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Therapeutic effect of stem cells and nano-biomaterials on Alzheimer's disease

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ABSTRACT

Today, neurodegenerative diseases such as Alzheimer's disease (AD) are very common among the people of the world, and many people suffer from this disease. Currently, there is no definite cure for the Alzheimer's disease and the existing drugs can only slow down the disease but cannot stop it. One approach for improvement of the effect of drugs is the use of drug delivery systems. The second approach is a combination of stem cells with nano-biomaterials to achieve this goal. Many studies have been done on stem cell therapy for Alzheimer's disease. Different sources of stem cells such as embryonic stem cells, adult stem cells and induced pluripotent stem cells (IPSs) were used to replace damaged cells in the Alzheimer's disease models. These cells are able to differentiate into neurons, through a process known as neurogenesis. Subsequently, cognitive deficits, including learning and memory are recovered. Also, an overview of the importance of stem cells as a model to study the effects of Alzheimer's disease drugs and the recognition of mechanisms of AD is done. The final approach is utilizing genetic engineering, surface modification methods and the use of biomaterials as cell carriers to the stimulate stem cells niche are considered good options in order to enhance efficiency.

Keywords: *Alzheimer's disease, stem cells, nano-scaffolds, neurodegenerative diseases, microglia inflammation, beta amyloid, cognitive defect.*

Abbreviations: *Alzheimer disease (AD), induced pluripotent stem cell (IPS), subunit of telomerase (TERT), nerve growth factor (NGF), acetylcholine (ACh), Choline acetyltransferase (ChAT), neurofibrillary tangle (NFT), mesenchymal stem cell (MSC), Beta amyloids (Aβ), human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSC), amyloid precursor protein (APP),Wharton's jelly mesenchymal stem cell (WJ-MSC), neural stem cell (NSC), nerve growth factor (NGF), drug delivery systems (DDS), blood-brain barrier (BBB).*

1. INTRODUCTION

Alzheimer is a neurodegenerative disease in which three events occur: neurons lose their connections with surrounding nerve cells, electrical signals responsible for cell movement cannot be transmitted properly and eventually neurons die [1]. In age-related AD, with increasing cellular oxidative stress, energy metabolism is impaired and subsequently neuronal calcium homeostasis may be lost and consequently, apoptosis occurs. In heredity, AD neuron degeneration takes place through the production of neurotoxic forms of amyloid β-peptide and impaired calcium homeostasis.

Unfortunately, some types neurodegenerative disease are prevailing and treatment are so difficult due to limited access to the human brain. With attention to difficulty in treatment of this disease, neuroprotective mechanisms become important. These mechanisms include: 1) decrease of calorie intake as a dietary restriction which increases the resistance of neurons to the disruption and destruction through a mechanism involving a mild stress response. DR can increase the stress proteins and neurotrophic factor (NTF) in brain cells, 2) Telomerase: This enzyme has anti-aging properties and it is believed that manipulating these enzymes can protect neurons from death. It was observed that a part of telomerase which called the catalytic subunit of telomerase (TERT) is presented in growing brain, but not in the adult brain. TERT showed neuroprotective effect. Therefore, by manipulation of telomerase protection against age-related neurodegeneration achieve, 3) stem cell therapy [2].

The most available method for treatment of AD is the usage of drugs that are only capable of reducing the speed of disease but don't stop it. Owing to the presence of BBB, access to the affected areas of the brain is difficult. With the help of drug delivery systems especially nano-carriers, this problem could be solved to some extent and anti-Alzheimer drugs could be loaded into these carriers [3].

Due to the complex structure of human brain and restriction to access it, the understanding of scientists about the mechanisms of this disease is not clear. Scientists discovered the structure of human brain with the study of cadaver but still mechanisms happen in living AD brain are not clear. To overcome these difficulties, stem cells are good candidates.

Today, the usage of stem cells play an important role in different medical fields such as cure of diseases, diagnosis of diseases, investigation of the effect of drugs on diseases, restorative treatment and so forth. Stem cells are divided into three categories based on their potential for differentiation which include: 1) totipotent stem cells (which can differentiated into all cell types existing in living body and can make both fetus and placenta), 2) pluripotent stem cells (which can differentiate into all kinds of cells and capable of making fetus but not placenta), 3) multipotent stem cells (which only differentiate into limited types

of cells). There is another category for stem cells which divided them into two groups of embryonic stem cells (stem cells which present in embryo) and adult stem cells (stem cells which present in tissues of an adult human) [4-6]. Previously, it was thought that multipotent stem cells have a limited capacity to differentiate but today it has been known that these cells have pluripotent properties, for instance: adult bone marrow stem cells can differentiate into skeletal muscle, brain microglia and astroglia, and hepatocytes [6].

Stem cells play a key role in neurodegenerative diseases such as AD Parkinson's disease and Huntington's disease. Stem cells have three advantages; they can be used as cell source to replace damaged cells in AD; they can be used as model of AD to clear mechanisms of disease and also to assess the effect of therapies such as drugs on AD, they are used as delivery vehicle for nerve growth factor (NGF) [1].

Despite all aforementioned advantages of stem cell therapy, cell survival is a major problem. In this regard, biomaterials are promising tools which can solve this problem since they can mimic natural niche of stem cells helping them to survive and differentiate into the desired lineage [7]. Among different scaffolds designed for AD treatment, nanofibrous scaffold made via electrospinning are important [8]. Recent efforts are designing scaffolds in nano and molecular levels to adjust and prevent molecular events during AD progression [9, 10].

