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Alzheimer Disease (AD) Cell Therapy Using Human Neural Stem Cells: Validity of the Approach

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Abstract

Background: Alzheimer's Disease (AD) is an increasing neurodegenerative disease in the world where dementia is the symptoms caused due to the death of functional neural cells; and could end up even to death. No real medicines or any therapeutic regiment, other than some palliatives, are available even to date.

Prevalence: Approximately 5.5 million people in the United States and 47 million people worldwide are currently affected by AD. It is expected that by 2050, nearly a million new cases per year may develop.

Symptoms: Memory loss is usually the first sign of Alzheimer's disease which is different than normal memory problems, being it as an irreversible.

Causes: In healthy neurons, tau protein normally binds to and stabilizes microtubules, which help normal neuronal functions for transporting neurotransmitters, nutrient, and also communication with other neural cells. However, loss of neurons and synapses can happen due to the accumulation of amyloid plaques and neurofibrillary tau tangles. Therapeutic approach: Here we will be revealing the scope of human neural stem cells (hNSCs) to be used for cell replacement therapy of AD. Further, modification of NSCs with melanocytes, a neural crest originated DOPA producing cells, whether and how could be possible to upgrade the NSCs for the purposes.

Keywords: Human neural stem cells • Melanocytes • Cell-cell interaction • Dopamine • Parkinson's disease

Introduction

Alzheimer Disease (AD), where the damage of the brain cells occurs throughout many areas of the brain, is still considered as sporadic with uncertain etiology [1]. In terms of molecular pathogenesis, an abnormal accumulation of misfolded amyloid beta (A) protein aggregates which disrupts all the normal neural communications [2].

Owing to the aging of the population worldwide and lack of a cure, the number AD cases will grow substantially in the next two to three decades [3].

Present Therapy of AD

Small molecule inhibitors: Inhibition of the secretase enzymes reduce the formation of beta-amyloid plaques, but cannot reverse the existing plaques or improve cognition [4].

Other target is the tau protein, which forms the neurofibrillary tangles [5]. Inhibition of tau tangle formation, as a new new strategy are being tested on seven tau immunotherapies in phase I and II trials [6].

Gene therapy: In animal study viral vector-mediated neurotrophic factors gene transfer can potentially halt the progression of neuro-degeneration in AD [7]. 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 [8].

Thoughts of Cell Therapy

Replacement of the loss of cells by transplanting a functional neural cells is considered as a possible and may be the best option for reversing the PD symptoms [9]. Likewise, 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 [10].

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 [11]. In order to achieve a successful cell-replacement therapy for AD, some important criteria are to be considered [12].

• Selection of cells whose growth potential and survival length is acceptable for having enough amount of cells for transplantation, but not a cancer cell [13].

• 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 based on considerations of some factors

Lewy bodies: Lewy bodies, a result of -synuclein agglutination in the brain, is known to impair the neural cells and cause Parkinson's Disease

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[14]. These Lewy bodies can also develop dementia, a marker of AD [15]. Therefore, neural stem cells, which are generally considered for PD cell therapy, can also be thought for AD cell-replacement therapy [16].

Low dopamine levels: A potential link between low Dopamine levels and increased risk of Alzheimer's Disease have been scanned by highly sensitive MRI studies [17].

Loss of dopamine especially in the hippocampus area causes dementia [18]. In PD, supplementation of DOPA or Dopamine palliate the PD-symptoms, and therefore it is expected that cell-replacement by DA-ergic NSCs could palliate dementia in AD, too [19].

Importance of neurotrophic factors for AD Therapy: Nerve Growth Factor (NGF), Brain-Derived Neurotrophic Factor (BDNF), and Glial cell-Derived Neurotrophic Factor (GDNF) are secreted proteins [20]. That prevents the progression of neuronal loss, maintaining neuronal connections and function, and inducing an additional regenerative response in these neurons [21]. They are severely affected in aging process with cognitive decline [22].

Selection of cells: Therefore we should choose a cell type, for replacement therapy, that can produce DA, BDNF, GDNF etc. for cognitive repairment, as well as for the survival and protection of the rest of the neural cells [23].

Embryonic Stem Cells (ESCs): ESCs can differentiate into DA neurons in vitro and therefore can be used for AD cell therapy [24]. However, ethical issues and propensity to form teratomas limit their uses clinically [25].

Gene-transfected cells including induced pluripotent cells (iPSCs): Gene-transfected cells including induced pluripotent cells (iPSCs) with over expression of DA-ergic neurons are not even safe to use [26]. Further, the process is cumbersome, time taking, and not cost-effective [27].

Neural Progenitor Cells (NPCs): The homing qualities of NPCs can allow them as delivery vehicles of therapeutic molecules such as enzymes or antibodies to the amyloid deposition areas. However, the character of AD,

Where the cellular damage was found in many areas of the brain, imposes a greater problem with specific molecule delivery. These experiments are still ongoing, but the possibility of such therapeutic approaches could have a significant impact [28].

