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Stem Cell Therapy and Nanomedicine for Alzheimer's Disease

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Editorial

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INTRODUCTION

Alzheimer's disease (AD) is recognized as the most prevalent form of dementia or mental deterioration, which is associated with the permanent loss of neurons specifically in Cortex and Hippocampus. According to the World Alzheimer's Report, there were an estimated 46.8 million people worldwide living with dementia in 2015 and this number is believed to be close to 50 million people in 2018. These numbers will almost double every 20 years, reaching 75 million in 2030 and 131.5 million in 2050 [1,2]. Clinically, the AD is diagnosed by progressive impairment in memory, judgment, decision making, orientation to physical surroundings, and language. In spite of vast research, presently no treatment could be developed to fully cure or prevent the progression of dementia because the mechanism of the AD has not been fully understood. Available treatments are only symptomatic, with a temporary effect, and without halting the progression of the disease [3,4]. For instance, Phase III trials of nonsteroidal anti-inflammatory drugs (NSAIDs), phenserine, statins, tarenflurbil, tramiprosate, Ginkgo biloba, and xaliproden have been completed. However, none of them has demonstrated a significant efficacy. Currently, available diagnostic approaches have failed to understand the correct mechanism of the AD. Furthermore, deterioration of cognitive, motor, emotional and sensory functions drastically affecting the social and behavioral skills of people living with this disease. Hence, it becomes important to fully understand the molecular mechanism of AD pathogenesis that can help to identify therapeutic targets to reduce cognitive decline and/or improve memory function [5,6].

Cause of Alzhiemer's Disease and Drawbacks of Current Treatment and Diagnosis

Although the molecular mechanisms of AD pathogenesis have not been clearly understood due to its complexity, polymerization/aggregation of Aβ into amyloid plaques is considered as a major mechanism in the pathogenesis. These amyloid plaques are composed primarily of 39–43 amino acid amyloid-β peptides (Aβ) that are derived by enzymatic cleavage of the amyloid precursor protein (APP) by β- and γ-secretases [6,7]. And then the AD is caused by an irreversible neuronal loss and vascular toxicity due to the extracellular deposition of acid amyloid-β peptides (Aβ) into senile plaques, together with neurofibrillary tangles of phosphorylated tau protein. This condition represents more than 90% of all AD cases. Therefore, inhibition of Aβ aggregation and destabilization of preformed Aβ fibrils are attractive therapeutic and preventive strategies for AD treatment [6-8].

Since 1998, there have been more than 100 attempts to develop an effective drug to treat the disease, but only four have been approved. Present therapy of AD is based on neurotransmitter or enzyme modulation such as Acetylcholinesterase (AChE) inhibitors and NMDA receptor. These drugs like tacrine, galantamine, and rivastigmine are associated with gastrointestinal adverse effects like nausea and vomiting that most commonly lead to discontinuation of treatment. Further, most of the drugs have a short half-life and fast degradation rate and that's why they are administered four times per day [7-9]. In addition, patients who used the drug required periodic blood monitoring due to hepatotoxicity. Hence, high doses are required to obtain therapeutic levels in the brain, with the risk of suffering adverse systemic effects. However, the presence of the blood-brain barrier is the principal barrier for most of the drugs as they are unable to cross it due to their hydrophilic nature or low lipophilicity, large molecular weight or charge. Thus, the effective concentration of drug cannot reach the brain which results in a higher dose of therapeutic drugs. Another problem is associated with the diagnosis of the AD. Initially, diagnosis of the AD is done on the basis

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of depression, which develops in most of the patients with the AD. Depression in the AD is often characterized by motivational disturbances, such as fatigue, psychomotor slowing, and apathy, anxiety, suicidality, and disturbances in sleep and appetite. Old imaging techniques like computed tomography (CT) or magnetic resonance imaging (MRI) and single-photon emission CT (SPECT) or positron emission tomography (PET), are being used in the diagnosis of the AD. But the low sensitivity and limited visualization are the major drawbacks of these techniques. Further, they are having the high cost, potential radiation damage, and poor affinity of tracers [7,10,11].

Nanotechnology for Alzheimer's Disease

On-going research is showing considerable efforts in searching for new therapies to control the neurodegenerative process. Various molecules such as growth factors, antioxidants, and metal chelators have been investigated as new therapeutical approaches. However, these molecules are also unable to arrive into the brain in effective concentration due to the blood-brain barrier, thus limiting the therapeutic effect. The development of nano drug delivery systems may permit a targeted and sustained release of old and new treatments offering a novel strategy to treat AD [10,11]. These nano drug delivery systems include polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, microemulsion, nanoemulsion, and liquid crystals. The researchers have proven that these systems can be assuring techniques for the delivery of therapeutic and diagnostic materials to the brain *via* various routes of administration, particularly the intranasal route. This brain targeted nanotechnology has raised a big hope to AD patients by helping to understand the mechanism and new targets of the AD. These nanoparticles can easily cross BBB due to their nanosize and enhanced permeation and retention effects (EPR effect). Further, they can encapsulate a variety of therapeutic molecule and diagnostic agents and easily functionalize with the desired ligand [12]. Nanoparticles below 100 nm are considered as a breakthrough approach as a drug delivery system which is able to cross BBB and can help in early detection of plaques, inhibition of Ab fibrillation, clearance of preformed fibrils, oxidative stress and/or neuroinflammation suppression, metal-chelation therapy, and photothermal therapy. For example, it was demonstrated that Fe biometal specifically accumulates in amyloid plaque core (APC) and crystalline magnetic NPs such as superparamagnetic iron oxide NPs (SPIONs) that has superparamagnetic properties, can be used for AD diagnosis. In spite of great advancement in nanotechnology, the use of nano drug delivery system for treatment and detection of the AD are still under investigation and could not be clinically approved [12,13].

