EDITORIAL

Treating Alzheimer's disease with stem cells: how far have we come?

Kaylene M Young and Solène Ferreira

"...we still lack a bone fide therapy for Alzheimer's disease that will modify the pathology, preserve existing neurons, and promote neural regeneration."

In 2015, 46.8 million people worldwide have been diagnosed with dementia. This figure is predicted to rise to 131.5 million people by 2050 [1]. Alzheimer's disease (AD) is the leading cause of dementia, and can be further divided into familial AD, which results from genetic mutation and has an early age of onset, and sporadic AD. Sporadic AD is by far the most prevalent form, and over the past decade numerous risk factors have been linked to its development. Aging is still the most significant risk factor, with more than 1 in 20 people over the age of 60 developing the disease. AD is characterized by the deposition of β-amyloid in the form of plaques, the aggregation of hyper-phosphorylated tau as intracellular neurofibrillary tangles, neuron loss, and brain atrophy. Many of the pathological features of AD were identified over a century ago, however new mechanisms driving the pathology are still being uncovered today [2].

Available therapeutic interventions for AD include drugs such as acetylcholinesterase and NMDA receptor-antagonists, which modulate the signalling of neuronal subsets in the central nervous system, and have some short-term beneficial effects on memory loss and cognitive decline, but do nothing to delay the progression of the disease. Currently patients that present with AD already display significant cell loss, so there has been a push to identify and validate serum and imaging biomarkers (such as

amyloid imaging). This will enable earlier diagnosis, so that other therapeutic interventions targeting amyloid and/or tau dysregulation, could be utilized early enough to prevent degeneration. Drugs that have been under therapeutic development in recent years, to counteract AD pathology include: anti-Aβ-therapies such as Tramiprosate, which failed to alter the trajectory of dementia in clinical trials; Tarenflurbil, a non-steroidal anti-inflammatory drug, which reduced Aβ production, but also failed clinical trials; and methylene blue, which interferes with the abnormal aggregation of the tau protein, and is currently in phase II clinical trials [3]. Therefore we still lack a bone fide therapy for AD that will modify the pathology, preserve existing neurons, and promote neural regeneration.

In the past two decades a large amount of neural regeneration research has focused on stem cells – but where has this gotten us? To look at this, we have divided stem cell-related therapies into three broad categories: activating endogenous stem cells; stem cell transplant approaches, and stem cells as a disease modelling tool. Each branch of stem cell research has gained some traction in the AD research field. However some approaches appear more feasible than others, as a treatment that could fit within the public healthcare system, and be used in combination with improved biomarker assessment and other therapeutics, to combat the growing burden that AD places on our communities.

The discovery of neural stem cells resident in the adult mouse and human brain provided hope that neural regeneration could be activated from within. Neural stem cells are found within the subventricular zone and hippocampal dentate gyrus, where they divide and give rise to new neurons that are highly plastic and important for learning and memory – a function clearly disrupted in AD. Furthermore, in response to some brain injuries, the newly generated cells have been shown to migrate to the site of damage, and even differentiate. This does not occur in mouse models of AD, which have impaired neural stem cell proliferation and neurogenesis, particularly in the hippocampus, suggesting that interventions designed to promote hippocampal neurogenesis may improve some aspects of learning and memory. Our understanding of neural stem cell biology has come a long way, and studies in rodents have shown that behavioral interventions, such as environmental enrichment, cognitive training, and exercise, promote adult neurogenesis. However exposure of mice that model AD to environmental enrichment has produced mixed results. Overall this research points to enrichment promoting neurogenesis in mouse models of AD, and leading to an improvement in cognition. It is possible that some of the variability in the data can be explained by the level of stress induced by the enrichment paradigm, as stress would be expected to supress neurogenesis.

In humans, education is known to reduce a person's risk of developing AD, yet it is not yet clear whether stimulating neurogenesis through environmental and cognitive enrichment later in life can also be beneficial. Imaging technologies to non-invasively measure neurogenesis in humans are still under development, so it is not possible to directly link education and neurogenesis. However trials are underway that have enrolled cognitively

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normal individuals in tertiary education programs, later in life, to determine whether this will have a beneficial outcome on the number of seniors that develop AD.

As people do not always adhere to a training regimen, it is fortunate that research conducted over the past 20 years has identified a number of hormones and growth factors that influence endogenous neurogenesis, including vascular endothelial growth factor, brain-derived neurotrophic factor, nerve growth factor, progesterone, and allopregnanolone (reviewed in 4). The clinical viability of many identified regulators is actually quite poor, due to factors such as protein stability, ability to cross the blood-brain-barrier, or the fact that many of the identified regulators have a diverse range of cellular targets. However the next generation of drug-design and drug-delivery approaches may help to overcome some of those hurdles. Another option is to consider the efficacy of pharmaceuticals already in use that activate endogenous stem cell populations, and repurpose them. For example, the beneficial effects of anti-depressants are thought to result from the stimulation of neural stem cell activity and neurogenesis [5]. However, stimulating endogenous neural stem cells may not be sufficient to overcome the memory impairments inflicted by AD. Exposing mice to acetylcholinesterase inhibitors has been shown to increase neural stem cell proliferation in the hippocampus [6,7], but these drugs have been used for the treatment of dementia for more than two decades, and are clearly not curative. Perhaps this is because the newborn neurons still find themselves in an unfavorable environment? It is likely that therapies that activate neurogenesis will be highly beneficial for the improvement of cognitive performance, but will need to be co-administered with an agent that suitably alters the brain environment, allowing the new cells to survive.

