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A Brief Notes on Gene Therapy, Cell Therapy and Cell-Based Gene Therapy for Alzheimer's Disease

Review Article

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Abstract

Alzheimer's disease (AD) is known as an age-related neurodegenerative disease where progressive loss of memory associated with cognition defects has been noticed. Molecular analysis of AD revealed the formation of aggregated amyloid-β protein and hyper phosphorylated tau tangles at the synaptic circuit, which causes the loss of neuronal communication. At present no cure has been found for AD, but there are many new therapeutic approaches being attempted. For instance, the development of stem cell therapy is one approach for AD. In this review we highlight the merits and demerits of stem cell-based therapy, gene therapy for AD and proposed gene-modified cell therapy for AD treatment.

Introduction:

Alzheimer's disease (AD) is one of the neurodegenerative diseases that recognized by a loss of memory and cognitive function. The disease continues to progress to Dementia, an irreversible loss of memory [1]. Normally, AD starts around the ages of 55-65 or even older [2]. The familial gene-related early-onset of Alzheimer's disease (EOAD) are found among people between 40 to 50 years old with a poor prognosis [3].

The molecular analysis of the disease shows an accumulation of aggregated amyloid-β (Aβ) protein and hyper-phosphorylated tau tangles. Both are known to interfere with signal transmission [4,5]. The two forms of Aβ peptide, Aβ 1–40, and Aβ 1–42, are associated with EOAD [6]. A transmembrane amyloid precursor protein (APP), which is present in neurons, produces soluble Aβ peptide after being cleaved of by β-secretase followed by γ-secretase, [7,8].

There are no cures for AD, however, different treatment strategies are being attempted to improve the AD symptoms or slow down the progression of the disease [9,10]. Some of the main approaches to treat AD patients are:

- Inhibition of cholinesterase activities.
- Inhibition of NMDA receptor mediated signal transduction.
- Immunotherapeutic degradation of Aβ and tau deposits [11,12,13].

These treatments though bring some relief to the patients with AD but are not a cure for the disease. Recently, a new approach with stem cells and gene-modified cells are being used in the therapeutic strategies for AD along with other neurodegenerative disorders like Parkinson's disease. This review highlights the various types of stem cells therapies, gene therapies and gene-modified cell therapies for potential treatments of AD.

Possible Therapies of AD:

Small molecule inhibitors: The most direct target in anti-Aβ therapy is the Inhibition of Aβ production. Various small molecule inhibitors of β- and γ-secretase enzymes can reduce the formation of β-amyloid plaques, however, cannot reverse the existing plaques or improve the impaired cognition [14,15,16,17,18,19,20,21,22].

The inhibition of the other target, tau protein, which forms the neurofibrillary tangles are being tested in phase I and II trials with small molecule inhibitors [23,24].

Gene Therapy: Familial early-onset familial AD (EOAD) cases are related with the mutation of genes encoding PSEN1, PSEN2 and APP. Soluble Aβ-oligomers are also causing impaired synaptic and neuronal functions [25]. However, none of the transgenic mouse models that accumulate Aβ-oligomers and Aβ-plaques have reproduced the neurodegenerative pathologies. There are other proteins like hyper-phosphorylated tau, apolipoprotein E (APOE)-associated lipid metabolism and inflammation that are linked to AD cases [26,27,28].

Several proteases such as neprilysin, insulin degrading enzyme (IDE), cathepsin B, matrix metalloproteinases, plasmin, endothelin-converting enzyme (ECE) and angiotensin converting enzyme (ACE) have been implicated in Aβ-degradation [29,30]. Therefore, the therapeutic approaches should be aimed for enhancing the gene for Aβ-degradation activity in AD patients.

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In animal study viral vector-mediated neurotrophic factors gene transfer can potentially halt the progression of neuro-degeneration in AD [31,32,33]. However, systemic injection of certain growth factors results in strong peripheral side effects, and most of the proteins do not cross the blood–brain barrier.

Cell therapy: Thoughts of cell therapy for AD cases came from the achievement of doing replacement of the loss of DA-ergic neural cells by transplanting a functional neural cells in PD patients [34, 35]. Recently, it was shown that induced pluripotent stem cells (iPSCs) derived from astrocytes when transplanted into PD brain, turns into dopamine-producing cells inside there [36,37].

Since AD and PD at the their cellular and molecular level are more similar to each other [38], we believe cell replacement therapy for AD can also be done provided the right cell-type can be selected. However, in contrasts to PD, the possibilities in AD are a great challenge because of widespread pathological changes in their brain [39].

Here we will discuss, not only what cells but also why and how our strategic concept would be the best choice for AD cell-therapy. In order to achieve a successful cell-replacement therapy for AD, some important criteria are to be considered:

- Selection of cells whose growth potential and survival length is acceptable for having enough amount of cells for transplantation, but not a cancer cell.
- Should differentiate.
- Should have Axon extension ability.
- Should have ability to form functional synapses.
- Stable and long-term integration of the cells into the host brain circuitry.

Selection of cells:

1. Embryonic Stem Cells (ESCs): ESCs are derived from developing blastocyst, and they produce every type of cell and tissue in the body [40,41]. Transplantation of ESCs can possibly form teratomas or teratocarcinomas and shows immune rejection [42]. Nevertheless, ESCs after differentiation to neural stem cells (NSCs), mesenchymal stem cells (MSCs), or other types of cells can be used for cell replacement therapy.

