Title: Stem Cell Therapy: An emerging yet challenging treatment modality in Alzheimer's Disease

Authors: Antoine Sader[1], MD and Rita Khoury[1], MD

Antoine Sader, MD

[1]Department of Psychiatry American University of Beirut, Faculty of Medicine & the Medical Center Beirut, Lebanon

Key highlights:

- Stem cell (SC) therapy shows potential in combating Alzheimer's disease (AD) in animal models.
- Preclinical trials indicate improved cognitive functions and AD neuropathology using various SC therapies.
- Different types of SC therapies exist, varying by route of administration, tissue origin, and donor types, each demonstrating a distinct safety profile and efficacy.
- SC therapy faces hurdles such as tumorigenesis, thrombogenesis, non-selective differentiation and dispersion, immune rejection, and ethical concerns.
- An overlooked risk of SC therapy is the possibility of transmitting prion-like AD pathology, hence the importance of biomarker screening and genome sequencing prior to delivering these types of therapy.

Introduction:

Alzheimer's disease (AD) is a progressively debilitating neurodegenerative disorder, marked by the insidious accumulation of extracellular amyloid beta (Aβ) plaques and neurofibrillary tangles made of hyperphosphorylated tau. These pathological hallmarks accompany neuronal death, synapse loss, and extensive brain atrophy. Factors such as genetic predisposition, oxidative stress, free radical generation, metabolic dysfunction, and inflammatory cytokines trigger cellular death pathways and synaptic deficits in the hippocampus, culminating in severe cognitive impairment and memory decline.

Despite numerous attempts to devise effective therapies, treatments have achieved limited success in altering the trajectory of AD. Current therapeutic strategies include acetylcholinesterase inhibitors like donepezil, galantamine, and rivastigmine; the N-methyl-d-aspartate (NMDA) receptor antagonist memantine; and Aβ-targeted monoclonal antibodies such as the FDA-approved lecanemab [1]. While monoclonal antibody therapies are categorized as disease-modifying therapies, their efficacy is relatively modest in comparison to the risks they may pose [2]. Given the detrimental burden of AD on individuals, caregivers and societies, there is a pressing need for innovative and effective treatment modalities for AD with an increasing aging population. At the forefront of emerging interventions, stem cell (SC) therapy holds considerable promise at the preclinical stage, as a potential breakthrough in our approach to combating this challenging disease.

Overview of SC therapy:

SC therapy represents an innovative approach to treating AD, offering new hope in the battle against this devastating condition. This cutting-edge treatment strategy utilizes several types of SCs, which can be categorized into three main groups based on donor type: autologous (SC from the patient's own body), allogeneic (SC from a matched donor), and induced pluripotent SC (iPSCs) (somatic cells transformed into SC). SC therapy for AD is still being tested and optimized in pre-clinical trials (on animal models). Among the most utilized SCs in these trials are bone marrow-derived mesenchymal SCs (BM-MSCs), brain-derived neural SCs (NSCs), human umbilical cord blood-derived mesenchymal SCs (hUCB-MSCs), and embryonic SCs (ESCs) [3].

NSCs are particularly notable for their ability to secrete paracrine growth factors that promote neurogenesis and neuroprotective factors. These factors can mitigate tauopathy and neuroinflammation, which are critical aspects of AD pathology. However, the use of NSCs involves invasive procedures, such as surgical intrahippocampal or intraventricular injections, and carries risks such as tumorigenesis and a poor survival rate [3]. Alternatively, BM-MSCs are appealing due to their ease of handling, accessibility, and broad transdifferentiation potential. They produce neuroprotective factors like brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF), along with anti-inflammatory cytokines (IL-4 and IL-10). BM-MSC therapy in animal models of AD has shown improved spatial learning, cognitive abilities, and memory. Nonetheless, challenges such as low neuronal differentiation, risk of tumor

formation, thrombosis, and potential infiltration into multiple organs may limit their use [3]. Lastly, hUCB-MSCs and ESCs, known for their hypoimmunogenic properties, have shown promising results in experimental animal studies. These SCs contribute to functional reconstruction in the hippocampus by affecting neurons, oligodendrocytes, astrocytes, and microglia, thus establishing a new dynamic balance; their therapeutic potential has been shown through improved cognitive functions in AD animal models, as evidenced by tests like the Morris water maze and Y-maze alternation [3].

