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A review of neural regeneration therapy for Alzheimer's disease

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Abstract. The process of aging has been associated with the development of several disorders, including neurodegenerative conditions that are characterized by irreversible and incurable degeneration of the nervous system. Alzheimer's disease, a highly widespread neurodegenerative disorder globally, is characterized by a gradual deterioration of brain function, resulting in cerebral atrophy and neuronal demise. Despite the absence of pharmaceutical interventions capable of impeding or decelerating the progression of these conditions, stem cell therapy emerges as a viable therapeutic modality with considerable potential for mitigating the symptoms associated with Alzheimer's disease. The objective of this study is to present a comprehensive analysis of the current state of prospective treatments, trials including stem cell therapy in animal models, the existing clinical status of stem cell therapy in pre-transplant patients, and the advancements made in stem cell technology.

Keywords: stem cell, therapy Alzheimer's disease, neurodegenerative diseases.

1. Introduction

According to a report by Alzheimer's Disease International, the global prevalence of dementia is currently estimated to be over 55 million individuals. Projections indicate that this figure is expected to escalate to approximately 139 million by the year 2050. Furthermore, it is alarming to note that a new case of dementia is detected every three seconds globally, while a significant proportion, up to 75%, of individuals with dementia remain undiagnosed [1]. Alzheimer's disease is distinguished by the presence of Amyloid plaques and Neurofibrillary tangles, as well as the degeneration of neuronal synapses and subsequent neuronal cell death within the brain [2]. The clinical manifestations of Alzheimer's disease encompass various symptoms, including but not limited to memory impairment, motor dysfunction, and cognitive decline. The prevalence of this condition is primarily observed in individuals aged 65 years and older. This condition is characterized by a gradual progression towards a state of vegetative incapacitation, marked by immobility and eventual sacral demise. The comprehensive approach to addressing neuronal mortality caused by protein aggregation involves the restoration of damaged neural tissue and its functionality by the utilization of healthy tissue capable of regeneration [3].

This study utilizes a comprehensive examination of existing literature to present a comprehensive analysis of the current state of prospective treatments, trials conducted on animal models for stem cell therapy, the clinical status of pre-transplant patients undergoing stem cell therapy, and advancements in stem cell technology.

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2. Stem cell therapy and animal testing

Transplantation regeneration pertains to the process by which the adult hippocampus is replenished with new neurons derived from existing stem cells located in the dentate gyrus (DG). Nevertheless, the approach of graft regeneration is more frequently utilized. Embryonic stem cells, neural stem cells, induced pluripotent stem cells, and mesenchymal stem cells represent several categories of stem cells that are employed in therapeutic applications, as seen in Figure 1.

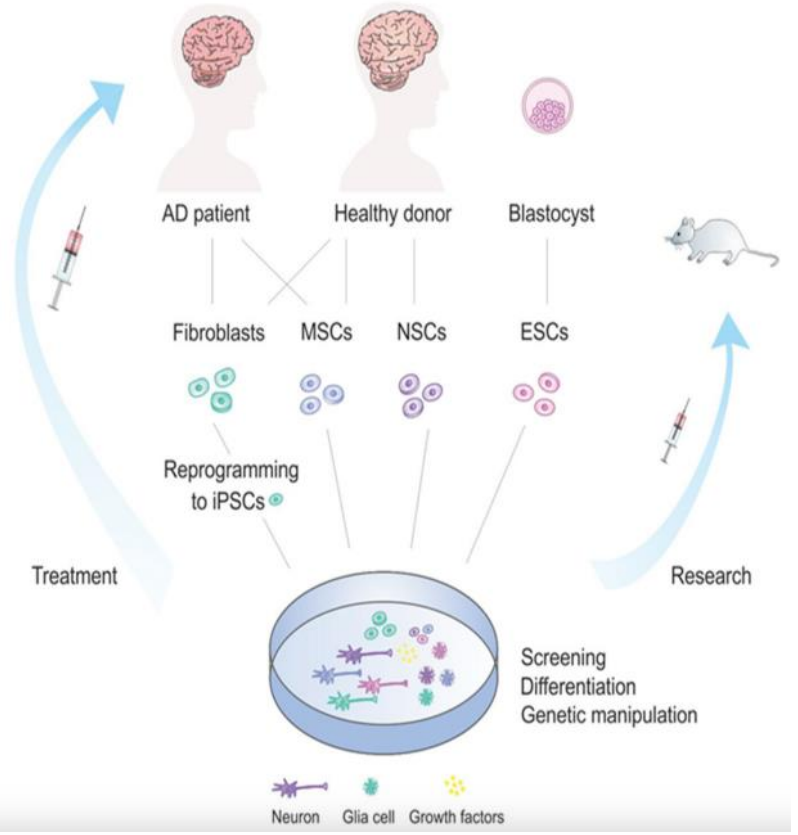

Figure 1. Stem cell treatments for Alzheimer's disease, 2019 [3].