Hence, after a brief review on AD mechanisms and pathways, this paper mainly focuses on the effect of stem cell therapy on AD and the positive roles biomaterials as nano and molecular scaffold play in stem cell differentiation AD treatment.

2. ALHIMER'S DISEASE

N eurodegenerative consist of two words: the first part (neuro) refers to the brain and second part refers to a process that leads to the decline of some parts of the central nervous system. AD is one of the neurodegenerative diseases which is proved to impact 10 percent of all people over age 65 and 50 percent of people over age 85 [1]. This disease has 3 stages described in Table 1.

Table 1. Stages of Alzheimer disease (summarized from [11]).

very early AD	Cells lose their connection with another cell (synapses) and then apoptosis occur. Regions of the brain responsible for cognitive function, memory and learning ability are affected. The patient loses cognitive ability.
mild to moderate AD	Behavioral and personality changes occur and patient loses speaking ability
severe AD	patients don't recognize their family

Table 2. The main factor involved in the disease (summarized from [12]).

Amyloid plaques	These plaques consist of deposits of beta amyloid protein, dead cells, and other factors.
Neurofibrillary tangles	Tau proteins which exist on the cytoskeleton within the cell are hyperphosphorylated and then being separated from cytoskeleton and form tangles, and also the cytoskeleton breaks apart.
Shrinking of brain tissue	As the disease progresses the number of cell injury and death increases and finally cause brain atrophy.

The first part of the brain affected by AD is hippocampus that spread to other areas of the brain with the progression of the disease. Finally, the whole of the brain will be surrounded. The effect of acetylcholine (ACh) on memory and learning function has been proved and also it has been showed that in AD, Choline acetyltransferase (ChAT), the enzyme that responsible for acetylcholine synthesis, is impaired followed by degeneration of cholinergic neurons in the basal forebrain [13].

Two key pathogen factors in AD are summarized in Table 2 which forms the major constituent of intracellular neurofibrillary tangles (NFTs) [12]. Beta amyloids (Aβ) form plaques that activate microglia and astrocytes that respond to cerebral amyloidosis by chronic proinflammatory activation[14]. Further, a series of the investigation showed that neuroinflammatory process is another contribution factor in AD.

AD can be divided into two categories: Sporadic (late-onset) and genetic (early-onset) disease. The first type is more common and allocates about 95 percent of whole patients. It is conceivable that some factors such as environmental factors as well as aging, stress, glucose intolerance, cardiovascular factors, obesity and educational background are effective in creating this type of AD [15]. Also, the only well-accepted genetic risk factor for sporadic AD is polymorphism within the ApoE gene [16]. The heredity or genetic type of this disease is caused by mutation of three genes which includes the genes for amyloid precursor protein (APP), presenilin 1 or presenilin 2 which presenilin is a member of the γ-secretase complex that acts with β-secretase to break up APP which results in releasing beta-amyloid peptides with different lengths. Aβ peptides with 40 and 42 amino acids are the dominant species named (Aβ1–40) and (Aβ1–42), respectively. Aβ1–42 is the most toxic species [11].

Due to limitations in the study of the human brain, animal models selected for the study of Alzheimer. These animals should have some basic features such as biological similarities with

humans to provide more reliable results. Rat, mice, and feline are good options based on the result of some researchers [17, 18].

3. STEM CELL THERAPY IN AD

One of the most advanced and newest therapies for AD is stem cell therapy. This treatment is based on usage of stem cells to replace damaged cells in AD. In addition, stem cells have other applications. They could be used as a model of AD through genetic manipulation to assess the effect of drug and diagnostic pathway of disease and delivery vehicle of some growth factor and genes useful for AD treatment. On the other hand, neurogenesis which is important for cognitive improvement in AD mice can be achieved by means of stem cells. It was showed in some AD mouse models including mutant APP model, mutant PS models and multi-mutant model that amyloid beta plaque and NFT produced in these models cause reduction of neurogenesis [17]. Therefore, neural stem cells can be differentiated into precursor cells and subsequently progenitor cells to become adult neurons.

Here an overview of some studies is presented to assess of therapeutic effect of different types of stem cells on AD. Scientists use stem cells from different sources which include embryonic stem cells, adult stem cells and IPS from adult tissues.

3.1. Embryonic stem cell. The embryonic stem can be found in the embryo. Some studies indicate efficacy of mesenchymal stem cells (MSCs) to improve the learning and memory abilities in AD models of the animal.

It was thought that the main cause of AD is beta amyloid plaques, however, another important factor is the neuroinflammatory process that mediated by Aβ plaque-induced microglia cells [19]. Microglial cells are a group of nerve cells that support and protect neurons. These cells have a duty to eliminate damaged cells and direct neuron progenitor cells to differentiate into the target cells of the affected area [20]. Alternatively-activated microglia is a state when these cells accumulated around Aβ deposit activate normally and their structure would change from ramified to amoeboid which is favorable for phagocytosis of damaged cells. Although, Excessive activation of these cells is undesirable owing to the production of additional cytotoxic factors such as superoxide, nitric oxide (NO), and tumor necrosis factor (TNF)- α. This type of activated microglia is called chronically activated microglia [21].

