Review article

Stem cell therapy for Alzheimer's disease: hype or hope?

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Alzheimer's disease (AD) is the most common neurodegenerative disease affecting millions of people in the world. Cognitive impairments such as progressive memory loss are devastating manifestations from this disease. Current pharmacological treatment has limited efficacy and only provides symptomatic relief without long-term cure. As a result, cell-replacement therapy using stem cells is an emerging potential treatment to AD. In the last decade, there have been animal trials using stem cells to treat and modulate cognitive impairment in AD models via three different mechanisms—replacing the damaged or dead cholinergic neurons; protecting neurons by reducing toxic amyloid protein aggregates or insoluble tau neurofibrillary tangles and promoting neurogenesis in hippocampus by neurotrophic secretions from stem cells. All of the trials showed promising results and improved our understandings about the mechanism of dementia in AD. With the continued improvement in safety profile of stem cell therapy and the creation of a better animal AD model in which to test them, it is feasible that stem cells could be trialled in humans for AD treatment in the next 5–10 years.

Introduction

Currently, Alzheimer's disease (AD) is the commonest cause of dementia (Dantuma, Merchant and Sugaya, 2010) affecting over 24 million people worldwide (Ferri *et al.*, 2005). For adults over 60s, dementia is even the fourth greatest global disease burden according to a World Health Organisation (2003) report published in 2003. Because of the gradual ageing population, it has been predicted that around 81 million people will have dementia by 2040 (Ferri *et al.*, 2005). Patients with AD suffer from memory dysfunction and inability to learn, and some can develop psychotic symptoms such as hallucination and delusions (Blennow, de Leon and Zetterberg, 2006). The disease was first described by a German neuropathologist, Alos Alzheimer (Goedert and Spillantini, 2006). He identified the presence of amyloid-beta (Aβ) plaques and neurofibrillary tangles in the brain as two classical hallmarks of AD. Aβ plaques are misfolded protein accumulated extracellularly, which are neurotoxic, and could lead to neuronal loss. Neurofibrillary tangles are insoluble aggregates of hyperphosphorylated tau protein, an intracellular cytoskeletal molecule (Mattson, 2004; Blennow, de Leon and Zetterberg, 2006). Although the causative mechanism between Aβ plaques and tau neurofibrillary tangles is still unclear, it is thought the combination of both leads to neuronal and synaptic loss in various cortical regions in the brain, resulting in cognitive decline and memory loss (Dantuma, Merchant and Sugaya, 2010).

Cholinergic neurons in the brain are especially vulnerable to damage by AD (Geula *et al.*, 2008). They produce the neurotransmitter acetylcholine, which is important in the control of sleep–wake cycle, consciousness, learning and memory processing (Schliebs and Arendt, 2011). These neurons originate

from the basal forebrain, in a region known as the nucleus basalis of Meynert (nbM) and project to various cortical regions in the brain (Selden *et al.*, 1998). In AD, a hypothesis called the 'cholinergic hypothesis' states that the level of cognitive decline in the AD patient directly correlates with the decrease of cholinergic neurons in the nbM (Bartus *et al.*, 1982). To rescue the effects of the damaged cholinergic neurons, there are two types of drugs currently used in AD patients—acetylcholinesterase inhibitors such as donepezil and galantamine, which prevent the degradation of acetylcholine at the synapse, and memantine, an *N*-methyl-ᴅ-aspartate receptor antagonist, which protects cholinergic neuronal death from excitotoxicity (Roberson and Mucke, 2006). However, these drugs have variable efficacy and only provide symptomatic reliefs without long-term cure (Borlongan, 2012). Therefore, a novel treatment is needed to be found to cure AD. Recently, there have been advancements using stem cell therapy to successfully treat neurological conditions such as stroke, Parkinson's disease, spinal cord injury and amyotrophic lateral sclerosis (Lu *et al.*, 2003; Goldman, 2005; Park *et al.*, 2006; Ebert *et al.*, 2008; Kim and de Vellis, 2009). As a result, the therapeutic potential of stem cell in restoring cognition has been investigated extensively. Over the past few years, there has been growing evidence from different animal trials (Table 1). Here I will review recent studies that have used stem cell therapy in animal models of AD or cognitive decline and consider the effectiveness of this approach for restoring cognitive function.

Which stem cell to use?

