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Pluripotent Stem Cell–Based Approaches in Alzheimer's Disease: Evidence from Disease Modelling, Therapeutic Screening, and Ethical Perspectives

Ms. Aarsheya Prashant Vasavada

Undergraduate Student, Psychology, Symbiosis International University

Abstract

Alzheimer's disease (AD), which contributes around 60-80% of cases, currently represents the most prevalent form of dementia. However, with predictions of such drastic increases in the global incidence of dementia, development of more informative models of Alzheimer's disease remains a prerequisite. Among various recent advances, one of the most promising support tools, along with more widely regarded technologies such as ESCs, has been given by iPSCs, which could represent one of the most acceptable alternatives to ESCs. From today's perspective, iPSC-derived models of Alzheimer's disease could undoubtedly revolutionize our current views of AD's early pathology. However, one of the most crucial facts associated with iPSC-based models of AD has been recognized as the difficulty of reproducing both senescence in AD as well as late AD.

1. Introduction

Dementia currently affects approximately 46.8 million people worldwide, a projected figure expected to increase to more than 130 million by 2050. Alzheimer's disease is considered the most prevalent cause of dementia. Decades of scientific efforts have failed to develop a disease-modifying treatment. One of the hindering aspects of Alzheimer's research is that there has been a lack of human-relevant models.

Recent breakthroughs in pluripotent stem cell biology, specifically induced pluripotent stem cells, have revolutionized the investigation of neurodegenerative diseases. Using iPSCs to "reprogram" a person's somatic cells into pluripotent cells has enabled scientists to grow distinct human neurons and glia cells for a particular patient; therefore, it presents a novel approach to studying Alzheimer's disease.

2. Pathological Hallmarks of Alzheimer's Disease

Alzheimer's disease is defined by progressive neuronal loss caused by the aggregation of toxic proteins and synaptic abnormalities.

2.1 Amyloid Beta Pla

Amyloid beta (Aβ) plaques are an extracellular deposit composed of the misfolded fragments of the amyloid beta protein precursor (APP). The deposition of these plaques distorts the synaptic communication pathways and the neuronal functions due to the inflammation initiated in the regions involving the hippocampus and the neocortex.

Neurofibrillary tangles are due to the aggregation of hyperphosphorylated tau protein within neurons. Tau

is the protein that maintains the integrity of microtubules. Microtubules are essentially internal roads that serve as the pathway for the transport of nutrients. Microtubule destabilization because of tau tangles leads to neuronal cell death. Tau pathology progresses along the neuronal circuits, hence the predictability of the progression of the disease course.

2.2 Neurotransmitter and Glial

Cholinergic neurons, which employ acetylcholine as their neurotransmitter, are one of the first populations of cells to be affected by AD. Neuron loss in this group was instrumental in creating the cholinergic hypothesis. Moreover, glial cells, including astrocytes and microglia cells, are very critical for modulating inflammation as well as glutamate. Glial cell dysfunction can induce excitotoxicity.

3. Induced Pluripotent Stem Cells: An Overview

Induced pluripotent stem cells can be created by the reprogramming of adult body cells, for example, fibroblast cells, by the transfection of particular transcription factors, for example, OCT4, SOX2, KLF4, and c-MYC. This reverses the cells to a pluripotent stage; hence, the cells can now differentiate into any type.

3.1Advantages of iPSCs

iPSCs have some benefits over embryonic stem cells:

- They can be generated from specific patients for personal disease modeling.
- Immune system rejection can be minimized for their possible applications in treatment.

3.2 Reprogramming Efficiency and Stability

The efficiency of reprogramming is influenced by several factors such as the type of cells to be reprogrammed, concentration of the transcription factors, cell cycle status of cells, metabolic status of cells, and cellular environment. Cellular genomicity and epigenetics are of utmost importance since reprogrammed cells may develop mutations or carry an epigenetic memory of the cells they were derived from.

4. Differentiation of iPSCs into Alzheimer's-Relevant Neural Cells

The iPSCs will have to be further differentiated to achieve the particular neuronal phenotype that is attacked in Alzheimer's.

4.1 Phases of Neural Differentiation

Differentiation of the neural cells, however, takes place in three major stages:
proliferation, where progenitor cells rapidly divide; migration, where newly formed neurons move to their final locations; and differentiation (or maturation), where the cells develop specific structures and functions (e.g., axons, dendrites, neurotransmitters).