In this regard, it was shown that intravenous injection of human placenta amniotic membrane-derived mesenchymal stem cells (AMSCs) in a Tg2576 (APPswe) transgenic mouse model of AD resulted in improvement of learning ability due to the reduction of Aβ plaques; additionally, the number of ED1-positive phagocytic microglia cells in AMSC-injected mice was more than control group (phosphate-buffered saline-injected mice). A number of proinflammatory cytokines, interleukin-1, and tumor necrosis factor-α was lower and anti-inflammatory cytokines, interleukin-10 and transforming growth factor-β was higher in AMSC-injected mice than control one. At last, observations showed that the level of Aβ degrading enzymes was higher in AMSC-injected mice than control. This result suggests that AD can be improved by modulating the immune system [22].

The role of the human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSC) in the treatment of neurological disorders such as Alzheimer was investigated and it was indicated that transplantation of hUCB-MSC into amyloid precursor protein and presenilin1 double-transgenic mice may lead to promoted alternative microglia activation by opposing proinflammatory and stimulating anti-inflammatory pathways, improved cognitive defects, reduced Aβ deposits, β-secretase 1 (BACE-1) level and tau hyperphosphorylation in the brain[23] .

Since dysfunction of cholinergic neurons is common in cognitive disorders, scientists are looking for a suitable cell source to restore cholinergic neurons and improve the cognitive problems that occur in AD. Wharton's jelly mesenchymal stem cells (WJ-MSCs) (Wharton's jelly of the umbilical cord is the embryonic mucous connective tissue lying between the amniotic epithelium and the umbilical vessels) is a promising cell source for such cell replacement [24]. These cells were transformed from spindle-shaped WJ-MSCs into bulbous cells with the ability to express markers of cholinergic neurons. As a result, secretion of acetylcholine from induced WJMSCs increased showing that WJ-MSCs have the Ability to differentiate into cholinergic-like neurons at In vitro [25].

3.2. Adult stem cell. Cholinergic system dysfunction occurred in Alzheimer causes reduction of choline acetyltransferase enzyme activity, which is responsible for the production of acetylcholine [26]. To solve this problem, a series of drugs act as blocking agents of enzymatic activity of Ache are used to increase the level of acetylcholine [27]. These drugs only slow down disease and cannot stop the destruction process. Thus, there is a need for an effective treatment.

Stem cell therapy is a good option. The effect of human neural stem cell (NSCs) in AD was investigated and it was found that these cells have the ability to differentiate into cholinergic neurons .which this occurs, is a favorable effect in improving AD [28].

It was observed that transplantation of NSC line over-expressing human choline acetyltransferase gene (F3.ChAT NSCs) into the brain of the rat as a model of AD leads to damage to cholinergic nerves. Transplantation caused increased level of acetylcholine in cerebrospinal fluid (CSF) and cognitive ability improved in these animal models.

Also, it was observed that F3.ChAT NSCs migrated to different areas of the brain including the cerebral cortex, hippocampus, striatum, and septum, and differentiated into nerve cells such as neurons and astrocytes [29].

It demonstrated that transplantation of bone marrow-derived mesenchymal stem cells (BM-MSCs) into the brains of AD C57BL/6 mice model that performed by injecting amyloid-β (Aβ) into the dentate gyrus (DG) of hippocampus increased the activity of the microglia and led to a reduction of Aβ deposition level [30].

Additionally, the effect of MSCs as a therapeutic agent and gene delivery vehicle in brain disease was investigated. Stem cells can be engineered genetically to stimulate the release of trophic factors with the neuroprotective role that improves angiogenesis, prevent fibrosis and apoptosis and also stimulate recruitment of tissue-residing stem cells followed by proliferation and differentiation [31].

The effect of brain-derived neurotrophic factor (BDNF) on NSCs function in AD was discussed in a series of studies. For example, NSCs obtained from the hippocampus transplanted into transfected rat basal forebrain and then BDNF was injected into the lateral ventricle. Finally, it was observed that NSCs were differentiated into neural cells (neurons and astrocytes) in the injected area. The Y-maze test was used to measure memory and learning abilities and results indicated that adding BDNF improved treatment [32].

Another approach is using genetically modified stem cells as carriers of nerve growth factors (NGF) [33]. This factor has a role in preventing cholinergic cell degeneration it cannot cross the BBB. This problem could be solved by means of releasing this factor from genetically modified cells. To apply this method to human, two items need to be considered: Host immune response should be regulated and tumorigenesis due to transplanting these genetically modified cells should be considered.

In a work done by Borlongan, genetically modified cell line called HB1.F3 transfected with the cholinergic acetyltransferase. It was concluded that these cells can improve cognitive defects, along with up-regulation of acetylcholine levels in cerebrospinal fluid [33].

Recent studies have shown that antidepressants are effective for increases of neurogenesis in the hippocampus of an adult human. A dose-dependent effect of fluoxetine on the proliferation and neural differentiation of NSCs into neurons was found [34].

SELADIN-1 (selective AD INdicator-1) is an anti-apoptotic gene that its expression decreases in AD. With attention to the point that SELADIN-1 catalyzes the transformation of desmosterol into cholesterol, cholesterol levels drop in AD. Disruption of cholesterol homeostasis in neurons increases the sensitivity of cells to toxic agents. In this regard, stem cells expressing SELADIN-1 can be used. Expression of this gene has a protective effect against toxicity of beta–amyloid oxidative stress in neuroglioma H4 cells and activity of caspase 3, which is a key factor in apoptosis [35].