Stem cells are characterized by their unique properties of self-renewal and their ability to differentiate into different cell lineages (Dantuma, Merchant and Sugaya, 2010). There are many types of stem cells in the body which can broadly be divided into embryonic and adult (somatic) stem cells. Embryonic stem (ES) cells are pluripotent, which means they have the ability to differentiate into different germ layers giving rise to different types of progenitor cells. ES cells develop into multipotent adult stem cells such as neural stem cells (NSCs) and mesenchymal stem cells (MSCs), which can only differentiate into a specific cell type (Mimeault, Hauke and Batra, 2007).

NSCs reside within the brain and can be differentiated into neurons, astrocytes and oligodendrocytes (Taupin, 2006). Originally, it was thought that neurogenesis only takes place in the foetus. However, recent studies showed that this process also happens in adult's brain and NSCs were found in the subgranular zone (SGZ) and subventricular zone (SVZ) (Taupin, 2006; Mu and Gage, 2011). The SGZ is located within the hippocampus, part of the brain which is important in learning and memory formation (Squire, 1992). Therefore, it seems like NSCs are obvious choice for the replacement of damaged neurons. Qu *et al.* (2001) were one of the earliest groups to prove this by implanting human NSCs into the brains of aged and mature rats. They showed

that the NSCs survived and were differentiated into neurons and astrocytes in the rats' brains. Also, a significant improvement in cognitive function for the aged rats with memory impairment was observed after the transplantation compared with the control, correlating with the differentiated neurons in the hippocampus. However, the neuronal marker used in this study, βIII tubulin, only labels immature neurons. Therefore, further physiological investigations were required to prove that neurons derived from the NSCs were fully functional. The group also discovered an increase in the astrocyte density within a part of the hippocampus (outside of the transplantation site) where astrocytes are not normally found. Because astrocytes are important structural and metabolic support cells within the brain (Doetsch, 2003), this suggests NSCs do not only replace or strengthen the neural circuit but they might also create an environment for the growth and support for neuronal fibres (Isacson *et al.*, 1995).

Pluripotent ES cells were once thought to be an ideal candidate for stem cell therapy as they have the most potential to divide and differentiate. However, safety is the greatest concern for the use of ES cells. One group compared the use of ES cells and ES cell-derived NSCs by transplanting them into the cortex of a mouse model of AD (Wang *et al.*, 2006). They found the cognitive deficits actually worsened with ES cell transplantation because the stem cells induced a teratoma (a tumour with mixed cell types). Moreover, the use of embryonic cells generates much ethical debate (Juengst and Fossel, 2000), hence NSCs are more commonly used.

Unfortunately, NSCs are very difficult to obtain from adult's brain and so current studies mainly use foetal NSCs, which could also generate ethical problems. Very recently, it was found that MSCs derived from bone marrow, umbilical cord blood and adipose tissue could be transdifferentiated into neuronal cells (Brazelton *et al.*, 2000; Mezey *et al.*, 2000; Kim *et al.*, 2012). Studies using MSC transplantation on AD animal models have shown promising results on their improvement in cognitive function (Babaei, Soltani Tehrani and Alizadeh, 2012; Lee *et al.*, 2012). Babaei, Soltani Tehrani and Alizadeh (2012) induced an nbM lesion in the rats with an excitotoxin to model cognitive decline in AD. The rats then received either MSC or a sham infusion into the hippocampus. They showed that learning and memory significantly improved in the group which received MSCs compared with the sham infusion. As the MSCs were derived from rat tibia, this shows we might be able to harvest stem cells from the adult bone marrow to develop a treatment for AD. However, no neuropathological investigation was done in this study to correlate the outcome with the differentiation of MSCs into functional neurons in the hippocampus. Also, interspecies variation could mean the results shown were only applicable when using murine MSCs. Therefore, it would be useful to transplant MSCs from human bone marrow and include neuropathological investigations to look at survival and differentiation of MSCs in future studies. In another study, MSCs derived from human umbilical cord blood were transplanted into the hippocampus of transgenic mice model of AD

Table 1. Summary of recent stem cell therapy studies on animal models of AD and cognitive decline

