating AD symptoms in animal models.

These MSCs were shown to reduce plaque formation and improve memory performance by secreting neuroprotective factors.

- Hypoxic Conditioned MSCs: Another study explored MSCs cultured under hypoxic conditions and found that these cells exhibited increased expression of angiogenic growth factors such as VEGF. These hypoxic-conditioned MSCs showed enhanced ability to migrate and integrate into brain tissue in AD models, improving overall neuroprotection.
Despite these promising preclinical results, challenges remain in translating these findings to human trials due to variability in study outcomes and methodologies

Human Trials
Several clinical trials have been conducted or are ongoing to evaluate MSC therapies in humans, particularly for neurodegenerative diseases. Key trials include:
- Phase I Trials:
- NCT01297218: This trial assessed the safety and tolerability of intracranially injected allogeneic human umbilical cord blood-derived MSCs. It included nine patients with probable AD, divided into low-dose (3×10^6 cells) and high-dose (6×10^6 cells) groups. The MSCs were injected into the hippocampus and precuneus. Follow-ups at 3 months and 24 months showed no serious adverse events, but there was no significant slowing of cognitive decline or changes in AD pathology.
- NCT01696591: This trial, closely related to NCT01297218, also focused on the safety and efficacy of umbilical cord blood-derived MSCs in AD patients. The results corroborated the findings of NCT01297218, highlighting the safety of the procedure but showing no significant clinical benefits in terms of cognitive function or disease progression.
- Ongoing Trials:
- NCT02054208: This trial is evaluating the safety and efficacy of MSCs administered via an intraventricular route using an Ommaya reservoir system. This method aims to improve the delivery of MSCs to the brain.
- NCT02912169: This trial is investigating the use of autologous adipose-derived stromal vascular fraction (SVF) for treating various medical conditions, including musculoskeletal disorders, degenerative diseases, and potentially certain chronic inflammatory conditions.
More Trials can be read on:
https://pubmed.ncbi.nlm.nih.gov/34521461/

https://pubmed.ncbi.nlm.nih.gov/35357079/

https://pubmed.ncbi.nlm.nih.gov/35572351/

https://pubmed.ncbi.nlm.nih.gov/34702870/

https://pubmed.ncbi.nlm.nih.gov/28528185/

https://pubmed.ncbi.nlm.nih.gov/31327120/

https://pubmed.ncbi.nlm.nih.gov/22751169/

https://pubmed.ncbi.nlm.nih.gov/38745011/

https://pubmed.ncbi.nlm.nih.gov/27510902/

https://pubmed.ncbi.nlm.nih.gov/17033629/

https://pubmed.ncbi.nlm.nih.gov/38715140/

CHALLENGES AND LIMITATIONS

Safety and Efficacy: Both approaches must be carefully evaluated for safety and efficacy. Risks include tumor formation, immune rejection, and unintended effects on brain function [27].
Delivery Methods: Efficiently delivering cells or stimulating agents to the brain, particularly across the blood-brain barrier, remains a significant challenge [17].
Disease Environment: The AD brain's chronic inflammation and pathological features pose challenges for both endogenous and exogenous therapies. Modulating this environment is crucial for the success of these therapies. [23]
Long-term Outcomes: The long-term stability and efficacy of both endogenous and exogenous stem cell therapies require extensive clinical trials and research [26]
Current technological barriers in stem cell engineering significantly impede progress in developing effective treatments for Alzheimer's disease. One of the foremost challenges is the limited capacity for self-renewal and differentiation of stem cells, which restricts the potential to generate sufficient quantities of neurons and glial cells needed for therapeutic applications [29]. This limitation complicates efforts to create stable, long-lasting cell lines that could effectively replace damaged cells in the Alzheimer's-affected brain. Furthermore, the heterogeneity of stem cell populations and their derived cell types poses additional challenges; variations in the differentiation potential and functional capabilities of these cells make it difficult to standardize treatments and predict outcomes [29]. As researchers strive to develop tailored therapies, understanding and managing this variability becomes critical.

Additionally, ethical concerns surrounding the use of embryonic stem cells hinder advancements in stem cell-based approaches, as regulatory frameworks often restrict access to these valuable resources, slowing down research efforts and innovation in this field [29]. Collectively, these barriers underscore the need for continued research and technological development to overcome the limitations posed by stem cell engineering in the context of Alzheimer's disease treatment.

Ethical considerations play a pivotal role in shaping the research and application of stem cell therapies for treating Alzheimer's disease. One major ethical dilemma arises from the use of embryonic stem cells, which can lead to moral questions regarding the status of the embryos and the implications of genetic engineering in therapy [30]. While stem cell therapy holds promise due to the unique ability of stem cells to differentiate into various cell types, the ethical concerns surrounding their source often impede progress in clinical applications [31]. Furthermore, the requirement for neurosurgical procedures and immunosuppression not only complicates the treatment process but also raises concerns about patient safety and the potential for adverse effects [5]. Although advancements in induced pluripotent stem cells (iPSCs), neural stem cells (NSCs), and mesenchymal stem cells (MSCs) have shown potential, the ethical issues related to these technologies remain significant barriers to their widespread use [32][33]. Additionally, ongoing challenges related to low differentiation efficiency and extended culture times further complicate the ethical landscape, as researchers must balance the urgency of developing effective treatments against the moral implications of their methods and the safety of patients involved in trials [29]. Ultimately, while stem cell therapies present a hopeful avenue for Alzheimer's treatment, the ethical ramifications must be carefully navigated to ensure that research advances responsibly and equitably.