In recent years, the neurogenic capacity of different stem cell types extracted from hair follicle and dental tissues has been assessed for AD treatment. Epidermal neural crest stem cells (EPI-NCSC) can be differentiated into neurons and glial cells (astrocytes and oligodendrocytes) or cholinergic cells [36]

Furthermore, dental pulp stem cells (DPSCs) are a good source for stem cell therapy. Before using these cells, the neurogenesis ability of these cells was assessed and was confirmed that this cell expresses neural marker and can differentiate to neuron. Generally, extraction of DPSCs from the human adult tooth is done via two methods: collagenase treatment and explants method. The efficiency of collagenase method and its proliferation potential was higher compared to explants method [37].

The potential of using hematopoietic stem cells in AD treatment is also investigated. In fact, the resident microglia cells of central nervous system surround plaque in the early stages of plaque formation. Other cells appear with time and presence of them causes Aβ plaque and consequent rate of diseases to reduce since these cells have a high degenerative effect on plaques. Blood –derived monocytes or their precursors are a good option for gene therapy because of their ability to populate in adult nervous systems [38, 39].

3.3. Use of IPSs. IPSs are artificial stem cells produced by reprogramming of adult cell obtained from an adult tissue in order to return them to stem cells state. These cells introduced by Yamanaka for the first time seems to have pluripotency. These cells could be used in diseases like Alzheimer in two ways. They can be used as a cell source to generate NSCs and replace damaged cells, as well as they can be used as AD models to understand pathways of disease and assess effects of drugs.

In one study, IPSs were generated via mutation in presenilin-1 (PSEN1) (agent cause inherent AD) of fibroblast cells received from AD patients. Control and AD IPS cells were differentiated into forebrain neurons by using both embryoid body (EB) and monolayer methods. The result showed that human IPS neuronal cells response to exogenous oligomerized beta by induction of pro-apoptotic proteins such as Bim. They also showed substantial biochemical and phenotypic differences between control and AD neuronal cells such as increasing the ratio of secreted Aβ 42/Aβ 40 and enhancing of cell death in response to apoptotic stimuli. This study revealed that IPS is a good AD model for study of this disease [40]

Somatic-derived IPS taken from patients gives us more information about AD diseases. As a case in point, animal and human fibroblast cells turned into IPS cells using four transgenes of Oct3/4, Sox2, c-Myc, and Klf4 [41]. To eliminate bad effects of the c-Myc such as tumor formation or cell transformation, Oct4, Sox2, Nanog, and LIN28 genes can be used [42]. It has been shown that these modified cells are genetically stable and identical to the natural cells, so these cells are suitable for the study of diseases.

The final step is to transform these modified cells into desired cells in the presence of some growth factors. For example fibroblast growth factors-2 (FGF-2), ß-mercaptoethanol, and L-glutamine will generate NSCs from IPSCs [43]. Specific progenitor cells make certain adult cells with the presence of specific growth factors. It means that progenitor cells like NSCs can only produce limited cell types such as a neuron, astrocytes, oligo aerocysts in the presence of platelet-derived growth factors, ketonic acid (RA), and some neurotrophins can [44] [45].

3.4. Combining nano-biomaterials with stem cells for ad treatment. Despite the excellent abilities of NSCs such as self-renewing and differentiating into the neuron, astrocytes, and oligodendrocytes, surviving sufficient amount of these cells and grafting integration is a major problem. Hence, creating a good environment similar to the natural niche of stem cells is critical to guide stem cells toward nerve regeneration.

The scaffolds not only act as a carrier for cells but should also stimulate specific cellular responses at the molecular level [46] which include supporting endogenous or exogenous cells

proliferation, migration and homing and even promoting axonal growth at the injured brain site.

Both biochemical and biophysical properties that involved in the niche of stem cells must be noted in the production of functionalized scaffolds. Biophysical properties include ECM architecture and mechanical properties while biochemical properties are chemical agents. These bioactive factors are soluble cytokines and growth factors secreted from adjacent cells, as well as cell-adhesion molecules of ECM. Understanding the relationship between neural stem cells and biomaterials parameters and their effect cell fate is a huge success for nerve tissue regeneration [47, 48].