Study	Types of stem cell transplanted	Models/methods of cognitive decline induction	Transplant site	Outcome in cognition and/or pathology in the brain post-transplantation
Babaei et al. (2012)	Murine BM-MSC	1. Aged rats (30 months) 2. Ibotenic acid-induced NBM lesion rats	Hippocampus (CA-1 region)	1. Aged rats—learn more rapidly 2. Ibo-induced memory impairment group—significant reduction in latency to find platform in Morris Water Maze
Blurton-Jones et al. (2009)	mNSC	Triple transgenic AD model mice (3xTg-AD)	Hippocampus	NSC transplant rescues learning and memory deficits No change in Aβ, tau pathology but increased synaptic density in mice's hippocampus
Esmaeilzade et al. (2012)	EPI-NCSC	Rat hippocampal Aβ injection	Hippocampus	Significant improvement in cognitive tasks (Y-maze and passive avoidance tests), increased neuron number and differentiation into other cell type
Kern et al. (2011)	mNSC	DS model mice (Ts65Dn)	Hippocampus	Decreased tau-positive clusters in trisomic (28.6%) and disomic (58.6%) mice
Kim et al. (2012)	Human ASC	Transgenic AD-model mice (Tg2576)	1. Intravenous 2. Hippocampus (bilateral dentate gyrus)	Both intravenous and intracerebral ASC transplantation rescued memory impairment and improved spatial learning; Reduced amyloid plaque formation, upregulated interleukin-10 and neurotrophic factors in the brain of Tg2576 mice
Lee et al. (2009)	Murine BM-MSC	Acute Aβ-induced model mice	Hippocampus (dentate gyrus)	BM-MSCs promoted microglial activation Reduced Aβ deposits of acutely induced AD mice
Lee et al. (2012)	Human UCB-MSC	APP and presenilin (PS1) double-transgenic mice	Hippocampus	Improved spatial learning and memory in Morris Water Maze tests Reduced Aβ load and tau hyperphosphorylation, inhibited proinflammatory cytokine release from microglia
Park et al. (2010)	hNSC	Aged rats (22 months)	Intracerebro-ventricular	SGZ increased in cell number
Park et al. (2012)	hNSC	AF64A cholinotoxin injection in rats	Right lateral ventricle	Rats receiving NSCs overexpressing ChAT showed full recovery in learning and memory functions, whereas those receiving NSCs only remained memory impaired
Qu et al. (2001)	hNSC	1. Matured rats (6 months) 2. Aged rats (24 months)—memory impaired and unimpaired	Right lateral ventricle	Cognitive function significantly improved in matured and aged memory-impaired groups Morphologically functional hNSC-derived cells were found in the hippocampus and cortex
Wang et al. (2006)	Murine ES and ES-derived NSC	Ibotenic acid-induced NBM lesion mice	Frontal association cortex and barrel field of S1 cortex	NPC restored memory, ES significantly decrease working memory; ES induced massive teratoma formation
Xuan et al. (2009)	mNSC and NSC-derived glial cells	Rat Fimbria-Fornix transaction	Basal forebrain	Improved memory and learning in Y-maze testing; Increased in the number of p75NGFR-positive neurons
Yamasaki et al. (2007)	mNSC	Double transgenic neuronal injury model mice (CaM/Tet-DT$_A$)	Hippocampus	Improved hippocampal-dependent memory and increased synaptic density and neuronal number

Aβ, amyloid-beta; AD, Alzheimer's disease; APP, amyloid precursor protein; ASC, adipose-derived stem cell; BM-MSC, bone marrow mesenchymal stem cell; ChAT, choline-acetyltransferase; EPI-NCSC, epidermal neural crest stem cell; ES, embryonic stem cell; NGFR, nerve growth factor receptor; NSC, human neural stem cell; hNSC, human neural stem cell; mNSC, murine neural stem cell; UCB-MSC, umbilical cord blood mesenchymal stem cell.

(Lee *et al.*, 2012). In this case, not only did the transplanted group show significant improvement in cognitive function, Aβ deposition in the brain and hyperphosphorylated tau were also decreased. The change in the AD pathology was associated with the modulation in neuroinflammation in which an upregulation of anti-inflammatory cytokines was found. These results were promising that it prompted for further research on humans to correlate neuroinflammation with AD, and the use of MSCs could potentially be developed as a novel immunomodulatory treatment for AD.