4.2 Cortical and Hippocamp

The pyramidal glutamatergic cells in the cortex and hippocampus are especially affected in AD. Neural induction is typically carried out in a 2D system through the inhibition of the SMAD pathway, and patterning through the regulation of the Wnt and SHH signalling activity. The differentiated cells express electrophysiological properties and form synapses, but full differentiation of NPCs would take a long time of around 100 days.

4.3 Accelerated Differentiation

Strategies to bypass this bottleneck include rapid protocols using forced expression of NGN2 or interference with developmental pathways through small molecules, producing functional cortical neurons

in a matter of weeks.

4.4 Generation of Other Brain Cell Types

Additionally, iPSCs can be differentiated into cholinergic neurons, inhibitory interneurons, and astrocytes. This is very advantageous because it enables the modelling of Alzheimer's disease.

5. Two-Dimensional and Three-Dimensional Culture Systems

2D cultures offer standardized environments, high reproducibility, and manipulability concerning genetics and pharmacology. Nevertheless, they do not possess the structural or cellular detail observed in the human brain and feature young development-stage neurons primarily. 3D cultures involve the use of hydrogels or fibre-type materials that act as a supporting medium for the directional outgrowths of neurons. Such models better mimic the shape and connectivity patterns of neurons but do not come close to that of an organized brain.

6. Brain Organoids as Advanced Alzheimer's Models

Brain organoids are self-organizing three-dimensional systems created from iPSCs. They recapitulate crucial developmental events in embryonic brains. Unlike cultures within a scaffold, brain organoids allow cells to self-organize and differentiate through purely cellular processes relying on their developmental programs.

Organoids are more human-like in neuronal development, particularly with regard to non-neuronal support cells like radial glia. As a result, they are more translatable to Alzheimer's disease because they have the potential to represent cellular processes that emerge.

7. Applications in Disease Modelling and Drug Discovery

The differentiated neuronal cells using Alzheimer's patients' iPSCs demonstrate typical features seen in Alzheimer's disease, like abnormalities in amyloid beta metabolism, tau protein defects, oxidative damage, and mitochondrial dysfunction.

These abnormalities can be present even before cell death and thus explain the pathogenesis of Alzheimer's disease.

iPSC platforms are currently widely used in drug screening, as well as in the application of personalized medicine. The differing reactions to drugs among differentiated cells obtained from different patients highlight the importance of personalized therapeutic techniques.

8. Limitations and Challenges

Although they show promise, there are many limitations that iPSC-based models must work through:

- abolishes cell-based senescence, so study of adult manifestations of disease is hard.
- They look like fetal cells, not elderly ones.
- The major disadvantage is the unavailability or insufficiency of the cellular diversity.
- Variability among labs reduces reproducibility

9. Ethical Considerations

iPSC technology avoids the unethicality associated with embryonic stem cells, as it relies on adult somatic cells. This ethical benefit has made it easier to achieve acceptance and has contributed to speedy progress in the area of modelling in neurodegenerative diseases

10. Conclusion

Induced pluripotent stem cell technology is a revolutionary area that is shifting the landscape of Alzheimer's disease research. Despite the limitations in simulating aging or late stages of disease in current models, they are extremely insightful for understanding early disease processes, genetic risk factors for disease, and response to therapy. Alongside other models of disease, iPSC technology is ready to revolutionize the treatment of Alzheimer's disease.

References

1. Israel, M. A. et al. (2012). Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells. *Nature*, 482, 216–220.
2. Mungenast, A. E., & Siegert, S. (2020). Modeling Alzheimer's disease with human induced pluripotent stem cells. *Cell and Tissue Research*, 380, 203–214.
3. Penney, J., Ralvenius, W. T., & Tsai, L. H. (2020). Modeling Alzheimer's disease with iPSC-derived neurons: A roadmap to drug discovery. *Neuron*, 108, 388–401.
4. Blurton-Jones, M. et al. (2009). Neural stem cells improve cognition via BDNF in a transgenic model of Alzheimer disease. *PNAS*, 106, 13594–13599.
5. Li, M., Izpisua Belmonte, J. C., & Zhang, Y. (2023). Intranasal delivery of induced pluripotent stem cell-derived neural secretome improves cognitive function in Alzheimer's disease mice. *Translational Neurodegeneration*, 12.
6. Wang, C. et al. (2018). Gain of toxic apolipoprotein E4 effects in human iPSC-derived neurons is ameliorated by CRISPR/Cas9 gene correction. *Science Translational Medicine*, 10.
7. D'Avanzo, C. et al. (2015). Alzheimer's disease patient-derived induced pluripotent stem cells: Challenges and promise. *Human Molecular Genetics*, 24, R82–R89.