To date, different scaffolds were designed and used as a substrate for nerve tissue engineering . Scaffolds made from nanofibers of poly (3-caprolactone)-gelatin showed a positive effect in differentiation and proliferation of c17.2 cells [49]. PCL-gelatin, [50] amine functionalized PCL[51] and nano-structured porous PLLA scaffolds [52] and nano-structured electrospun collagen scaffolds [53] were also utilized. It was showed that alignment of fibers in nanofibrous scaffolds is important for differentiation of NSCs into neural cells [50] and patterned fiber scaffolds can guide neural outgrowth [8]. The tensile strength of fibrous scaffolds is also important for neural differentiation in such a way that a composite scaffold made from copolymers of PLC-PLA (PLCL) and collagen improved differentiation because of increased tensile strength compared to PLCL alone [54]. In addition to fibrous scaffolds, other forms of scaffold applied for nerve regeneration, as a case in point a tubular PGA scaffold filled with porous collagen sponge could be noted which helped successfully to the regeneration of peripheral nerve gaps [55]. It is regarded that scaffolds used as nerve regeneration templates are better to have electrical conductivity. To this end, different methods used to induce conductivity into scaffolds through, for example, doping scaffold material with carbon nanotubes (CNTs) [56]. A review by Wong et al [7] presented valuable information about different materials used as cell carriers and scaffolds for nerve tissue regeneration. Besides the scaffold material and physical and biochemical properties of that, the surface and coating of the scaffold is paramount importance in determining the interaction of cells with biomaterial and biomedical application[57]. Different functional groups can be fixed onto a substrate to alter differentiation. For example, the morphology of NSCs change in response to SO_3H immobilized surfaces or COOH, NH_2, SH; CH_3 functional groups cause differentiation of NSCs into neurons, Olgodanrocyt, and astrocytes [47]. Another new approach to fight AD is using molecular scaffolds. These scaffolds are capable of adjusting molecular events leading to AD. Benzazole scaffolds are a group of these molecular mediators in AD treatment. Benzazole compounds not only play a therapeutic effect on AD through interfering in Aβ aggregation but also are used for monitoring of this aggregation and detecting plaques [10]. Another group of molecular scaffolds for AD treatment is compounded containing α,β-unsaturated carbonyl groups such as chalcones and coumarins. These scaffolds help to the improvement of AD disease through the mechanism of inhibiting Aβ aggregation and breaking preformed Aβ oligomers [9].

3.5. Drug delivery system (dds) for ad treatment. Drug delivery system is important in the treatment of Alzheimer diseases. The importance of these systems is that not only they can help to cross drugs from blood brain barrier (BBB) and reaching to the desired portion of the brain, but also solve the problem of poor solubility and bioavailability of some drugs. Despite many drugs exist for Alzheimer therapy including anti-AB targeting molecules, AB aggregation inhibitor drugs[58], and acetylcholine esterase inhibitor, results of in vivo testing of them has not been successful adequately owing to the presence of this brain barrier. Administration of existing drugs such as donepezil, galantamine, rivastigmine, and memantine with the help of carriers could be done from different routes including oral, sublingual, intranasal, intramuscular and transdermal [59], therefore, many attempts have been made to design delivery systems in the form of nanoparticles with the ability to traverse BBB and target amyloid self-aggregate[60]. In this approach, PLGA nanoparticles, PLA nanoparticles, nanoliposomes [61], nano and microemulsion, liquid crystals [3] , magnetic nanoparticles[62]and gold nanoparticles have shown enhanced BBB permeation. One approach to boost permeation through BBB is inducing a positive charge to the surface of the nanoparticle, especially through amino groups. This helps to the stronger electrostatic interaction between particles and endothelial cell membrane and consequently drug uptake in these regions. In this regard, cationic polymers such as chitosan have been used successfully. Another approach is functionalizing nanoparticles with cell penetrating peptide to enhance endocytotic uptake [3, 63]. When using nanoparticles as a delivery vehicle, distribution of them into the brain could be controlled to achieve a localized delivery of anti-Alzheimer drugs. These nanoparticles could be conjugated with ligands that recognize amyloid. It was found that intraperitoneal injection of silver nanoparticles cause aggregation of this particle into the hippocampus of the brain hence these particles could be bond to drugs and be utilized as delivery vehicles [64, 65]. The surface of nanoparticles could be functionalized with antibodies that target BBB receptors or AB peptides although these particles could be coated with cationic molecules or polysorbate 80 [66]. Further studies on the design of drug delivery systems are needed to enhance drug permeation through BBB and increase local delivery of drugs to the suffered regions of the brain in Alzheimer disease and increase drug effect.

4. CONCLUSIONS

Alzheimer is a neurodegenerative disease in which neurons are damaged and communication between cells is impaired due to the low level of acetylcholine and finally cells die. Patients in the first stage of disease suffer from impaired cognitive abilities including memory and learning. Many mechanisms are involved in this disease, Such as amyloid plaques, inflammation caused by microglia cells and tau protein fibers. Existing drugs for the treatment of disease only slow down the progression of the disease. On the other hand, BBB restricts access of effective amount of drugs to the injured brain of patients .therefore DDS is suggested for enhancement of Alzheimer therapy. Besides such methods which are based on drugs, stem cells are used to replace damaged regions by means of differentiating into neurons. Stem cells have the ability to

differentiate into neurons and then the level of the beta-amyloid deposition and also the secretion of inflammatory cytokines decrease while the level of acetylcholine increased and subsequently cognitive deficits improved. Also, for investigation of effects of drugs and understanding of pathways of disease, stem cells can be used as a model for AD disease. Recently, genetic manipulation of stem cells is used to increase efficiency. Also, it was observed that changing the parameters of biomaterials as stem cell niche direct differentiation of stem cells into the desired type. A better understanding of disease mechanisms and the application of genetic engineering and biomaterials is crucial to achieving the highest level of differentiation and survival of neurons and enhance the quality of treatment.

