Alzheimer's Disease: Stem Cell Therapy

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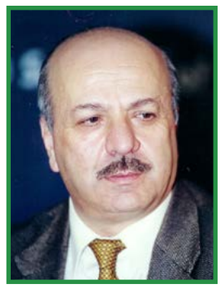

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1. Alzheimer's Disease

Alzheimer's disease (AD) is an insidious, progressive and irreversible neurodegenerative disorder leading to a life expectancy of 3-9 years after diagnosis (Todd et al.2013). AD is the world's most common dementing illness. Dementia begins with loss of memory that typically begins with subtle and poorly recognized failure of memory to slowly become more severe and, eventually, incapacitating. AD progression and final stages are characterized by confusion, poor judgment, language disturbance, agitation, withdrawal, extreme exhaustion, emotional apathy and hallucinations.

1.1 Its incidence is highest in people aged over 65. The current number of AD and related dementia cases is estimated to be 46.8 million worldwide in 2015, while the cost is around 818 billion dollars making AD a major burden to patients and society (Meek et al.1998).

1.2 Diagnosis can be either a behavioral, cognitive test or a physical examination of the patient.AD requires at least 8 years to develop fully detectible symptoms, consequently, AD is difficult to diagnose at its early stages. Therefore, it is important to use of medical imaging techniques for early stages diagnosis, but these techniques may be expensive and not very accessible.

1.3 AD could be subdivided into two categories:

1) Early-onset or familial type AD: affecting people younger than 65 years old.

2) Late-onset or non-familial type AD: affecting people older than 65 years old.

The two categories have similar symptoms but different molecular pathophysiology.

2. Causes of Alzheimer's Disease

2.1 Neuronal and synaptic loss

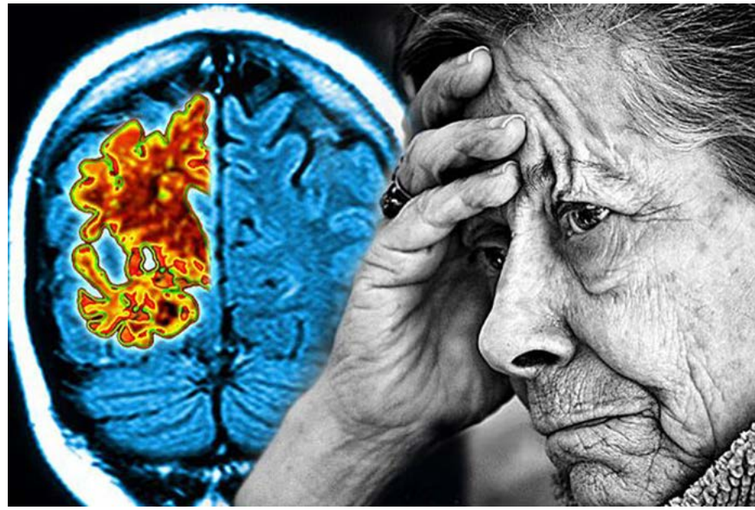
Neuronal and synaptic loss in different brain regions (parietal lobes, temporal lobes, parts of the frontal cortex..) leading to:

- alteration of levels of neurotransmitters, specially, increase in glutamate and decrease in acetylcholine (Ach) levels knowing that Ach modulates neuronal activity which plays a crucial role in building up and maintenance of memory. Consequently, decreased levels of Ach in AD contribute to memory loss, depression and exicotoxicity. Ach deficit is not the main cause of AD; previous studies showed that when inhibiting Acetylcholineesterase, enzyme that degrades Ach , only symptoms were treated.

2.2 Protein misfolding

- Further studies have considered that protein misfolding is the main cause of AD and turned the spotlight on two misfolded proteins. The first misfolded protein is Beta-amyloid (Aβ) found in two forms. Thus, neuritic and cerebrovascular plaques are composed of insoluble amyloid fibers making the Aβ plaque the origin of the AD hallmark.Aβ plaque causes cytotoxicity by inhibiting inter-cellular communications, causing oxidative damage, modulating immune response and inducing inflammation and microglial activation which leads to apoptosis contributing to Ach deficit.

- Another hallmark of AD is Tau, the second misfolded protein. In Tau hypothesis, Tau is considered to be the primary cause of AD (Billingsley and Kincaid 1997) due to the fact that it leads to cognitive impairment by modulating the axonal microtubule stability in the brain. The synaptic transmission is then blocked, synapses degenerate contributing to cognitive impairment.



In addition, Tau was also found to affect adult hippocampal neurogenesis by reducing the proliferation of stem/progenitor cells in the dentate gyrus of the brain (Pristerà et al.2013). Most of the drugs are designed to target Tau hyperphosphorylation and its aseembly. However, fully treating AD by targeting Tau or Aβ alone still fail to interest neurologists.

- As the differentiated neuronal cells could replace the AD affected neurons and potentially recover the patient's brain to a normal state, stem cells could be regarded as an alternative therapy of AD.

3. Animal models in AD therapy with stem cells

Even though the stem cell treatment for AD has not been initiated in human, experiments in several animal models have validated its potential(Han et al.2015); natural age-induced models, Aβ-infused models, chemically-induced models, surgery- induced models and transgenic models were used to study stem cell transplantation.