The challenges associated with the differentiation and integration of stem cells within the Alzheimer's-affected brain environment are multifaceted and significant. While certain methods of stem cell transplantation have shown promise in enhancing cognitive function, the intricacies of how these cells differentiate and survive in a compromised environment present critical hurdles to overcome [5]. Notably, the transplantation of embryonic stem cells (ESCs) often leads to the formation of teratomas, underscoring the difficulties in achieving proper differentiation into functional neurons, which raises safety concerns about their use [5]. Furthermore, the outcomes of integrating stem cells into Alzheimer's models can be highly variable; some studies demonstrate success in generating cholinergic neurons, while others report inadequate functional integration of the cells, highlighting the unpredictable nature of this approach [5]. The long-term survival and effective integration of neural stem cells (NSCs) are further complicated by inconsistent results across various studies, indicating that these are critical factors that need to be addressed for successful clinical application [5]. Additionally, the limitations of in vitro cultures, which often lack a representative population of astrocytes, contribute to an imbalance in cell types that may affect neuronal maturity and exacerbate non-cell autonomous disease mechanisms associated with Alzheimer's [4]. A further challenge arises from the gliogenic switch that occurs later in development, leading to a neuronal versus glial bias that complicates the differentiation process and may adversely affect the functional outcome of stem cell therapies [4]. Thus, overcoming these challenges is essential for advancing stem cell therapies as viable treatments for Alzheimer's disease.

FUTURE DIRECTIONS

https://link.springer.com/article/10.1186/s13287-017-0567-5

Preclinical studies suggest that stem cells have potential for the treatment of AD; however, this area is notable for poor translation between animal studies and human trials. Indeed, researchers have effectively treated AD in transgenic mouse models in more than 50 different ways [35]. Transgenic models demonstrate little, if any, predictive utility. Their outcomes are frequently model-dependent and, disappointingly, each approach has failed in human clinical trials. Transgenic models are largely based on familial AD-related hypotheses in a genetically homogeneous population, while the vast majority of human AD occurs sporadically amongst a distinctly heterogeneous population. Moreover, they do not recapitulate the extensive neuronal and synaptic loss that is central to AD. Clearly, rodent models and their aetiological hypotheses are inadequate for predicting human clinical outcomes. AD cell therapies will therefore need to demonstrate success in higher-order animals that more faithfully mimic the clinical and neurodegenerative features of the human condition.

Several key questions also need to be addressed, including long-term safety, optimum cell source and the delivery system, understanding donor cell response to the pathogenic AD environment, and clarifying the mechanisms of action. Many of the studies discussed here utilised inherently heterotopic stem cells. While this is a clinically relevant strategy due to the inaccessible nature of the adult NSC niche, this too requires careful consideration. Human and rodent studies have reported tumour formation resulting from autologous haematopoietic stem cell [36], allogeneic fetal NSC [37], and genetically engineered MSC [38] transplantation. While neuroreplacement therapies may not be able to fully compensate for widespread and progressive neuronal loss, they may serve to temporarily enhance existing depleted circuits, which is sufficient to improve cognition function, restore daily function, and improve quality of life. Upon diagnosis, lifespan for individuals with AD dementia is 4–5 years, and so if a neuroreplacement therapy could rescue and protect brain function for that timespan it is commensurate to a functional cure. Alternatively, due to the complex nature of AD pathophysiology, a multimodal approach may be required, incorporating pharmacological targeting of pathology, stimulation of endogenous neurogenesis and synaptogenesis, as well as exogenous neuroreplacement.

CONCLUSION

Stem cell engineering holds tremendous promise for the treatment of Alzheimer's disease, offering a potential path to not only slow disease progression but also repair the damage that has long been thought irreversible. As we advance in our understanding of neurodegeneration and the mechanisms underlying Alzheimer's, stem cells offer a unique toolset—one that could replace lost neurons, reduce harmful inflammation, and clear toxic proteins like amyloid and tau.

However, this is not without its challenges. While preclinical models and early trials show promise, there is still much work to be done before stem cell-based therapies can become a standard treatment for Alzheimer's. Safety concerns, such as tumor formation and immune rejection, must be carefully managed, and we must continue to refine techniques for guiding stem cells to act precisely and effectively in the human brain.

Despite these hurdles, the progress in this field is undeniable. With each discovery, we move closer to a future where stem cell engineering could provide real hope for millions of people living with Alzheimer's. Continued research, collaboration, and ethical consideration will be key as we push forward.

While we are not there yet, stem cell therapy has the potential to dramatically change the landscape of Alzheimer's treatment, offering not just symptom management but real healing.

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