In terms of administration, intranasal and intravenous methods are favored for their non-invasiveness and potential for broad distribution; though they carry risks such as thrombogenicity and less targeted effects. Direct brain delivery methods, while more invasive, offer targeted effects and better control in specific brain regions, but also increase intracranial pressure and carry surgical risks [3]. Figure 1 shows an overview of different SC therapies and their effects in AD animal models.

Future pre-clinical and clinical research on SC therapy is crucial to confirm its efficacy in humans and enhance our understanding of the long-term effects of these treatments. Safety and ethical concerns including risks of tumorigenesis, immune rejection, and the ethical implications of destroying an early human embryo or creating human-animal chimeras constitute important barriers hindering the advancement of SC therapies in AD treatment [4].

A new overlooked risk of SC therapy?

In their recent publication, Singh, Johns [5] and colleagues revealed the risk of iatrogenic transmission of AD via hematopoietic stem cell (HSC) therapy and peripheral APP formation in mice. The experiment utilized amyloid precursor protein gene-knockout (APP-KO) mice and wild type (WT) mice to explore the effects of transplanting bone marrow SC harboring a mutant human APP transgene. This mutation leads to overproduction of APP and subsequent development of familial AD. Notably, the study revealed that this procedure can induce AD pathology in recipient mice, including those that do not produce endogenous APP (APP-KO mice) or produce it at normal levels (WT mice) [5]. The authors were able to demonstrate a rapid onset of AD symptoms, within 6-9 months post-transplantation, significantly faster than in AD transgenic mouse models (12 months). This accelerated pathology in the WT and APP-KO mice includes compromised blood-brain barrier integrity, heightened cerebral vascular neoangiogenesis, increased brain-associated beta-amyloid levels, and cognitive impairment. Moreover, the experiment highlighted the role of beta-amyloid burden produced by cells other than neurons, originating outside the central nervous system in contributing to AD pathogenesis within the brain. These results suggest that transplantable treatment methods may transmit central nervous system diseases in a prion-like manner from affected donors to healthy recipients, replicating the donor's pathogenesis [5]. This correlates with well-established clinical observations that human recipients of soft and solid tissue transplants often exhibit an increased risk of neurotoxicity and neurological symptoms post-transplantation.

Thus, future research is needed to better understand which forms of AD are characterized by prion-like transmission, and which alleles are considered to be deleterious and penetrable in these presentations. Experimental studies in transgenic mice have shown that certain strain-like features of aggregated Aβ can be transferred from donor to host by exogenous seeding [6]. Considerable evidence now supports the inclusion of tauopathy among the disorders that share a prion-like mechanism of pathogenesis, all of which can be incriminated in the rare occurrence of iatrogenic AD [6, 7].