Another major avenue of stem cell therapeutics is stem cell transplantation. Stem cells, in the form of bone-marrow transplants, have been in clinical use since the 1960s, and stem cells from a variety of sources have been proposed for use in the treatment of neurodegenerative disease [8]. Human neural stem cells cannot be readily obtained, and mesenchymal stem cells have a more limited ability to generate neural cell types, while human embryonic stem cells can be expanded in vitro and retain their ability to differentiate in each of the major neural cell types [9]. However the benefits observed in response to stem cell transplantation in mouse models, are not the result of the transplanted cells differentiating into functional neurons on a large scale, which was the original expectation. They instead appear to secrete paracrine factors. Both neural and mesenchymal stem cells have been transplanted into the brains of mice that model AD, and were shown to produce beneficial neurotrophic and anti-inflammatory effects, while also reducing tau phosphorylation, and promoting Aβ clearance (reviewed in 4).

In recent years a number of stem cell transplant approaches have been evaluated for safety in clinical trials. For example, ischemia-tolerant mesenchymal stem cells are currently being administered to patients with AD as part of a phase IIA clinical trial. The efficacy of stem cell transplantation for the treatment of AD is yet to be demonstrated in phase

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IIB clinical trials. However the field is certainly moving in that direction. The past decade has seen the evolution of protocols that produce more consistent and defined cell populations for transplants, making it more feasible that the cells can be engineered to maximize their paracrine influence and better abrogate disease pathology.

The final way in which stem cells are being utilized for the development of an AD therapy is to develop a human cell-based model of AD. Takahashi and Yamanaka (2006) reprogrammed somatic cells by the insertion of four critical genes that endowed them with stem cell-like properties [10]. These induced pluripotent stem cells can be obtained from a patient's skin biopsy [11], and retain their genetic information, including genetic mutations or alleles that influence their likelihood of developing AD. The generation of induced pluripotent stem cells from patients with AD was initially linked to the development of a personalized approach to medicine, particularly as an option for autologous transplantation therapies. Such an approach does not seem therapeutically viable in the context of treating AD through the public health system. However there is certainly value in producing induced pluripotent stem cell lines that can be used to further our understanding of the pathophysiological mechanisms of AD, whereby the cells could also be differentiated and used for the large-scale screening of novel pharmacological agents.

In the past 25 years researchers working on AD have made significant progress, developing an understanding of the mechanisms driving AD pathology. At the same time, they have gained a detailed knowledge of endogenous neural stem cell function, and improved their ability to consistently produce cell preparations that are safe for transplantation. Stem cell-based therapies for AD have attracted significant and sustained attention, and it is exciting to see this work being carefully translated from the laboratory to the clinic. In the context of AD, stem cells are now therapeutic targets, disease modifiers, and a way to generate a human-cell based model of disease. However no single stem cell therapy currently in development represents a cure for AD. Instead they should be seen as valuable components that could be integrated into a combinatorial treatment for this very complex disease.

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REFERENCES

1. International AD. World Alzheimer Report 2015, The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends. 2015; 1–87.
2. Willem M, Tahirovic S, Busche MA *et al.* η-Secretase processing of APP inhibits neuronal activity in the hippocampus. *Nature* 2015; 526(7573), 443–7.
3. Wischik CM, Staff RT, Wischik DJ *et al.* Tau aggregation inhibitor therapy: an exploratory phase 2 study in mild or moderate Alzheimer's disease. *J. Alzheimer's Dis.* 2015; 44(2), 705–20.
4. Li X, Bao X, Wang R. Potential of neural stem cell-based therapies for Alzheimer's disease. *J. Neurosci. Res.* 2015; 93(9), 1313–24.
5. Chang K, Kim JA, Kim S *et al.* Therapeutic potential of neural stem cells treated with fluoxetine in Alzheimer's disease. *Neurochem. Int.* 2012; 1–7.
6. Kim J, Kim YJ, Chang YP. Administration of dexamethasone to neonatal rats induces hypomyelination and changes in the morphology of oligodendrocyte precursors. *Comparative Med.* 2013; 63(1), 48–54.
7. Itou Y, Nochi R, Kuribayashi H *et al.* Cholinergic activation of hippocampal neural stem cells in aged dentate gyrus. *Hippocampus* 2011; 21(4), 446–59.
8. Bottai D, Adami R, Scesa G. Stem cell transplantation in neurological diseases: improving effectiveness in animal models. *Front. Cell Develop. Biol.* 2014; 2.
9. Pick DL, Thomson JA. Embryonic Stem Cell Lines Derived from Human Blastocysts. *Science* 2015; 282(5391), 1145–7.
10. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell* 2006; 126(4), 663–76.
11. Takahashi K, Tanabe K, Ohnuki M *et al.* Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 2007; 131(5), 861–72.

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