Usage of Stem Cell Therapy for Alzheimer's Disease

Recent developments in stem cell technology have stimulated new prospective therapies for neurodegenerative disorders such as the AD. In the present time, regulatory bodies such as the FDA has started to authorize clinically the use of a number of new stem cell therapies, although these are mostly applied as hematopoietic stem cells transplantation. Hematopoietic stem cell transplantation is the accepted therapy for a variety of malignant and non-malignant diseases in children and adults. Earlier it is developed as a life-saving therapy for a patient with cancer after high doses of chemotherapy and radiation as well as the correction of severe deficiencies in the hematopoietic system, it has evolved into an adoptive immune therapy for malignancies and autoimmune disorders [14,15].

Neurogenesis is a process in the hippocampus, involved in learning and memory formation. The hippocampus-dependent learning tasks can significantly increase the proliferation of endogenous neuronal progenitors, survival of new neurons and, the task performance by animals correlates positively with the amount of adult-born neurons. Hence it has been proven that neural progenitor/stem cells still reside in the adult central nervous system and involved in the neurogenesis process. During injury, endogenous neural progenitor/stem cells populations have activated and migrate to the injured regions, proliferate and functionally integrate into the existing circuit represents a significant strategy to promote neural regeneration in the diseased brain. So the possibility of using stem cells as a tool for AD patient to regenerate diseased or damaged neurons. Specific model systems, however, remains at best challenging. Further, among stem cells, adipose-derived stem cells (ASCs), mesenchymal stem cells isolated from adipose tissue, are well known for their pluripotency and ability to differentiate into mesenchymal and non-mesenchymal lineages [14,15]. These stem cells are under intense investigation as a potential therapeutic source of neurons to replace damaged or lost cells. For example, administration of bone marrow-derived mesenchymal stem cells (BM-MSCs) has shown beneficial effects in animal models with several neurodegenerative diseases like Parkinson's disease, experimental autoimmune encephalomyelitis, and amyotrophic lateral sclerosis [16,17].

Although BMMSC transplantation has been suggested as a potential therapeutic approach for the AD, the actual therapeutic effect of BM-MSCs for AD treatment and their mechanism of action have not yet been ascertained. Also, BM-MSCs reduced Ab deposition and memory deficits in AD model mice by modulating the immune response. In other research work, it is observed that neural stem cells relieve in memory impairment in AD model mice by releasing brain-derived neurotrophic factor (BDNF). However, it would almost be impossible to perform intravenous transplantation of neural stem cells and BM-MSCs. ASCs are readily accessible and show high proliferation rates *in vitro* with lower senescence ratios than BM-MSCs [18,19]. Considering clinical applications, adipose-derived stem cells (ASCs) are the most suitable source of stem cells due to the possibility of intravenous transplantation of autologous ASCs with no immune rejections, ethical problems or tumorigenesis and it is realized as a highly convenient, simple and safest method. Intracerebral injection of human ASCs (hASCs) is successfully applied in neurodegenerative diseases like Huntington's disease (HD) and ischemia mouse models. Since the AD pathophysiology AD is not the same of

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stroke and HD, therefore, it cannot be said that human ASCs (hASCs) would be beneficial or successful in AD treatment. Further, these cells demand more caring as fully differentiated cells are associated with a smaller efficiency due to poor viability, while undifferentiated cells present a higher risk of undirected differentiation and uncontrolled proliferation. Thus, a possibility of using stem cells as a tool for development of AD patient-specific model systems still remains challenging. But a regular advancement in techniques and mode of delivery can be a great breakthrough in full cure of AD [18,19].

Stem Cells Tracking via Nanoparticles

Stem cell tracking is essential to assure so that stem cells can give the maximum therapeutic benefit with the minimum number of cells and reducing the potential for side-effects. A large number of stem cell tracking methods are being developed to achieve this. Of all the current methods of tracking stem cells, MRI is widely used as it is non-invasive in contrast to other traditional invasive techniques which need a biopsy at the site of treatment. During *in vivo*, the use of magnetic nanoparticles in MRI is the most promising. Nanoparticles with magnetic properties are very widely accepted. Nanoparticles with magnetic properties are very interactive with neighboring protons in water molecules when a magnetic field is applied. This change of behavior can be detected using an MRI scanner and shows up as a hypointense area in an MRI image [16-19].