5. REFERENCES

[1] Lawrence S.B. Goldstein, Meg Schneider, Chapter 9- Using stem cells to understand and treat neurodegenerative disease. Stem Cells for Dummies, **2010.**

[2] Mattson M.P. Emerging neuroprotective strategies for Alzheimer's disease: dietary restriction, telomerase activation, and stem cell therapy. Experimental Gerontology**,** 35,489-502, **2000.**

[3] Fonseca-Santos B.G.M., Chorilli M. Nanotechnology-based drug delivery systems for the treatment of Alzheimer's disease, 10,4981-5003, **2015**.

[4] Raff M. Adult Stem Cell Plasticity: Fact or Artifact? Annual Review of Cell and Developmental Biology**,** 19,1-22, **2003.**

[5] Smith A.G. Embryo-Derived Stem Cells: Of Mice and Men. Annual Review of Cell and Developmental Biology**,** 17,435-62, 2**001.**

[6] Henningson C.T, Jr., Stanislaus M.A, Gewirtz A.M. Embryonic and adult stem cell therapy. Journal of Allergy and Clinical Immunology,111, 745-753, **2003.**

[7] Wong F.S.Y., Chan B.P., Lo A.C.Y. Carriers in Cell-Based Therapies for Neurological Disorders. International Journal of Molecular Sciences,15,10669-723, **2014**.

[8] Richard J.M. Patterned and functionalized nanofiber scaffolds in three-dimensional hydrogel constructs enhance neurite outgrowth and directional control. Journal of Neural Engineering,11,066009, **2014**.

[9] Bag S., Ghosh S., Tulsan R., Sood A., Zhou W., Schifone C., *et al*. Design, synthesis and biological activity of multifunctional α,β-unsaturated carbonyl scaffolds for Alzheimer's disease. Bioorganic & Medicinal Chemistry Letters, 23,2614-8, **2013**.

[10] Noel S., Cadet S., Gras E., Hureau C. The benzazole scaffold: a SWAT to combat Alzheimer's disease. Chemical Society Reviews, 42,7747-62, **2013**.

[11] Selkoe D.J., Wolfe M.S. Presenilin: Running with Scissors in the Membrane. Cell, 131,215-21, **2007**.

[12] Huang H.C, Jiang Z.F. Accumulated amyloid-beta peptide and hyperphosphorylated tau protein: relationship and links in Alzheimer's disease. J Alzheimers Dis, 16,15-27, **2009.**

[13] Francis P.T., Palmer A.M., Snape M., Wilcock G.K. The cholinergic hypothesis of Alzheimer's disease: a review of progress. Journal of Neurology, Neurosurgery & Psychiatry, 66,137-47, **1999**.

[14] Praticò D., Trojanowski J.Q. Inflammatory hypotheses: novel mechanisms of Alzheimer's neurodegeneration and new therapeutic targets? Neurobiology of Aging, 21,441-5, **2000**.

[15] Small G.W. The pathogenesis of Alzheimer's disease. J Clin Psychiatry, 59,l 9:7-14, **1998**.

[16] Roses A.D. Apolipoprotein E and ALzheimer's Disease: The Tip of the Susceptibility Iceberg. Annals of the New York Academy of Sciences, 855,738-43, **1998**.

[17] Chuang T.T. Neurogenesis in mouse models of Alzheimer's disease. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1802,872-80, **2010**.

[18] Munoz J.L., Greco S.J., Patel S.A., Sherman L.S., Bhatt S., Bhatt R.S., *et al*. Feline bone marrow-derived mesenchymal stromal cells (MSCs) show similar phenotype and functions with regards to neuronal differentiation as human MSCs. Differentiation, 84,214-22, **2012**.

[19] Salloway S., Mintzer J., Weiner M.F., Cummings J.L. Disease-modifying therapies in Alzheimer's disease. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 4, 65-79, **2008**.

[20] Ekdahl C.T., Kokaia Z., Lindvall O. Brain inflammation and adult neurogenesis: The dual role of microglia. Neuroscience, 158,1021-9, **2009**.

[21] Heneka M.T., O'Banion M.K. Inflammatory processes in Alzheimer's disease. Journal of Neuroimmunology, 184, 69-91, **2012.**

[22] Kim K.S, Kim H.S., Park J.M., Kim H.W., Park M.K., Lee H.S., *et al*. Long-term immunomodulatory effect of amniotic stem cells in an Alzheimer's disease model. Neurobiology of Aging, 34, 2408-20, **2013.**

[23] Lee H.J., Lee J.K., Lee H., Carter J.E, Chang J.W., Oh W., *et al*. Human umbilical cord blood-derived mesenchymal stem cells improve neuropathology and cognitive impairment in an Alzheimer's disease mouse model through modulation of neuroinflammation. Neurobiology of Aging, 33, 588-602, **2012.**

[24] Nekanti U., Dastidar S., Venugopal P., Totey S., Ta M. Increased Proliferation and Analysis of Differential Gene Expression in Human Wharton's Jelly-derived Mesenchymal Stromal Cells under Hypoxia. International Journal of Biological Sciences, 6, 499-512, **2010**.

[25] Liang J., Wu S., Zhao H., Li S.L., Liu Z.X., Wu J., *et al.* Human umbilical cord mesenchymal stem cells derived from Wharton's jelly differentiate into cholinergic-like neurons in vitro. Neuroscience Letters, 532, 59-63, **2013**.

[26] Kása P., Rakonczay Z,, Gulya K. The cholinergic system in Alzheimer's disease. Progress in Neurobiology, 52, 511-35, **1997**.