Replacing cholinergic neurons with stem cells

Cholinergic neurons that originate from the nbM are essential for cognitive functioning. Therefore, an induced lesion on the cholinergic system is commonly used as AD models to determine whether stem cell therapy could replace cholinergic neurons and restore cognitive function. Xuan *et al.* (2009) demonstrated that engrafted NSCs do increase the number of cholinergic neurons and enhance memory and learning in AD-model rats. They simulated cognitive impairment by performing a unilateral fimbria–fornix transaction in the rat's brain to disrupt the cholinergic neuronal circuit between the brain septum and the hippocampus. Significant improvement in learning and memory was observed after transplantation of the NSCs. Also, immunohistochemistry studies showed that a significantly higher number of cholinergic neurons were found on the transplanted group compared with the lesioned group. However, the study did not show whether the stem cells actually differentiate into cholinergic neurons or whether the NSCs were secreting neurotrophic factors to stimulate neurogenesis. Interestingly, NSCs seem to preferably differentiate into glial cells, which are structural neuronal cells. But there were no improvement in cognitive function nor an increase in cholinergic neurons when isolated glial cells were transplanted into the rats' brains. This suggests glial cells do not have a direct role in cognitive functioning, but their presence might be important for NSCs to stimulate neurogenesis to replace or protect cholinergic neurons.

Since the replacement of cholinergic neurons is important to restore memory and learning, would it not be more efficient if we transplant cells that could secrete more acetylcholine? Park *et al.* (2012) answered this question by transplanting NSCs, which are genetically programmed to over-express choline acetyltransferase (ChAT), an enzyme used for the synthesis of acetylcholine, into an AD-model rat. They found that the modified NSCs synthesized more ChAT than the normal NSCs and could significantly improve cognitive function. However, strangely, they showed normal NSCs had actually no effects on restoring memory on the rats. One major caveat about this study is the model they used to simulate cognitive decline in AD. A cholinotoxin, AF64A, was used to reduce the release of acetylcholine in the brain by altering ChAT mRNA expression in cholinergic neurons.

This means the transplanted NSCs might actually be affected by the cholinotoxin. Hence, only the genetically programmed NSCs could overcome the effect by over-synthesizing ChAT enzyme. Nevertheless, this study suggests the simple replacement of cholinergic neurons is not sufficient in restoring cognitive function in AD.

Clearing up the misfolded protein aggregates using stem cell therapy

As previously mentioned, Aβ plaques and tau neurofibrillary tangles are toxic aggregates, which might damage neurons in the brain. Since implanted stem cells typically differentiate and migrate to areas with neuronal loss (Imitola *et al.*, 2004), would stem cells have a role in the clearance of the misfolded protein? To tackle this question, Kern *et al.* (2011) investigated the effects of neural stem cell transplantation in the mice model of Down syndrome (DS). DS and AD are similar in a way that many patients with DS have progressive memory decline and possess typical plaques and tangles on neuropathological studies. In this particular mouse model, there is neuronal cell loss and an increase in tau-clustered granules especially in the hippocampal region. The group implanted murine NSCs or saline as a control into the hippocampus of DS mice. One month after transplantation, they found the number of tau clusters were significantly lower in the NSC-transplanted group, suggesting NSCs might have a role in the reduction of tau aggregates. Interestingly, the clearance of tau neurofibrillary tangles was also found on the opposite side of the transplantation without the migration of NSCs. This suggests NSCs do not physically reduce tau tangles, but soluble growth factors secreted by NSCs might regulate tau phosphorylation throughout the brain. However, it would be wrong to assume that the same will happen in humans as the appearance of tau neurofibrillary tangles is different between humans and mouse (Gotz, 2001), which is one main flaw of this study.

Another group has looked at bone marrow-derived MSC's role in the reduction of brain Aβ plaques. Lee, Jin and Bae (2009) injected soluble aggregated Aβ into the mouse hippocampus to induce an acute AD model. They transplanted murine MSCs from the bone marrow into the hippocampus and found Aβ deposition disappeared after 7 days of transplantation. Activated microglia, the macrophages in the brain, was shown to be increased in the transplanted group compared with the control. The study therefore concluded that grafted bone marrow–MSCs might induce microglial activation and recruitment, leading to phagocytosis to clear up Aβ plaques in the brain (Lee, Jin and Bae, 2009).

Altering neurogenesis to restore memory function

From the two studies above, stem cells were shown to reduce or protect neurons from toxic aggregation of misfolded protein. However, both studies failed to investigate the effects of

plaques or neurofibrillary tangles clearance on cognitive function. A year later, Blurton-Jones et al. (2009) published a study showing that cognitive decline in a transgenic mice model of AD could actually be rescued by NSC therapy without altering the levels of Aβ or tau protein. Interestingly, a previous imaging study showed similar findings which suggested that plaques and tangles could accumulate for many years before cognitive function starts declining (Kemppainen et al., 2007). Blurton-Jones et al. (2009) also demonstrated that cognitive improvement correlated positively with neurogenesis as they found an increase in brain-derived neurotrophic factor (BDNF), which has role in synaptogenesis and neuronal networking (Aguado et al., 2003). From this we could hypothesize that the cause of dementia in AD is due to the reduction in neurogenesis caused by the exhaustion of NSCs from long-term toxic damage by Aβ plaques or tau neurofibrillary tangles. Post-mortem immunohistochemical studies in AD cases to investigate co-localization between NSCs and aggregated proteins could be helpful to identify the interaction between Aβ, tau and NSCs.

