

Stem Cells: Current Therapeutic Strategies for Alzheimer's Disease

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Abstract

The loss of neuronal cells in the central nervous system may happen in numerous neurodegenerative illnesses. Alzheimer's Disease (AD) is an intricate, irreversible, dynamic neurodegenerative sickness. It is the main source of age-related dementia, influencing roughly 5.3 million individuals in the United States alone AD is a common senile disease in people over 65 years of age, bringing on impairment described by decrease in memory, failure to learn and do every day exercises and intellectual weakness and influences the personal satisfaction of patients. Pathologic characteristics of AD are an irregular development of specific proteins called Beta-amyloid "plaques" and Tau "Tangles" in the brain. Current treatments against AD are just to relieve symptoms and palliative, not the cure and a few promising drug candidates have failed in recent clinical trials. There is consequently a critical need to enhance our comprehension for pathogenesis of this sickness, making new and creative prescient models with powerful treatments. Recent advances indicate that stem cell treatment appears to be a promising approach to deal with different illnesses, including neurodegenerative disorders. Stem cell substitution procedures have been challenging extremely treatment approach to treat AD. Stem Cell therapy may offer an effective new approach in AD treatment and furthermore, may be used as a model for other neurodegenerative diseases. Patient derived induced Pluripotent Stem Cells (iPSCs), for instance, may further our understanding of disease mechanism. In this review we will discuss the potential of stem cells and their use in treatment options to this challenging disease.

Keywords: Alzheimer's disease; Induced pluripotent stem cells; Neurogenesis; Oxidative stress; Stem cell therapy; Transplantation

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accumulation of harmful types of the "beta-amyloid" (A β) plaques, Neurofibrillary Tangles (NFT) and neurodegeneration, representing progressing pathological characteristics.

A β peptides are observed to be the fundamental constituents of senile plaques and AB fibrils from pores in neurons have been appeared to prompt calcium influx and neuronal passing [6]. NFT comprises of neurofibrillary protein aggregates, shaped as irregular hyper phosphorylation of "tau" protein, which is one of the microtubule-related proteins [7]. Furthermore, microglia has been reported to play an important role in the immune defense system of the Central Nervous System (CNS). Microglia activation and the release of associated inflammatory factors have been accounted to add to chronic neurodegenerative issues in AD [8]. More recently, stem cell treatment has been seen as a potential way to deal with its treatment. In this review, we concentrate on stem cell treatments for AD.

Introduction

Alzheimer's Disease (AD), the most widely recognized type of age related dementia, which is the real reason for incapacity among the older age individuals around the world. AD is gradual, influences memory with resulting loss of the ability to reason and declining memory. Patients exhibit diminished capacity to grasp or utilize words, poor coordination, absence of judgment and basic leadership capacity, frequent state of mind swings and lack of comprehension [1,2]. It is the most widely recognized category of dementia, at present influencing 35.6 million individuals around the world, which is expected to grow by 2050 [3]. AD has been divided in to familial AD and sporadic AD. The transformation of three qualities: the amyloid Antecedent Protein (APP), Presenilin-1 (PS-1) and Presenilin-2 (PS-2) are key mutations present in Familial AD [4]. Sporadic AD is a result of the aftereffect of ecological elements with apolipoprotein (ApoE) reportedly being the most important marker [5]. The widespread loss of neurons and neurotransmitters in AD appears to be caused by the

Pathogenesis of AD

The definite reason for AD is not surely understood. Considering the commonness and poor prognosis of AD, there has been a research priority in creating disease models for concentrating on pathogenicity and to help begin development of therapeutic approaches. In United States starting 2012, 1 out of 8 senior nationals (13%) are experiencing AD, making it the 6th most regular reason for death. More than 5.4 million AD patients are currently receiving medical treatment in the USA and the costs are as high as \$200 billion a year [9]. AD is normally characterized by a steady decrease of memory, dialect and psychological capacity.

The two pathological trademarks known to be present in patient's brain are senile plaques and Neurofibrillary Tangles (NFT) [10,11]. Senile plaques are stores of protein products called beta-amyloid (A β), which causes neuronal cytotoxicity and neurofibrillary tangles

are irregular structures that are framed by changes in the tau protein inside the nerve cells. The nerve cells shrink and die progressively in the brain of Alzheimer's patients. Such neuronal cell demise happens principally, in areas in charge of the memory and subsequently spreads to all other parts of the brain. Decreased acetylcholine, which is a neurotransmitter that is responsible in the intracellular signaling and insufficiency in the creation of different neurotransmitters, for example, somatostatin, serotonin and norepinephrine results in impaired neuronal networking in Alzheimer's patients [12]. The aggregation of the A β observed in the Familial Alzheimer's Disease (FAD) is a result of mutation of the A β precursor protein, which is part of the senile plaques. The trans entorhinal cortex of the mind is the spot where disease begins to manifests and rapidly spreads to the entorhinal cortex, the hippocampus and the cerebral cortex. With dramatic neuronal cell death, memory loss and cognitive dysfunction alongside progression of dementia, also leads to the death of the patient [13-15].

