Current Trends in Biomedical Engineering & Biosciences
ISSN: 2572-1151

Juniper Publishers
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Mini Review
Volume 23 Issue 1 - July 2024
DOI: 10.19080/CTBEB.2024.23.556104

Curr Trends Biomedical Eng & Biosci

Brain Organoids: Unlocking New Avenues for Alzheimer's Disease Remodeling and Treatment

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Submission: July 8, 2024; **Published:** July 18, 2024

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Abstract

The use of brain organoids in Alzheimer's disease (AD) research has shown promising results in recent years. Studies have demonstrated the potential of cerebral organoids to model early pathogenesis of AD, evaluate drug effectiveness, and identify early alterations associated with the disease. These advancements highlight the utility of brain organoids in drug screening, examining specific compounds' effects, and modeling disease-related changes such as mitophagy alterations. Additionally, the use of retinal organoids has provided insights into early changes within the central nervous system and their implications for early AD diagnosis. The ability of brain organoids to recapitulate disease characteristics and model pathological changes associated with AD offers a valuable tool for studying AD and exploring potential treatment strategies.

Keywords: Brain organoids; Alzheimer's disease; Disease modeling; Induced pluripotent stem cells; Drug screening; Neurodegenerative disorders; Neurodegeneration

Abbreviations: AD: Alzheimer's Disease; Aβ: amyloid-β; NFTs: Neurofibrillary Tangles; iPSCs: induced Pluripotent Stem Cells; 3D: Three-Dimensional

Introduction

Alzheimer's disease (AD) is a prevalent, age-related neurodegenerative disorder that accounts for a significant proportion of dementia cases globally [1]. This incurable condition is characterized by the gradual deterioration of cognitive functions, leading to progressive impairments in basic tasks such as walking, swallowing, memory, and attention [2,3]. The hallmark pathological features of AD include the excessive accumulation of amyloid-β (Aβ) peptide and the formation of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein, ultimately resulting in neurodegeneration [4].

Although recent studies on the pathophysiological process or treatment of AD have been successfully conducted through studies using cell or animal models, even drugs with successful preclinical assessment have not been effective in reversing or slowing AD progression in clinical trials [5]. The disappointing outcomes seen in the translation of therapies from animal models to humans have prompted the exploration of alternative approaches, such as the utilization of human induced pluripotent stem cells (iPSCs) to develop three-dimensional (3D) human brain organoids [6,7.

This review paper aims to explore the role of brain organoids in the remodeling and treatment of Alzheimer's disease, drawing insights from the existing literature and highlighting the potential of this innovative approach to enhance the management of this debilitating condition.

Advancements in Organoid Models for Alzheimer's Disease Research

Since their introduction in 2006, iPSCs have become a widely employed technology for disease modeling, stem cell therapies, drug discovery, and specific cell line differentiation [3]. More recently, brain organoid models have been suggested to recapitulate both normal brain development and the pathological characteristics observed in neurodegenerative disease models [8-10]. These human brain organoids, also referred to as "mini-brains" or "brain-on-a-chip," are 3D cultures derived from human stem cells and designed to mimic the structural and functional features of the human brain [11]. Brain organoids offer several advantages, including the ability to model disease progression

over a comprehensive timeline, maintain the complexity of a multicellular tissue/organ while being maintained in a cell-culture-like environment (12), and recapitulate human brain development in vitro [13].

In 2019, Fan et al. generated AD cerebral organoids by overexpressing familial AD mutations in mouse induced pluripotent stem cells, demonstrating the suitability of cerebral organoids for investigating the early pathogenesis of AD [14]. Moving on to 2022, Kim et al. evaluated the effectiveness of cerebral organoids treated with Aβ peptide as a platform for drug screening in AD research. Their study demonstrated that estrogen could reduce neurotoxicity in the organoids, highlighting their potential for in vitro drug screening applications [15].

In 2023, Hernandez et al. showcased the potential of retinal organoids as a model for identifying early retinal alterations associated with AD, emphasizing their utility in exploring early changes within the central nervous system and their implications for early AD diagnosis [16]. Similarly, Kim et al. (2023) successfully generated AD cortical brain organoids using patient-derived iPSCs, providing a platform for drug screening and examining the effects of specific compounds on AD cortical brain organoids [10]. Furthermore, Zhang et al. (2023) treated brain organoids with Aβ to model changes in mitophagy observed in AD brains, revealing a significant reduction in mitophagy, thus validating the reliability of brain organoid culturing as a method for modeling mitophagy changes in AD [11]. Lavekar et al. (2023) also identified hallmark features of AD within retinal organoids and investigated additional pathological changes associated with the disease state through transcriptional profiling of retinal organoids after differentiation [17].

Lastly, in 2024, Choe et al. developed a modeling strategy using transgenic human pluripotent stem cells to replicate AD pathology in cerebral organoids and neuronal cells. This approach facilitates the study of genetic variants and the development of new AD models [18]. These studies collectively demonstrate the valuable role of brain organoids in modeling and treating Alzheimer's disease, offering insights into early alterations, drug screening, pathogenesis, mitophagy changes, and potential applications for studying genetic variants and developing new models for various human diseases.

What are The Deficiencies of Organoids?

Organoid technology has significantly transformed the landscape of biomedical research, offering profound insights into human biology and disease mechanisms. Brain organoids, in particular, hold immense promise for advancing future research endeavors [19-24]; however, certain technical challenges persist and must be addressed to fully harness their potential [24] (Table 1).

Table 1: Some of the deficiencies of organoids, their causes and the results.

Barriers and Shortcomings	Cause	Result	References
Lack OF MICROGLIAL CELLS	Background of progenitor cells	Low mimicry of organoid from brain	[25]
aging simulation	-	-	[26]
low experimental repeatability	Diversity in growth factors and dosage, timing of procedures		[27]
variability of growth factors and nutrients	-	Low reproducibility and repeatability	[28]
unwanted mutations OCCURE	growth factors and nutrients	Shorten the chance of	[28]
The batch and quality of original CELLS VARY from ONE laboratory to ANOTHER	-	Low reproducibility and repeatability	[29]
THE UNABILITY OF cells TO FULLY maturE and develop IN ORGANOIDS	Background of progenitor cells and adverse vascularization	Organoid doesn't possess the ability to demonstrate features of a real tissue, neither in term of size nor function	[30]
inappropriate vascularization		Necrosis and disorder in cell growth and maturation	[30]

Conclusions

Recent research has shown promising results in using brain organoids for Alzheimer's disease studies. These studies have demonstrated that cerebral organoids can effectively model early stages of AD, assess the efficacy of drugs, and identify early changes linked to the disease. These findings underscore the value of brain organoids in drug screening, evaluating the effects of specific compounds, and simulating disease-related alterations like mitophagy disruptions. Moreover, the use of retinal organoids has provided insights into early CNS changes and their relevance for early AD detection. The capacity of brain organoids to replicate disease features and mimic pathological changes associated with AD presents a valuable resource for investigating AD and exploring potential treatment options. However, it is important to acknowledge the mentioned limitations in current organoid models that underscore the need for ongoing research efforts to enhance organoid models and address these deficiencies, ultimately improving their relevance for Alzheimer's disease research and potential treatment development.

How to cite this article: Sana R, Hossein N. Brain Organoids: Unlocking New Avenues for Alzheimer's Disease Remodeling and Treatment. Curr Trends Biomedical Eng & Biosci. 2024; 23(1): 556104. DOI: 10.19080/CTBEB.2024.23.5560104

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