Increasing evidence has shown that cognitive function is linked to the alteration of neurogenesis in the adult hippocampus. Surprisingly, it emerges that depression could also be caused by a decrease in hippocampal neurogenesis (Duman, 2004) like AD and antidepressive medication could promote neurogenesis in the hippocampus of rodents. Therefore, Chang et al. (2012) carried out an in vitro study which demonstrated that fluoxetine, an antidepressant, could stimulate NSCs proliferation and protect stem cells from Aβ cytotoxicity (Chang et al., 2012). This provides a potential use of fluoxetine in future studies of stem cell transplantation in restoring cognitive function.

With regard to stem cell therapy, it is now believed that the increase in neurogenesis rather than purely the replacement of cholinergic neurons leads to an improvement in cognition. As mentioned earlier, stem cells could provide a neurotrophic environment by the production of BDNF (Blurton-Jones et al., 2009). They could also differentiate into glial cells which secrete different neurotrophic factors (Xuan et al., 2009) to promote neurogenesis. Therefore, in future studies, we might see the rise in the use of genetically modified stem cells to deliver neurotrophic factors, which stimulate neurogenesis for the treatment of cognitive decline in AD models.

The future of stem cell therapy for Alzheimer's disease

AD is a complex disease which affects different neural cell types and has a diffuse pathology (Chen and Blurton-Jones, 2012). Therefore, there are limitations on the animal studies as only certain aspects of AD could be modelled. Transgenic models of AD are the most current animal model used, which display the nature of cognitive decline with typical AD pathology in familial AD. However, only <5% of AD is

familial (Young and Goldstein, 2012) and there are yet no animal models which can simulate the sporadic and progressive nature of AD. Moreover, co-morbidity factors such as age and cardiovascular events could not be accounted for in current AD models (Borlongan, 2012).

Recent animal studies have shown that learning and memory deficit could be improved by stem cell therapy. But, in all studies, the assessments of cognitive improvement were performed only shortly after stem cell transplantation without much follow-up. As AD is a progressive disease, longer term studies are needed to look at lasting effects as well as safety profile of the treatments (Borlongan, 2012).

With the recent advancements of reprogramming technology, there is a great potential in the use of inducible pluripotent stem cell (iPSC) in the treatment of AD. Somatic cells from patients could be reprogrammed to generate iPSCs, which could then be directed into the differentiation of neural precursor cells for transplantation (Jung et al., 2012). This means tissue rejections due to immunological incompatibility will no longer be an issue and there will be fewer ethical problems. Also, it can improve the modelling of neurodegenerative diseases like AD because iPSCs could differentiate into neurons, which contain the unique genetic phenotype of the patient (Young and Goldstein, 2012). This creates a model which offers the closest approximation to the sporadic form of the disease and hopefully could be translated into human studies to find a cure for AD.

Conclusion

Stem cell therapy in recent years has shown promising results in rescuing cognitive decline on animal models of AD. These help us understand more about cognitive functioning and the mechanisms which leads to memory loss in AD. More evidence has also shown that the decline of neurogenesis, rather than simply the accumulation of protein aggregates, contributes to dementia in the AD patients. Therefore, future studies should focus on using stem cells to deliver neurotrophic factors for the alteration of neurogenesis in AD models. However, most of the current research is hype as there were safety (e.g. ES induced tumourigenesis) and ethical issues involved in the use of foetal stem cells. Also, there is not a single animal model which could simulate the full aspect of AD. Nevertheless, there is still hope—the use of MSCs is free from ethical problems and could potentially be a type of immunomodulatory treatment for AD. Also, with the advancement in the use of iPSC, hopefully we could model the disease better and eventually translate stem cell research into human studies with the aim to finally solve the enigma of restoring the memory.

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Author biography

A.K.L.L. is a fourth year medical student currently studying an intercalated BSc in Neuroscience and Mental Health at Imperial College London. He has a particular interest in prion disease, neurodegenerative conditions and cognitive neuroscience. He is hoping to pursue an MBBS/PhD in neuropathology or neuroscience after this year and a career in academic medicine in the future.

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