Conclusion

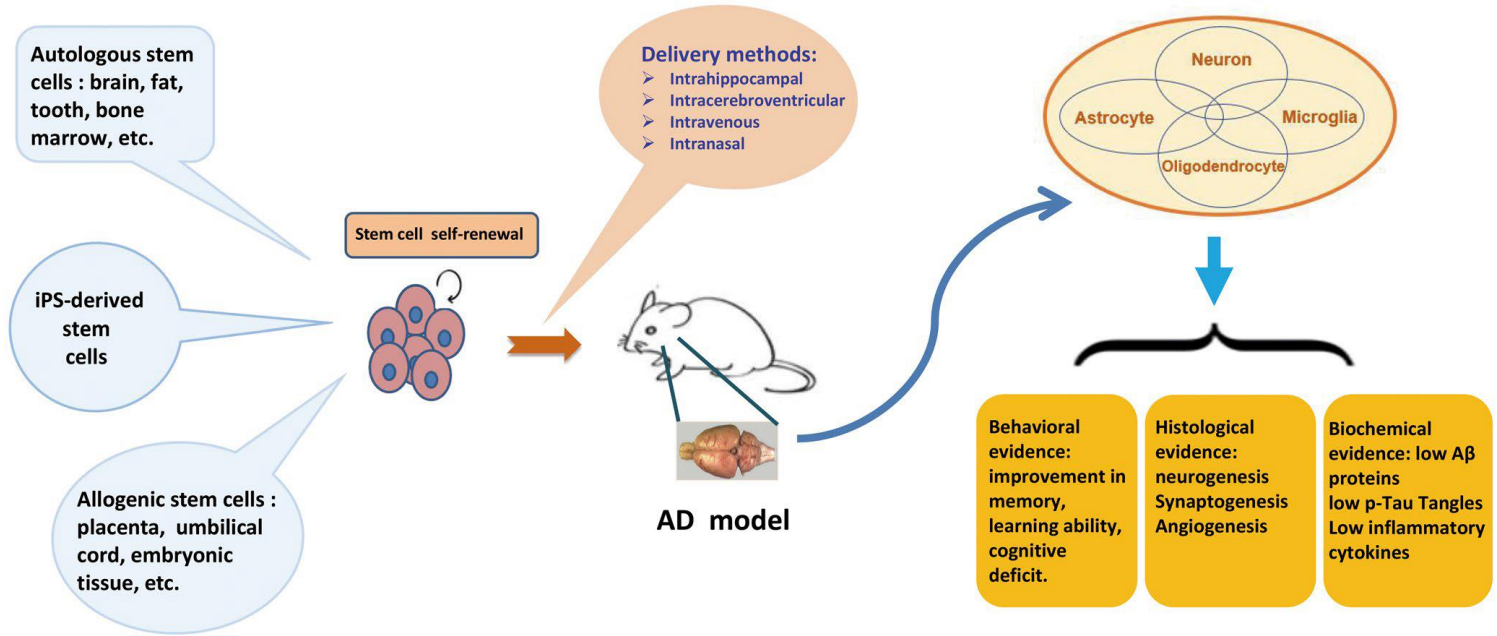
To enhance the safety and effectiveness of SC therapy, integration of biomarker screening and genetic sequencing of candidate cell, tissue, or organ donors for deleterious disease-associated alleles may be needed to eliminate the potential for disease transfer. This strategy is also associated with the ethical dilemma of what to do with extracted SCs carrying unwanted alleles. Although many preclinical trials show SC therapy as a promising potential cure for AD, significant safety and ethical concerns persist. By adopting safer transplantation methods, we can pave the way for further research in human subjects, which is crucial for validating positive preclinical findings and their real-world relevance, while also navigating associated ethical challenges.

References:

1. Reardon, S., FDA approves Alzheimer's drug lecanemab amid safety concerns. Nature (London), 2023. 613(7943): p. 227-228.

2. Ramanan, V.K., et al., Antiamyloid Monoclonal Antibody Therapy for Alzheimer Disease: Emerging Issues in Neurology. Neurology, 2023. 101(19): p. 842-852.
3. Qin, C., et al., Stem cell therapy for Alzheimer's disease: An overview of experimental models and reality. Animal Model Exp Med, 2022. 5(1): p. 15-26.
4. Volarevic, V., et al., Ethical and Safety Issues of Stem Cell-Based Therapy. International journal of medical sciences, 2018. 15(1): p. 36-45.
5. Singh, C.S.B., et al., Conclusive demonstration of iatrogenic Alzheimer's disease transmission in a model of stem cell transplantation. Stem Cell Reports, 2024. 19(4): p. 456-468.
6. Jucker, M. and L.C. Walker, Evidence for iatrogenic transmission of Alzheimer's disease. Nature medicine, 2024. 30(2): p. 344-345.
7. Walker, L.C., Prion-like mechanisms in Alzheimer disease, in Handbook of Clinical Neurology. 2018, Elsevier Health Sciences: The Netherlands. p. 303-319.

Figure 1: This figure portays the different types of Stem cell therapy, along with different routes of administration, and the behavioral, histological, and biochemical evidence of SC therapy in treating AD in animal models. (source: [3])



Antoine Sader, MD, holds a medical degree from the University of Balamand and has been a Research Fellow in the Department of Psychiatry at the American University of Beirut since 2023. His primary research interests are neuropsychiatric symptoms associated with neurodegenerative diseases, particularly Alzheimer's and Parkinson's, and novel interventional treatments for Alzheimer's disease.