2. Neural Stem Cells (NSCs): NSCs produce neuroblasts that mature to neurons involved in the sense of smell, memory and other cognitive functions [43,44]. Therefore, the transplantation of NSCs in patients with AD signifies the use for cell replacement therapy [45]. Commercially available NSC lines (HB1.F3) have been explored for their efficacy using the PD and AD animal model [46,47,48], which showed promising improvement in their impaired cognitive function as well as their difficult movement [49]. Blurton-Jones et al. showed that NSCs transplanted into the hippocampus of aged triple transgenic mice (3xTg-AD) reversed their cognitive impairment [50]. We recently demonstrated that modification of commercially available NSCs by cell-cell interaction with human normal melanocytes increases the growth potential of NSCs and their ability to produce Dopamine, BDNF, GDNF, etc. in cell culture media [51]. In addition, NSCs can be differentiated into cholinergic neurons that are especially vulnerable in AD patients [52,53].

3. Mesenchymal Stem Cells (MSCs): MSCs are multipotent cells that can differentiate into neuronal cells and glial cells both in vitro and in vivo [54,55]. MSCs can easily be grown in large numbers as well [56,57]. MSCs can also be used for autologous transplantation [58], which bypasses the need for immunosuppressant. Bone marrow-derived MSCs transplantation into the hippocampus of APP/PS1 mice has led to reduction in Aβ deposition and tau hyper-phosphorylation and showed an improvement in spatial learning and memory [59,60]. Similar results were also obtained when MSCs derived from human umbilical chord were transplanted into AD-mouse model [61,62].

4. Induced Pluripotent Stem Cells (iPSCs): Yamanaka and Takahashi et. al. first showed that somatic cells could be transformed to induced pluripotent stem cells (iPSCs) by reprogramming with Klf4, Sox2, c-Myc, and Oct4 transcription factors [63]. In addition, similar results were documented with Nanog, and Lin28, too. [64,65].

5. Astrocytes: Several studies have shown that there are large numbers of activated astrocytes and microglia around the Aβ plaques in AD patients [66,67,68]. This indicates the involvement of astrocytes and microglia in the clearance of Aβ deposits from the AD brain. Both cultured adult and neonatal mouse astrocytes showed Aβ clearance by phagocytosis [69]. Therefore, it appears that transplantation of astrocytes could be useful in AD treatment, also.

Gene-Modified Cell-Based Therapy for AD:

Stem cells could be genetically modified to increase their growth rate and for longer survival time, but should differentiate [69]. These modified stem cells could also deliver several factors that can ameliorate neurological disorders [70].

Due to the loss of cholinergic neurotransmitters in AD, some researchers are interested in developing gene-modified cells that can produce acetylcholine (Ach). Primary fibroblast cells that are genetically engineered to express induced choline acetyltransferase have shown to produce acetylcholine (Ach) in the hippocampus of transplanted rats [71].

MSCs that overexpressed the Neprilysin (NEP) gene demonstrated the ability to degrade Aβ peptides in vitro [72]. Similar results were obtained when fibroblasts transfected with a lentivirus carrying NEP gene were transplanted into the transgenic mice [73].

Wu et al. [74] was showed that genetically modified NSCs expressing human nerve growth factor (hNGF) could integrate into host tissue and replace damaged or lost neuronal cells. Based on a phase I clinical trial, implantation of fibroblasts loaded with the hNGF gene into the forebrain of eight AD patients showed an impressive improvement in their cognitive impairment [75].

NSCs are also able to express several growth factors that can improve memory function in AD patients [76]. hNGF is one that can rescue cholinergic neurons in the rodent and primate brains and enhance cholinergic function of neurons in them [77,78]. Another growth factor, brain derived growth factor (BDNF) that is produced in brain, effects neuronal activity, their function, and survival [79]. Delivery of BDNF gene in mice and primates have reversed the loss of synapses, improved cell signaling and restored cognitive functions [80]. Furthermore, NSCs carrying transfected BDNF-gene exhibit higher efficacy in spatial learning and memory than NSCs alone [81].

Recently we have created a modified neural stem cell by cell-cell interaction with normal human melanocytes, and the modi-

fied cells can survive for long time but differentiate, produce dopamine and BDNF/GDNF [82,83,84]. Our notion, therefore, is that the cell-replacement therapy of AD/PD/Dementia patients with a modified neural cells could be relevant and productive [84,85,86,87], however various challenges like immune rejection, availability of enough amount of cells, methodologies of transplantation of cells are still remain as unanswered. Intra-cranial deep-brain surgery (DBS) for delivery of cells is loaded with many risks. Therefore, the development of extra-cranial methods of cell delivery across the blood-brain barrier (BBB) may solve this issue and simplify the procedure [89,90].

Summary:

Many studies have been done to help aid AD patients yet there are no cures that can stop or reverse the progression of the AD pathology. Different stem cells have been used to study their efficacy against AD, which are showing promising results in both in vitro and in vivo studies. Cell-based therapy using stem cells or gene-modified cells offers several advantages such as direct targeting of the pathology by incorporating new cells to replace the existing nonfunctional or non-supportive cells. Clinical studies have started and have shown satisfactory results. However some practical challenges such as cell longevity and immune-tolerance added with surgical complicacy still needs to be considered.

Intra-cranial delivery includes brain surgery which has many risk factors, therefore the development of extra-cranial methods of cell delivery across the blood-brain barrier (BBB) may be warranted. Second, the best site for graft placement is another issue to be considered, and also should it be tailored to each patient's separately. Further the methodology of cell transplantation is the another challenge in this therapeutic approach and should be carefully discussed. Finally, we need to consider the risk–benefit analysis of cell therapy for AD, as well.

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Authors Contribution:

Both the authors contributed equally.

Conflict of Interest:

The authors declare no conflict of interest, financial or otherwise.

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