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Mini-Review

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Organoids and their Applications in Parkinson's Disease

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Abstract

Parkinson's disease is the second largest neurodegenerative disease which usually causes a huge economic and living burden for the patients and their families no matter in developed countries or developing countries; so far, there is no ideal treatment for it. With the rapid development of regenerative medicine, especially stem cell technology, 3D brain organoid models have been developed and demonstrated great potential applications in pathogenesis, new drug development and new therapeutic method of nervous system diseases. Here, we will summarize the recent progress on organoid models and their application in Parkinson's disease, and discuss the challenges and the limitation of organoids application in Parkinson's disease, which may provide some clues for understanding the pathogenesis of Parkinson's disease and developing the drugs for the Parkinson's disease.

Keywords: Organoids • Parkinson's disease • Stem cells • Drug development

Introduction

Parkinson's Disease (PD) is one kind of common degenerative diseases of the nervous system. which commonly occurred in the elderly population aged above 60 years old, and the prevalence of PD in people over 65 years old in China is about 1.7%; the epidemic characteristics of PD are generally sporadic, less than 10% PD patients have a family history; the main pathological characteristics of PD is the degeneration and death of dopaminergic neurons in the substantia nigra of the midbrain [1-4]. So far, the exact pathogenic cause of PD is still unclear. Many influence factors including heredity, environment, aging, oxidative stress may participate in the process of degeneration and death of PD dopaminergic neurons and finally leading to PD [5-8]. For understanding the pathogenesis and the underlying mechanism of PD, there are several kinds of commonly used and classic animal models including 1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine (MPTP)-induced or 6-Hydroxydopamine (6-OHDA) induced PD animal model, transgenic Parkinson's animal model, and induced Pluripotent Stem Cells (iPS) induced PD animal model. In particular, with the unique characteristics of self-renewal and multi-directional differentiation, iPS could differentiate into various tissue cells under certain conditions, and iPS-induced PD animal model have incomparable advantages for PD application. However, because the complexity of PD symptoms and the unclear mechanisms of PD, different animal models can only simulate some symptoms at present.

Recently, with the rapid development of stem cell technology, scientists could obtain 3D stem cell populations (organoids) with self-renewal characteristics through special culture methods or with the help of special material structures (devices) [9,10].Organoids could provide a highly physiological related system usually contain spatial tissue structures similar to human organs and contain some special key functions of human organs. So far, scientists have been successfully applied to various tissue cultures including intestine [11,12], liver [13-15], pancreas [16,17], kidney [18,19], prostate [20,21], lung [22] and brain [23,24], and there are many amazing articles reported that brain organoids and its applications in PD research. In this review, we will summarize the recent research progress on preparation methods, applications and application limitations of PD organoids.

Literature Review

Preparation methods of PD organoids

A successful and reliable 3D organoid model is the key to the study mechanism, pathology or applications of PD. To maximize and effectively mimic the characteristics of PD patients, there are many preparation methods of PD including adding the growth factors, small molecules, transcription factors or signal pathway regulators into culture medium; co-culture and special 3D culture device. The detailed information of several classical organoid preparation methods for PD organoids was listed as follows (Table 1).

Table 1. Several classical PD organoid preparation methods.

	Preparation methods			
Cell lines	**Culture medium**	**Whether needs 3D**	**Supplement**	**Refrences**
hiPSCs, EB	Human embryonic stem cell growth medium, neural stem cell medium	No	Fibroblast growth factor 2 (20 ng/mL) epidermal growth factor (20 ng/mL) ,200 nM ascorbic acid, 20 ng/mL BDNF, 100 ng/mL SHH, and 20 ng/mL GDNF	[25]
pNSCs	Spontaneous differentiation medium (differentiation medium with 10 ng/mL BDNF and 10 ng/mL GDNF), midbrain-specification medium (differentiation medium with 100 ng/mL Shh and 100 ng/mL FGF8)	Activin A	/	[26]

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hESCs, EB	DMEM/F12	Matrigel, orbital shaker	20% Knockout Serum Replacement (KSR), 3% FBS, 2 mM GlutaMAX, 1% nonessential amino acids, 50 nM β-mercaptoethanol, and bFGF (4 ng/ml). ROCK inhibitor Y27632 (50 μM) ,1× N2 supplement, 1% nonessential amino acids, 2 mM GlutaMAX, and heparin (1 μg/ml)	[27]
hPSC	Neural induction medium, neural differentiation medium	Orbital shaker	ROCK inhibitor Y27632, B27, SB431542, Noggin, ascorbic acid, insulin, sonic hedgehog, purmorphamine, CHIR99021, FGF8b	[28]
iPSCs	N2B27 medium	Activin A	Ascorbic acid, CHIR 99021, Smoothened Agonist, SB-431542, LDN-193189, BDNF, GNDF, TGF-β3, cAMP, DAPT, Activin A	[29]
hiPSC	Stem cell medium	Matrigel, spinning bioreactor	Dorsomorphine, A83-01, WNT-3A, CHIR99021, SB-431542, 2-Mercaptoenthanol, Insulin, Ascorbic Acid, TGF-β, cAMPb	[30]
iPSCs	Neural induction medium, midbrain patterning medium	Matrigel, orbital shaker, PLGA or CF fiber	Noggin, SB431542, CHIR99021, FGF8, sonic hedgehog,	[31]
iPSCs	Neurobasal medium	Collagen type I	SB/noggin, retinoic acid, FGF-2, TGFβ1, DAPT	[32]