Embryonic stem cells (ESCs) possess significant promise because to their pluripotent nature, enabling the generation of many cell lineages derived from ectoderm, mesoderm, and endoderm. Additionally, ESCs exhibit the remarkable ability to sustain self-renewal indefinitely [4]. Nevertheless, there exist limitations regarding the utilization of embryonic stem cells (ESCs) in scientific investigations, with several nations having implemented prohibitions on their usage. Research has demonstrated that the implantation of embryonic stem cells (ESCs) resulted in the restoration of cognitive function in rats [5]. The primary advantage of embryonic stem cells (ESCs) lies in their pluripotency, however they do present challenges due to their propensity for multidirectional differentiation, which increases the likelihood of tumor formation [6]. The research indicated that pre-differentiating embryonic stem cells (ESCs) into neuronal stem cells before transplantation can effectively address the issue of non-specific differentiation in vivo, leading to improved spatial memory performance [7]. Additionally, another study highlighted the significance of the timing of pre-differentiation in vitro, as improper timing can lead to the development of uncontrolled ESCs-derived somatic cells [8]. Neural stem cells (NSCs) has the capacity to differentiate into neurons, oligodendrocytes, or astrocytes, all of which exhibit the ability for self-renewal. Glial cells, characterized by their pluripotent nature and ability to undergo self-renewal, have been identified [9].

The transplantation of NSCS cells results in the secretion of nerve growth factors and immunological factors, which serve to facilitate the processes of differentiation and retention [10]. A study shown that

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the transplantation of neural stem cells (NSCs) resulted in enhanced neuronal regeneration and cognitive function recovery in a rat model [11]. However, the specific mechanism behind this effect remains unclear [12]. At present, the outcomes pertaining to the viability of neural stem cells (NSCs) in clinical transplantation are not encouraging [13-14]. Nevertheless, there exist therapeutic strategies that can be employed to enhance the regenerative potential of the central nervous system (CNS) through the integration of genetic engineering techniques [15].Autologous transplantation of induced pluripotent stem cells (IPSc) offers the advantage of circumventing immunological rejection and mitigating moral and ethical concerns. However, the small number of researches conducted thus far can be attributed to the novelty of this approach. The induction of induced pluripotent stem cells (iPSCs) to generate neuronal precursor cells has been shown to have potential benefits in terms of reducing the risk of tumorigenicity and neuronal degeneration [16-17]. However, Zhou et al. have recently proposed an alternative approach using protein small molecule induction to mitigate the issue of introducing exogenous genes that may have carcinogenic effects [18]. Nevertheless, there have been concerns over the capacity of induced pluripotent stem cell (IPSC) models to accurately replicate aging-related disorders like Alzheimer's disease. These concerns arise from the observation that certain IPSCs display a loss of genetic characteristics and exhibit age- and environment-dependent changes during the programming process [19-20]. To mitigate these issues, a strategy known as direct reprogramming, which involves bypassing the intermediate stage of induced pluripotent stem cells (IPSCs), has been developed. This approach enables the direct conversion of fibroblasts and other somatic cells into neurons [21-26].

In a recent investigation, researchers conducted a study wherein they transplanted cholinergic neuron precursors derived from induced pluripotent stem cells (IPSCs) into a mouse model that mimics Alzheimer's disease. The findings of this study revealed that the transplanted precursors successfully underwent differentiation into fully developed cholinergic neurons. Furthermore, these neurons exhibited the ability to reverse impairments in spatial memory [27]. However, it is important to note that the potential risk of tumorigenicity associated with this transplantation approach must be effectively addressed in order to ensure its safety and viability. Mesenchymal stem cells (MSCs) are highly accessible stem cells that may be obtained from bone marrow and possess the advantageous property of mitigating the likelihood of immunological rejection. In comparison to alternative stem cell transplantation methods, the transplantation of mesenchymal stem cells (MSCs) has been found to enhance cognitive performance, mitigate memory impairment, and decrease the presence of Aβ plaques [28].

In recent studies, it has been shown that mesenchymal stem cells (MSCs) secrete enzymes that facilitate the degradation of Aβ plaques. Specifically, the protease NEF, which has an inverse relationship with secreted Aβ, has been identified as one of these enzymes. Furthermore, investigations have demonstrated that MSCs-derived ICAM-1 and CCL5 can elevate NEF levels, hence promoting a decrease in Aβ plaques. Nevertheless, there exists limited knowledge regarding this protease, necessitating more investigations. The rate of differentiation for MSCS is reported to be modest [29-30]. However, the administration of intravenous injection has the potential to facilitate the migration of cells through the blood-brain barrier towards the specific location of injury, thereby exhibiting efficacy in the treatment of patients [31]. Nerve growth factor (NGF) is classified as a growth factor that possesses the ability to induce the stimulation of cholinergic activity. Research has demonstrated that nerve growth factor (NGF) possesses the ability to induce the proliferation of cholinergic neurons located in the basal medulla oblongata, while concurrently exerting a protective effect against cellular apoptosis. In experimental trials, the delivery of NGF to the brains of mice yielded positive results. However, the limited duration of NGF's effectiveness, as well as its restricted migratory capabilities, hinder its longevity [32]. Nevertheless, the efficacy of NGF gene therapy has been extensively investigated in several mice models and has demonstrated promising results in clinical trials involving patients with Alzheimer's disease [30]. One notable new development in the field of graft site delivery involves the utilization of hydrogel technology for encapsulating. This approach overcomes earlier constraints and contributes to the process of differentiation. Hydrogels are constructs with a three-dimensional structure,

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comprising hydrophilic polymers, which serve to offer a certain degree of mechanical reinforcement for the purpose of delivering growth ingredients [33].