[27] Musial A., Recent Developments in Cholinesterases Inhibitors for Alzheimers Disease Treatment. Current Medicinal Chemistry, 14, 265 - 79, **2007.**

[28] Xuan A.G., Luo M., Ji W.D., Long D.H. Effects of engrafted neural stem cells in Alzheimer's disease rats. Neuroscience Letters, 450, 167-71, **2009**.

[29] Park D., Lee H.J., Joo S.S., Bae D.K., Yang G., Yang Y.H., *et al*. Human neural stem cells over-expressing choline acetyltransferase restore cognition in rat model of cognitive dysfunction. Experimental Neurology, 234, 521-6, **2012**.

[30] Lee J.K., Jin H.K., Bae J.S. Bone marrow-derived mesenchymal stem cells reduce brain amyloid-β deposition and accelerate the activation of microglia in an acutely induced Alzheimer's disease mouse model. Neuroscience Letters, 450, 136-41, **2009**.

[31] Huang B., Tabata Y., Gao J.Q. Mesenchymal stem cells as therapeutic agents and potential targeted gene delivery vehicle for brain diseases. Journal of Controlled Release, 162, 464-73, **2012**.

[32] Xuan A.G., Long D.H., Gu H.G., Yang D.D., Hong L.P., Leng S.L. BDNF improves the effects of neural stem cells on the rat model of Alzheimer's disease with unilateral lesion of fimbria-fornix. Neuroscience Letters, 440, 331-5, **2008**.

[33] Borlongan C.V. Recent preclinical evidence advancing cell therapy for Alzheimer's disease. Experimental Neurology ,237, 142-6, **2012**.

[34] Chang K.A., Kim J.A., Kim S., Joo Y., Shin K.Y., Kim S., *et al*. Therapeutic potentials of neural stem cells treated with fluoxetine in Alzheimer's disease. Neurochemistry International, 61, 885-91, **2012**.

[35] Benvenuti S., Saccardi R., Luciani P., Urbani S., Deledda C., Cellai I., *et al*. Neuronal differentiation of human mesenchymal stem cells: Changes in the expression of the Alzheimer's disease-related gene seladin-1. Experimental Cell Research, 312, 2592-604, **2006**.

[36] Najafzadeh N., Esmaeilzade B., Dastan Imcheh M.. Hair follicle stem cells: In vitro and in vivo neural differentiation. World Journal of Stem Cells, 7, 866-72, 2**015**.

[37] Verma K., Bains R., Bains V.K., Rawtiya M., Loomba K., Srivastava S.C. Therapeutic potential of dental pulp stem cells in regenerative medicine: An overview. Dental Research Journal, 11, 302-8, **2014**.

[38] Shin J.W., Lee J.K., Lee J.E., Min W.K., Schuchman E.H., Jin H.K., *et al*. Combined Effects of Hematopoietic Progenitor Cell Mobilization from Bone Marrow by Granulocyte Colony Stimulating Factor and AMD3100 and Chemotaxis into the Brain Using Stromal Cell-Derived Factor-1α in an Alzheimer's Disease Mouse Model. STEM CELLS, 29, 1075-89, **2011**.

[39] Naert G., Rivest S. Hematopoietic CC-Chemokine Receptor 2 (CCR2) Competent Cells Are Protective for the Cognitive Impairments and Amyloid Pathology in a Transgenic Mouse Model of Alzheimer's Disease. Molecular Medicine, 18, 297-313, **2012**.

[40] Hossini A.M., Megges M., Prigione A., Lichtner B., Toliat M.R., Wruck W., *et al.* Induced pluripotent stem cell-derived neuronal cells from a sporadic Alzheimer's disease donor as a model for investigating AD-associated gene regulatory networks. BMC Genomics, 16, 84, **2015**.

[41] Takahashi K., Tanabe K., Ohnuki M., Narita M., Ichisaka T., Tomoda K, *et al*. Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors. Cell, 131, 861-72, **2007.**

[42] Yu J., Vodyanik M.A., Smuga-Otto K., Antosiewicz-Bourget J., Frane J.L., Tian S., *et al*. Induced Pluripotent Stem Cell Lines Derived from Human Somatic Cells. Science, 318, 1917-20, **2007**.

[43] Jensen M.B., Yan H., Krishnaney-Davison R., Al Sawaf A., Zhang S.C. Survival and Differentiation of Transplanted Neural Stem Cells Derived from Human Induced Pluripotent Stem Cells in A Rat Stroke Model. Journal of Stroke and Cerebrovascular Diseases, 22, 304-8, **2013**.

[44] Jandial R.S.I., Ames C.P., Snyder E.Y. Genetic modification of neural stem cells. Mol Ther, 16, 450-7, **2008**.

[45] Gao A., Peng Y., Deng Y., Qing H. Potential therapeutic applications of differentiated induced pluripotent stem cells (iPSCs) in the treatment of neurodegenerative diseases. Neuroscience, 228, 47-59, **2013**.

[46] Khayyatan F., Nemati S., Kiani S., Hojjati Emami S., Baharvand H. Behaviour of Human Induced Pluripotent Stem Cell-Derived Neural Progenitors on Collagen Scaffolds Varied in Freezing Temperature and Laminin Concentration. Cell Journal (Yakhteh)16, 53-62, **2014.**

[47] Yao S., Liu X., Wang X., Merolli A., Chen X., Cui F. Directing neural stem cell fate with biomaterial parameters for injured brain regeneration. Progress in Natural Science: Materials International, 23, 103-12, **2013**.