Current Therapies for AD

The cysteine Protease family based Cathepsin B (CatB) degrades peptides and proteins through endocytosis or phagocytosis. It is associated with amyloid plaques in a relative constrained way in AD brains. So inhibitors of cathepsin B might be considered as therapeutic agents to diminish A β in AD [16]. Neprilysin (Nep) has been recently recognized as a noteworthy extracellular A β degrading enzymes in the brain and proposes that gene transfer approaches might have the potential for the treatment of Alzheimer's Disease [17]. Other pharmacological alternatives are available for the symptomatic treatment of AD which incorporates Acetylcholinesterase inhibitors (AChEIs) and memantine, a N-methyl-D-aspartic acid antagonist, utilized as a combination therapy [18]. High plasma levels of vitamin E are connected with a reduced risk of AD in an advanced age, acting as an anti-oxidant and securing against lipid peroxidation [19].

Proposed Stem Cell Therapies for AD

Stem cells are defined as cells that have the ability to renew themselves continuously and possess pluripotent ability to differentiate into many cell types. Two types of mammalian pluripotent stem cells, Embryonic Stem Cells (ESCs) derived from the internal cell mass of blastocysts and Embryonic Germ Cells (EGCs) acquired from post implantation embryo, have been identified and these stem cells give rise to different organs and tissues. Recently, another class of pluripotent stem cells, induced pluripotent stem cells (iPS cells), from adult somatic cell have been included an improvement. In addition, ESCs and iPS cells, tissue-specific stem cells could be isolated from various tissues such as hematopoietic stem cells, Bone Marrow Mesenchymal Stem Cells (BMMSCs), adipose-tissue derived stem cells, amniotic liquid stem cells and neural stem cells [20].

Degeneration or dysfunction of Medial Ganglionic Eminence like cell (MGE) progeny prominence is often associated with learning and memory disorders. Progeny of the MGE like progenitors, especially Basal Forebrain Cholinergic Neurons (BFCNs), may encourage the advancement of cell treatments for AD [21]. Stem cell transplantation increased Brain Derived Neurotrophic Factors (BDNF) and Nerve Growth Factor (NGF) and restored cholinergic neuronal integrity [21]. The extracellular ligand, Wnt, and its receptors are involved in signal transduction and assume a critical part in axis formation and neuronal development. In AD, a decrease in the intracellular Wnt

effector, β -catenin, has been connected to amyloid- β -peptide-induced neurotoxicity. Secreted Frizzled-Related Proteins (sFRPs), which are group of Wnt mediators, may have potential ramifications in treatment of AD in study models [22]. Transplantation of Adipose-Determined Mesenchymal Stem Cells (ADMSCs) enhances intellectual capacity by increasing acetylcholine synthesis and restoring neuronal integrity. Bone marrow mesenchymal stem cells are similarly important to expel A β plaques from the hippocampus and to diminish A β deposits through the activation of endogenous microglia in an induced AD mouse model [23].

Embryonic stem cells are self-renewing totipotent cells that can differentiate into neuron progenitor cells and are transplanted in AD animal models. Human neural stem cells (HNSCs) transplanted into aged rat brains separated into neural cells and resulted in enhanced cognitive function of the animals, showing that HNSCs might be a promising source for cell-replacement therapy for neurodegenerative diseases including Alzheimer's disease (AD). RNA interference of APP or reduced APP levels in the brain can essentially diminish glial differentiation of stem cells and might be helpful in promoting neurogenesis after stem cell transplantation [24]. Presence of multipotent Neural Stem Cells (NSCs) in developing or adult mammalian brain with properties of inconclusive growth and multipotent potential can be separated into three CNS cell types, neurons, astrocytes and oligodendrocytes. Nerve Growth Factor (NGF) counteracts neuronal demise, excitotoxicity, amyloid toxicity and appears to enhance memory in aging models, suggesting that NGF may be a useful growth factor for treating neuronal degeneration and cell death in AD. Gene therapy possibly valuable in delivery of NGF into the brain. Stem cells can be genetically modified to convey new genes and have high transient/migratory capacity after transplantation in brain. They could be utilized in place of fibroblasts since fibroblasts are known for their immobility following transplantation for delivery of NGF to counteract degeneration of basal forebrain cholinergic neurons [25].

Although stem cell therapy appears to be the future for treatment, further studies are needed to understand and to decide appropriate conditions and procedures to achieve success to enhance the therapeutic effects for AD pathology.

Understanding the Pathogenesis of Alzheimer's Disease (AD) Using Induced Pluripotent Stem Cells (iPSCs)

The iPSCs model system obtained from familial and sporadic AD patients could be helpful in understanding the molecular basis of sporadic AD as well as if it can be effective in testing the drug proficiency for AD. The usefulness of iPSCs could be focused by targeted advanced gene editing techniques in familial known mutation and could be utilized for further cell transplantation therapies [26]. Studies used dermal fibroblast taken from the patient diagnosed to have late stage AD and reprogrammed to iPSCs. These iPSCs lines indicated pluripotent properties similar to human embryonic stem cells which could be differentiated into neuronal cells *in vitro*. These neuronal cells have demonstrated the AD phenotype and articulation of p-tau proteins, up regulation of GSK3B protein and its phosphorylation as which was not seen in parental dermal cells. Numerous genes are revealed by neuronal differentiation experiments with AD-iPSCs line [27,28]. The studies may indicate that the gene regulation units and subunits

of proteasome complex are influenced in neurons derived from AD patients [27].