PD organoids as the disease models for PD research

Because of the multi-lineage differentiation potentials of stem cells including induced Pluripotent Stem Cells (iPSCs) and Mesenchymal Stem Cell (MSCs), stem cells have been widely used in the research and application of Parkinson's disease, but stem cells model as a two-dimensional model in vitro, it is difficult to mimic the 3D complex structure of human brain. Instead, organoids have the similar function and 3D structure of human organs, also could mimic the complex pathophysiological process, which provide a powerful tool for PD research, and has attracted great interest of scientists. For example, Andrea Becerra-Calixto, et al. generated a kind of αSyn gene (SNCA)-expressing PD organoids by iPSCs which came from a healthy female aged 80 years old and a female fPD patient aged 55 years old with SNCA gene triplication, and evaluation of organoid phenotype by immunohistochemistry and immunofluorescence staining found the organoids could express SOX2, Nestin, En-1, Otx2, Lmx1a, Nurr1, MAP2, and TH; the αSyn gene (SNCA)-expressing PD organoids could also mimic the pathogenesis of Lewy bodies of PD. Those data provide a method for obtaining midbrain organoids, those midbrain organoids could mimic the formation of Lewy bodies in space and morphology, and provide an evidence that the accumulation of αSyn was paralleled by the loss and apoptosis of DA neurons. Therefore, the αSyn gene (SNCA)-expressing PD organoids may be applied to relevant drug screening in the future [33]; for understanding the effect of LRRK2 and PINK1, Zhi Dong Zhou, et al. developed a kind of midbrain organoids from iPSCs with or without LRRK2 and PINK1 mutation, compared with transgenetic mouse and Drosophila models, found the gene LRRK2 and PINK1 have the unique regulatory mechanism in pathogenesis of PD[34]; and David Pamies, et al. developed a kind of PD organoids from the iPSC-derived neural progenitor cells, to study the neurotoxicity of 6-OHDA, MPTP, and MPP+. After analyzed and compared by Resazurin assay, ROS assay, mitotracker, transendothelial electrical resistance recording, Immunocytochemistry, RT-qPCR, and metabolomics analysis, found that 6-OHDA, MPTP, and MPP+ have different pathological mechanisms of PD, especially 6-OHDA can effectively increase ROS production and reduce mitochondrial function in the three chemicals [35]. These evidences demonstrated that PD organoids can be used as a powerful tool to study the pathogenesis and underlying mechanism of PD.

Discussion

PD organoids applications in drug discovery and drug screening

It can be said that, the drug development involves multiple stages from molecular synthesis to clinical application, animal models are often used to verify the effectiveness and toxicity of the drug, but animal model has the obvious difference from human organ structure and physiological and pathological process of human disease, therefore, an economical and effective disease model close to human organ is often needed for drug research and development to reduce the cost and time of new drug research and development. The appearance of PD organoids has great attraction for drug discovery or drug screening. For example, Tae Hwan Kwak, et al. generated a kind of homogeneous midbrain organoids including multiple nerve cell types (neurons, astrocytes and oligodendrocytes) from ESCs with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced neuron death characteristic, which may provide a neurotoxicity model in vitro for PD drug development [36]; Renner, H.et al. developed a kind of midbrain organoids from Human small molecule Neural Precursor Cell (smNPC), and compared the 3D midbrain organoids and 2D culture application in high throughput drug screening, found the 3D midbrain organoids have the higher sensitivity in dose-response neurotoxicity experiment [37]; Due to the limitation of technologies, there are many problems of organoids produced by current methods, such as lack of homogeneity. For solving this problem, Henrik Renner, et al. developed a high-throughput screening automated workflow, this kind automated workflow could obtain the organoids with homogeneous morphology, similar gene expression patterning and highly unified structure, which may provide an excellent PD drug development platform [38]; and Nguyen-Vi Mohamed, et al. invented a kind of organoid workflow which could produce large-scale and uniform PD organoids at one time, reduce human operation, the reagent volumes and save the cost, this method can not only meet the needs of PD research, but also be applied to the drugs screening for PD [39].

Conclusion

The main challenges of organoids applications in PD is how to obtain a large number of homogeneous organoids that are close to the structure and function of human organs according to different purposes. Because of technical limitations, the applications of PD organoids is limited to the academic research stage, which is difficult to apply to large-scale industrial production. For this reason, we think there are several problems need to solve: 1) how to obtain PD organoids with high consistency of pathophysiology characteristic and complex structure of neuron-glial interaction; 2) how to make large-scale industrial production of PD organoids; 3) how to store and transport the PD organoids, and to establish standardized operation process to reduce mechanical damage of PD organoids. Anyway, with the continuous progress and development of technologies, PD organoids will make a major breakthrough in the future, which will play a great role in mechanism study and drug development of PD.

Conflict of Interest

The authors declared that there are no conflicts of interests in this review.

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