The level of cellular differentiation in cultivated cells expressing soluble NGF is positively correlated with the utilization of hydrogel scaffolds [31]. Previous studies have demonstrated that these scaffolds have the capacity to enhance both the differentiation and spreading of NSCs [32]. The utilization of stem cell therapy in the management of neurological disorders shows great potential, particularly when combined with the rapidly advancing field of nanotechnology in nanoneurology. Nanoparticles, widely employed in medicine, possess the ability to traverse the blood-brain barrier and accurately target specific regions of the brain [33], while minimizing harm to adjacent areas. Furthermore, research has indicated that the utilization of nanotechnology has the potential to enhance the effectiveness and safety of current Alzheimer's disease (AD) medications. Additionally, it has been seen that nanotechnology can provide protection to neurons against the detrimental impact of Aβ proteins, dissociated tau proteins, and oxidative stress [24]. Additionally, a scaffold fabricated through 3D printing utilizing a distinct material has been proposed as a potential vehicle for delivering neural stem cells. These stem cells can subsequently undergo differentiation with the application of low-level light therapy (LLLT), a technique that has demonstrated efficacy in suppressing cell death and enhancing cellular proliferation and motility [25].

3. Patient clinical trials

The preclinical efficacy of mesenchymal stem cells (MSCs) fulfills the necessary requirements for their potential utilization in human trials for Alzheimer's disease (AD). However, a recent subsequent analysis of clinical trials revealed that patients who received MSC injections did not exhibit any deceleration in cognitive decline after a period of 24 months. Additionally, no reduction in amyloid-beta (AB) pathology was observed, and no patients experienced any adverse effects following the surgical procedure or transplantation [16]. The clinical outcomes do not align with the experimental validation of animal models, and this discrepancy may be related to the association between neuroimaging and biochemical analyses conducted on animals after death. An additional area of investigation pertains to the application of gene programming therapy for the purpose of inducing the production of nerve growth factor (NGF) from fibroblasts, with the aim of promoting the development of cholinergic neurons in the basal forebrain. In this particular study, ten patients were subjected to gene therapy, resulting in the observation of axonal growth towards the graft site in all participants. Moreover, three patients exhibited cholinergic hypertrophy, although it remains unclear whether these changes translated into any discernible improvement in the patients' symptoms. Notably, no adverse effects were detected during the course of the study, which is presently ongoing [33].

4. Conclusion

This review elucidates the potential efficacy of neuronal restoration as a therapeutic approach for neurodegenerative disorders, including Alzheimer's disease. It posits that the utilization of stem cell therapies, entailing the targeted transplantation of stem cells into designated regions of the patient's brain, holds promise for the regeneration of impaired neural tissue.

The regenerative capacity of the central nervous system can be enhanced and the retention time of transplanted stem cells can be prolonged through the utilization of gene therapy in conjunction with nerve growth factors. This approach has demonstrated the potential to ameliorate memory deficits. Additionally, the induction of induced pluripotent stem (iPS) cells can generate neuronal precursor cells, which can be employed to mitigate the risks of tumorigenesis and neuronal degeneration. It is imperative to conduct a thorough safety assessment to evaluate the viability of this strategy. The utilization of hydrogels, nanotechnology, and light treatment in stem cell technologies has the potential to enhance medication delivery efficacy. This approach is currently under extensive investigation, particularly in conjunction with neuroregenerative therapies. Stem cell therapy has demonstrated certain levels of efficacy in animal models of Alzheimer's disease (AD), a progressive neurodegenerative disorder that conventional pharmacological treatments have proven to be ineffective against. Stem cell

therapy exhibits considerable promise in the treatment of neurodegenerative disorders, including Alzheimer's disease. However, several challenges persist, necessitating further investigation and resolution. These challenges encompass issues such as immune rejection, tumor formation, difficulties in cellular differentiation, transduction efficiency, and the successful translation of findings from animal model studies to clinical trials involving human patients, among others. Obtaining conclusive evidence regarding the effectiveness of stem cell therapy in individuals with Alzheimer's disease (AD) who are currently under investigation is anticipated to be a time-consuming process. Given the nascent stage of human clinical trials, additional animal studies and clinical trials will be imperative to ensure the successful translation of this research into clinical practice.

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