Due to the fact that mice and rats are mammals,have short lifespans allowing faster study of the disease progression, exhibit high order brain functions like human and their AD brain exhibit Aβ hallmark similar to humans (Webster et al.2014), they are the most suitable models.It is noticed that rats are preferred over mice in all models except in transgenic models(Charreau et al.1996).Note that, a single gene mutation could not induce complete AD symptoms. In order to obtain an Aβ pathology similar to Aβ in long term, a triple mutation model of APP (amyloid precursor protein), PS1 presenilin1), Tau is needed. However, progressive neurodegeneration in the hippocampus and other neocortical areas of the brain is not prominen

4. Stem cells as a model to study AD

Due to the failure of AD drug development efforts in late-phase clinical trials and presence of genetic discrepancies between rodents and humans, other alternative cell – based approaches have been developed. Human stem cells differentiated into various cell types can be used to study the effect on AD molecular pathology. Induced Pluripotent stem cells (iPSCs) are sources of Human Stem cells: Somatic cells from blood or skin reprogrammed from patients with mutation (Mutations responsible for the most aggressive form of AD) give rise to iPSCs that will later on differentiate into neurons that have remarkable Aβ production. These iPSCs-derived neurons may be considered as a platform for development of drugs against AD.

Human embryonic stem cells engineered as an AD model to overexpress wild-type or mutant human APP also differentiate into neural lineage. The N-terminal fragment of the APP is crucial for this effect.Thus,the importance of AD-related molecules in stem cells differentiation and neurogenesis.

5. The use of Stem cells in AD therapy

NSCs (normal and genetically modified stem cells) in AD therapy and their therapeutic effects

Many neuronal systems with multiple neurotransmitter

phenotypes are randomly affected in AD. In order to target all affected areas,through conventional therapy, use of neural stem cells (NSCs) is important to overcome this problem; NSCs after giving rise to different cell types in neural lineage,could migrate from injection site to different areas in the brain,differentiate and then integrate into particular neuronal systems.This was shown in murine AD models 2 years after transplantation of NSCs from healthy mice into transgenic AD hippocampi leading to an increase of cholinergic neuron numbers.

The production of neurotrophin (class of growth factor that induces survival,development and functions of neurons) was the first effect of NSCs. Neurotrophin is important in maintaining the strength and number of synapses which are crucial for synaptic plasticity and memory maintenance (Arancio and Chao 2007). Therefore, Neurotrophin production of NSCs is essential in the treatment of AD.
In addition, the fact that genetically modified NSCs produce therapeutic molecules. In the longer term, such molecules are found to be more effective than drug administration, NSCs could be engineered to express higher levels of neurotrophin contributing to a higher survival rate, improved differentiation into neurons and astrocytes and memory restoration. Moreover, a study showed that memory function was improved with an increase in the acetylcholine level after transplantation (Park et al.2012b). This could be done by genetically modifying NSCs to express choline acetyl-transferase (ChAT) responsible for acetylcholine synthesis.
NSCs were also shown to improve endogenous neurogenesis and ischemia(restriction in blood supply to tissues) -induced axonal transport deficit in the cases of stroke (Jin at al.2011). Moreover, NSC's also showed an anti-inflammatory effect by reducing microgliosis and pro-inflammatory cytokines (Ryu et al.2009). However, these two effects of NSCs in AD treatment are still far less clear and uncertain.

Other types of Stem Cells?
Besides NSCs, other stem cells could be important cell sources for AD therapy including neural precursor cells found in embryonic medial ganglionic eminence (MGE), embryonic stem cells (ESCs) and mesenchymal stem cells (MSCs):
1-Neural precursor cells, which produce acetylcholine as neurotransmitters, consequently play a role in the building of memory: It has been shown that MGE cells transplanted in the AD hippocampus could develop into mature interneurons, restoring memory and learning (Tong et al.2014).
2-ESCs-derived MGE-like cells (ESCs treated with Sonic Hedgehog protein) after being transplanted into murine AD models, can differentiate into GABA cholinergic neurons and improve host's cognitive function.
3-Bone marrow derived MSCs were shown to reduce Aβ plaque deposition, tau hyperphosphorylation, inflammation and improved memory restoration in a transgenic murine AD model. This suggestion leads to a belief that MSCs could contribute to AD therapy (Lee et al.2009, 2010).
In order to maintain successful neural restoration in the brain for long term, endogenous neurogenesis must be justified. Many compounds were found to modulate this process; Allopregnanolone has been demonstrated to improve learning and cognitive function in triple mutated AD mice, it also increases the activation and proliferation of neural precursor cells as well as microglial cells involved in neuroprotection (Wang et al.2005). Fluoxetine is another compound that follows this process by inducing neural differentiation and protection in case of Aβ accumulation without glial differentiation.

Besides, co-culturing NSCs grafted with other cell types can also promote survival and proliferation of neurons in the AD model.

What are the challenges in the stem cell therapy of AD?
Using patient's own NSCs may constitutively be limited in numbers and take long time for a successful and expanded treatment; therefore, use of different origins of NSCs may be more suitable. However, immune rejection of the donor cells by the patient's tissues is a serious limitation. The human leukocyte antigen haplotype of the donor cells must at least match with the recipients, who are required to take immunosuppression drugs to prevent the immune rejection (Chinen and Buckley 2010).
In addition, variability of donor cells and their engineering methods may give rise to another challenge: variation of clinical effects and differentiation efficacy.

6. Conclusion

With the continued improvement in safety profile of stem cell therapy and the creation of a better rodent AD model in which to test them, it is feasible to overcome all challenges so stem cells could be trailed in humans to potentially treat AD in the next few years.