[48] Emami S.H., Chaudhry M.A.S. Self-renewal and Proliferation of Murine Embryonic Stem Cells: A Study of Glycosaminoglycans Effect on Feeder-Free Cultures. Journal of Bioactive and Compatible Polymers, 22, 314-22, **2007**.

[49] Ghasemi-Mobarakeh L., Prabhakaran M.P., Morshed M., Nasr-Esfahani M.H., Ramakrishna S. Electrospun poly(ε-caprolactone)/gelatin nanofibrous scaffolds for nerve tissue engineering. Biomaterials, 29, 4532-9, **2008.**

[50] Gupta D., Venugopal J., Prabhakaran M.P., Dev V.R.G., Low S., Choon A.T., *et al.* Aligned and random nanofibrous substrate for the in vitro culture of Schwann cells for neural tissue engineering. Acta Biomaterialia, 5, 2560-9, **2009.**

[51] Omrani M.M., Kiaie N., Ansari M., Kordestani S.S. Enhanced Protein Adsorption, Cell Attachment, and Neural Differentiation with the Help of Amine Functionalized Polycaprolactone Scaffolds. Journal of Macromolecular Science, Part B, 55, 617-26, **2016**.

[52] Yang F., Murugan R., Ramakrishna S., Wang X., Ma Y.X., Wang S. Fabrication of nano-structured porous PLLA scaffold intended for nerve tissue engineering. Biomaterials, 25, 1891-900, **2004**.

[53] Timnak Fyg A., Ramin Pajoum Shariati S., Bahrami S.H., Hojati Emami S., *et al*., Fabrication of nano-structured electrospun collagen scaffold intended for nerve tissue engineering. Journal of Materials Science-Materials In Medicine, 22, 1555 -67, **2011.**

[54] Prabhakaran M.P., Venugopal J.R., Ramakrishna S. Mesenchymal stem cell differentiation to neuronal cells on electrospun nanofibrous substrates for nerve tissue engineering. Biomaterials, 30, 4996-5003, **2009**.

[55] Nakamura T., Inada Y., Fukuda S., Yoshitani M., Nakada A., Itoi S.I, *et al.* Experimental study on the regeneration of peripheral nerve gaps through a polyglycolic acid–collagen (PGA–collagen) tube. Brain Research, 1027, 18-29, **2004**.

[56] Lau C., Cooney M.J., Atanassov P. Conductive Macroporous Composite Chitosan−Carbon Nanotube Scaffolds. Langmuir, 24, 7004-10, **2008.**

[57] Naghib S.M., Ansari M., Pedram A., Moztarzadeh F., Feizpour A., Mozafari M. Bioactivation of 304 stainless steel surface through 45S5 bioglass coating for biomedical applications. International Journal of Electrochemical Science, 7, 2890-903, **2012**.

[58] Mojtaba A., Mehran H.R., Soheila S.K., Ali A.M.M., Najmeh P. Prevention of Serum Albumin Glycation/Fibrillation by B-Cyclodextrin Functionalized Magnetic Nanoparticles. Protein & Peptide Letters, 22, 594-600, 2**015**.

[59] Di Stefano A., Iannitelli A., Laserra S., Sozio P. Drug delivery strategies for Alzheimer's disease treatment. Expert Opinion on Drug Delivery, 8, 581-603, **2011.**

[60] Ansari M., Salahshour-Kordestani S., Habibi-Rezaei M., Movahedi A.A.M. Synthesis and Characterization of Acylated Polycaprolactone (PCL) Nanospheres and Investigation of Their Influence on Aggregation of Amyloid Proteins. Journal of Macromolecular Science, Part B, 54, 71-80, **2015.**

[61] Carlos Spuch C.N. Liposomes for Targeted Delivery of Active Agents against Neurodegenerative Diseases (Alzheimer's Disease and Parkinson's Disease). Journal of Drug Delivery, 469679, **2011**.

[62] Ansari M., Habibi-Rezaei M., Salahshour-Kordestani S., Ferdousi M., Movahedi A.A.M. An investigation on the effect of β-CD modified Fe3O4 magnetic nanoparticles on aggregation of amyloid b peptide (25-35). Materials Technology, 31, 315-21, **2016.**

[63] Robinson M. Drugs and drug delivery systems targeting amyloid-β in Alzheimer's disease. molecular science, 2, 332-58, **2015**.

[64] Aliev G.D.J., Herrera A.S., Del Carmen Arias Esparza M., Morales L., Echeverria V., Bachurin S.O., Barreto G.E. Nanoparticles as Alternative Strategies for Drug Delivery to the Alzheimer Brain: Electron Microscopy Ultrastructural Analysis. CNS Neurol Disord Drug Targets 14, 9, 1235-42, **2015**.

[65] Roney C., Kulkarni P., Arora V., Antich P., Bonte F., Wu A., *et al.* Targeted nanoparticles for drug delivery through the blood–brain barrier for Alzheimer's disease. Journal of Controlled Release, 108, 193-214, **2005**.

[66] Rocha S. Targeted drug delivery across the blood brain barrier in Alzheimer's disease. Curr Pharm Des, 19, 6635-46, **2013**.

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