Human Neural Stem Cells (hNSCs): These cells are efficient in production and release of Dopamine, BDNF and GDNF, and therefore can therefore be considered for AD cell therapy. The most important physiological aspect of functional hNSCs is their capability to synthesize DA as well as catabolize any excess of it, and maintains their physiological label in the system [29]. These cells, further, differentiate and produce axons, too [30].

However, hNSCs is a slow proliferating cells and senesce after a couple of passages, rendering a low level of supply for treatment. Attempts are going to develop a natural cell modification method in our laboratory to increase the growth potential and survival length of hNSCs by a cell-cell interaction techniques [31].

Cell-cell interaction to upgrade the NSCs: A single cell can interact with other cells through physical contact and/or via secreted factors such as protein or peptide-based growth factors, cytokines, etc. [32]. In addition, cell–cell interactions are affected by the physical and biochemical properties of the surrounding extracellular matrix [33]. In humans and other mammalian systems, Lipoxin (LX) biosynthesis is an example of LO–LO (lipoxygenases) interactions via transcellular circuits [34].

Together, it appears that cell-cell interaction contribute to coordinated cellular behavior and complex biological functions in tissues, such as, embryonic development, neurotransmission, wound healing, inflammation, and many more [35].

Cell–cell interactions increases neuron formation: Neurons of the same type are often born at the same time and have similar time course in their developmental program. Neurons and axons certainly have the opportunities to interact with each other during path-finding [36].

It has been shown that nicotinic acetylcholine receptor (AChR) subunit transcript levels are differentially regulated by innervation and target tissue interactions in developing chick ciliary ganglion neurons in situ [37].

Further, Mesenchymal Stem Cells (MSCs), with a phenotype overlapping with pericytes, have promotion effects on neurogenesis and angiogenesis, which are mainly attributed to secreted growth factors and extracellular matrices [38].

Cell-cell Interaction increases Dopamine production: Dopamine is a neurotransmitter and is involved for the functions, such as movement, endocrine regulation and cardiovascular function, etc. In the periphery, dopamine is the precursor of noradrenaline, a major neurotransmitter of the sympathetic nerve system; and adrenaline, a major adrenomedullary hormone [39].

In dopamine-producing cells, the key rate-limiting enzyme tyrosine hydroxylase (TH) oxidizes tyrosine to dihydroxyphenylalanine (DOPA), which is decarboxylated to dopamine by aromatic L-amino acid decarboxylase. TH is activated by an increased level of cAMP [40].

In hemi parkinsonian rodents, the phosphorylation level of the dopamine- and cAMP-regulated phosphoprotein, (DARPP-32 kDa) at Thr34 is dramatically elevated in the lesioned striatum in response to acute dopaminergic stimulation by L-DOPA. DARPP-32 is an important component of dopamine signaling, inhibiting the dephosphorylation of proteins which are the phosphorylation targets of PKA, creating positive feedback for D1DR-mediated signaling for c-AMP formation [41].

Therefore, it appears that cAMP and/or its inducer can increase dopamine production; and dopamine or its precursor DOPA in turn can increase the cAMP level via D1-receptor mediated signaling, hence a cross talk can be expected between the neighboring cells provided they are both DOPA producing and also a cAMP inducers [42].

Selection of an effector cells for cell-cell Interaction with NSCs: Melanocyte is a neural crest originated cells, and it has melanocortin (MC1) receptor, can produce cAMP, and also converts tyrosine to DOPA (a precursor of melanin in the skin; and converts to Dopamine in the Brain) [43].

Discussion

The mean interictal and preictal EEG classification accuracy for the ordinary cross validation experiment is 93.15%. The best OCV accuracy values are obtained for patients 6, 9, 14, 18, 20 and 24 with OCV accuracy values >95% while patients 1, 4, 13 and 15 recorded the least OCV accuracy values with 89.56%, 88.72%, 89.45% and 89.35% respectively. The OCV accuracy values is >90% in nearly all the patients.

The true cross validation classification experiment gave interictal and preictal EEG classification accuracy mean of 97.57%. This is remarkably very high. All the interictal and preictal EEG signals in the datasets of some patients specifically, patients 6, 14, 18, 20 and 24 are correctly classified. Furthermore, the TCV classification accuracy value is >92% for all the patients.

A mean test classification accuracy value of 91.33% was obtained from the test classification experiment. The highest test classification accuracy result of 97.19 was realized in patient 20 while the lowest test accuracy value of 83.12% was obtained in patient 1. Test accuracy values >95% was recorded in approximately 24% of the patients.

Conclusion

The AD therapies that are available to-date are only relief based, and are unable to stop the progression of the disease. Therefore, a new effective regenerative therapeutic strategy demands a model like ours, which can stop the development and progression of these type of neurodegenerative diseases. The selection strategy of the curative cell and its modification by an effector cells, may give us a hope in near future for discovering a new remedies of such a disease.

Ethical Statements

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