CONCLUSION

After Parkinson's disease, Alzheimer's disease is the second most prevalent neurodegenerative diseases globally. In spite of exhaustive research done by the scientist, currently available treatments have failed to fully cure AD-associated neuronal damage and dementia. They have only symptomatic relieve without halting the progression of the disease. A number of new drugs are clinically developed but the symptomatic and disease-modifying treatment of AD has resulted in both promise and disappointment. Further, the effective diagnosis and treatment of AD are restricted due to the limitations posed by the blood-brain barrier (BBB) as well as due to opsonization by plasma proteins in the systemic circulation and peripheral side-effects. Since last decade, nano drug delivery systems characterized as an effective tool to enhance the penetration of several therapeutic and diagnostic molecules across BBB and lead to improved therapeutic outcomes. Though there are no clinical studied performed till now for nano drug delivery systems, but they are providing the novel and effective methods for the treatment of AD. Currently, neural stem cell therapies have evolved with hope for the treatment of neurodegenerative disorders but its selection, generation, and transplantation are quite complicated. But as per various studies findings, stem cell treatment can be a cell substitution for the destroyed spinal cord or CNS, axon regeneration and/or application of a neurotrophic factor to recover the neural tissue. The reported data are promising, but future studies must continue to establish whether stem cells can serve as a safe and functional autologous source for treatment of the neurological disorders. Further, there is also a need to develop noninvasive tools to track the location and fate of transplanted stem cells. As well, the development of better animal models is required to allow the study of tissue regeneration *via* stem cell therapy that is more relevant for human disease.

REFERENCES

1. Sahni JK, et al. Neurotherapeutic applications of nanoparticles in Alzheimer's disease. J Control Release. 2011;152:208-31.
2. Gong Y, et al. Alzheimer's disease-affected brain: Presence of oligomeric A beta ligands (ADDLs) suggests a molecular basis for reversible memory loss. Proc Natl Acad Sci. 2003;100:10417-22.
3. Hernando S, et al. Advances in nanomedicine for the treatment of Alzheimer's and Parkinson's diseases. Nanomedicine (Lond). 2016;11:1267-85.
4. Wen MM, et al. Nanotechnology-based drug delivery systems for Alzheimer's disease management: technical, industrial, and clinical challenges. J Control Release. 2017;245:95-107.
5. Li M, et al. Using graphene oxide high near-infrared absorbance for photothermal treatment of Alzheimer's disease. Adv Mater. 2012;24:1722-28.
6. Cui Z, et al. Sensitive imaging and effective capture of Cu(2+): Towards highly efficient theranostics of Alzheimer's disease. Biomaterials. 2016;104:158-67.
7. Hajipour MJ, et al. Advances in Alzheimer's diagnosis and therapy: The implications of nanotechnology. Trends Biotechnol. 2017;35:937-53.
8. Roney C, et al. Targeted nanoparticles for drug delivery through the blood-brain barrier for Alzheimer's disease. J Control Release. 2005;108:193-214.
9. Georganopoulou DG, et al. Nanoparticle-based detection in cerebral spinal fluid of a soluble pathogenic biomarker for Alzheimer's disease. Proc Natl Acad Sci. 2005;102:2273-76.
10. Liu Y, et al. Brain-targeted co-delivery of therapeutic gene and peptide by multifunctional nanoparticles in Alzheimer's disease mice. Biomaterials. 2016;80:33-45.
11. Elnaggar YSR, et al. Intranasal piperine-loaded chitosan nanoparticles as brain-targeted therapy in Alzheimer's disease: Optimization, biological efficacy, and potential toxicity. J Pharm Sci. 2015;104:3544-56.

12. Cheng KK, et al. Curcumin-conjugated magnetic nanoparticles for detecting amyloid plaques in Alzheimer's disease mice using magnetic resonance imaging (MRI). Biomaterials. 2015;44:155-72.

13. Massimi L, et al. Exploring Alzheimer's disease mouse brain through X-ray phase contrast tomography: From the cell to the organ. Neuroimage. 2018;184:490-95.

14. McGinley LM, et al. Human neural stem cell transplantation improves cognition in a murine model of Alzheimer's disease. Sci Rep. 2018;8:14776.

15. Nguyen H, et al. Stem cell therapy for neurological disorders: A focus on aging. Neurobiol Dis. 2018.

16. Edmundson M, et al. Nanoparticles based stem cell tracking in regenerative medicine. Theranostics. 2013; 3:573-82.

17. Hsieh FY, et al. 3D bioprinting of neural stem cell-laden thermoresponsive biodegradable polyurethane hydrogel and potential in central nervous system repair. Biomaterials. 2015;71:48-57.

18. Lee JK, et al. Intracerebral transplantation of bone marrow-derived mesenchymal stem cells reduces amyloid-beta deposition and rescues memory deficits in Alzheimer's disease mice by modulation of immune responses. Stem Cells. 2010;28:329-43.

19. Lindvall O and Kokaia Z. Stem cells for the treatment of neurological disorders. Nature. 2006;441:1094-96.