The scholarly study by Yagiet al., also generated iPSCs from patient with familial AD where mutations in Presenilin1 and Presenilin2 were observed [29]. Which results to frame an incorrect cleavage and deposition of amyloid- β protein which is considered to shape plaque [30,31].

Limitation in Stem Cell Therapy in Alzheimer's Disease

There are impediments to pursue the underlying genomic pathology due to some ethical issues in accessibility of viable neuronal cells from AD patients. Secondly availability and utilization of iPSCs on large scale requires various and feasible advanced techniques and the cost effectiveness to produce iPSCs on a large scale [32]. To generate iPSCs from somatic cells, reconstructing factors must be included by two techniques utilizing integrity and non-integrity system. These strategies, although exceptionally productive, the process and methods or system appears to have the potential risk for causing cancer [33]. There are couples of errors in application of iPSCs in humans, since the disease testing methodologies utilized in animal models may be different from genomic stability and precise microenvironment in humans. In addition, the delayed utilization of common immunosuppressant drugs in aged mice used for study causes toxic side effects to the mice which may modify the pathology related to AD. In this manner it influences the interpretations also [34,35]. However, the study in mouse model may give important useful insights in stem cell therapy.

As there are different and multiple neuronal systems and neuro-phenotypes are affected in AD, it has become challenging in making cell substitution approach. Another approach to research could be changed by using AD transgenic model with inept or incompetent background, such a model has yet to be developed and has not been published [36]. Likewise, if stem cells are transfused intravenously, they may block blood capillaries.

Several unanswered questions exist such as how many cells are needed, and frequency of supply of cells and where to, to manage or prevent the disease.

Future Direction

Immunotherapy for AD

Active and Passive Immunization: Anti-A β strategies have been pursued, where targeting A β peptide may be helpful therapeutic approach. By inhibiting or blocking the enzymes responsible for A β generation, formation of A β aggregates can be prevented which may lead to clearance of A β from the brain. The A β immunotherapy utilizes anti-A β antibodies, generated vaccines or introduced passively, which results in the clearance and prevents aggregates of A β [37]. The first active Vaccine for AD, AN1792 was abandoned in 2002 because of the development of meningoencephalitis in ~6% of the enlisted moderate-to-severe AD patients, in the clinical trials [38]. Yet proficient immunization and vaccine development research approaches are in progress, some in the phase I clinical trials. The pre-clinical studies on transgenic mice when treated with anti-A β monoclonal antibodies indicated promising impacts with a significant decrease in brain A β

levels, decreased brain senile plaque pathology, and enhanced cognition [39,40]. Bapineuzumab and solanezumab, the anti-A β monoclonal antibodies, emerged as the possible hopefuls following passive immunization route, and were assessed in several Phase III clinical trials [41,42]. However, several of these clinical trials have failed to accomplish the anticipated results [43]. At present, at least, five other anti-A β monoclonal antibodies, with similar properties as bapineuzumab and solanezumab, are in different phases of development [44].

Nanotechnology for AD

Nano Carriers: The focus on drug delivery is a critical aspect of the application of Nano medicine [45]. It is also challenging and complicated to deliver the molecules in the Central Nervous System (CNS) tissues, against the Blood Brain Barrier (BBB) [46]. The navigation of these therapeutic molecules over the BBB has been broadly investigated previously, by the utilization of biocompatible nanoparticles [47], for example, curcumin, which is the chemical agent and an active ingredient of Turmeric, the yellow spice which has been as of late found as a potential treatment for AD [48,49]. The recent application of nanotechnology in molecular diagnostics for detection of biomarkers for AD is found to be promising. Early diagnosis of AD using nanotechnology can be achieved by the means of signal transduction approach. With that follows, DNA-Nanoparticles conjugates helps detect protein biomarkers of the attomolar scale [50], through the technique termed as bio-barcode assay. This assay can be used to detect ultra-low concentration of protein biomarkers using gold as carrier nanoparticles. In recent years, the amount of research towards "neuroprotective agents" and "neuroregenerative agents" has been significantly increased. These two approaches together are known as "disease-modifying approaches" [51]. The therapeutic characteristics of nanotechnology for AD show disease-modifying approaches [52].

Conclusion and Discussion

In the current review, we have discussed many current and future studies that examine the use of stem cells including immunotherapy and nanoparticles to treat and model AD. Evidence indicates that the stem cell based therapies could prove beneficial in the treatment of AD, since stem cells not only have the potential to generate new neurons but also replace the damaged neurons. With further understanding and clarification, stem cell may prove as a safe and possibly efficient treatment for AD. Similarly, with the knowledge of causes of AD safer cell therapies may be developed in future.

Author Contributions

Authors contributed equally to prepare this manuscript.

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