Applications of human brain organoids

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Introduction

The human brain is formed inside the womb. Current imaging technologies are not sensitive enough to investigate how human brains are formed at the molecular and cellular levels. By recreating neurodevelopment in the lab, we have a unique opportunity to learn how the human brain develops from the embryo.

The brain organoid technology was initially developed by Dr. Yoshiki Sasai in 2008 [1]. His pioneer publication revealed that it was possible to push neural differentiation of human pluripotent stem cells in suspension and let the cells self-aggregate, after which they form a tissue that resembles the human fetal cortex. Several other labs have developed other improved ways to create brain organoids, making them more robust and more reliable [2]. Brain organoids are not fully vascularized, not all cell types are represented, and there are no optimized culture conditions to grow human brain organoids [3].

Applications of human brain organoids

One of the applications of these organoids is brain malformation. The Zika virus is an excellent example. Exposing the organoid to the Zika virus, we learned that the virus could kill some of the intermediate progenitor cells, reducing cortical thickness [4,5]. More importantly, just 2 years after the outbreak, researchers could repurpose an antiviral that could be used for Zika [6].

Modeling brain tumors is another potential application of human brain organoids. It is possible to seed glioblastoma cells inside these organoids, for example. That strategy allows us to screen for drugs that kill tumor cells while keeping healthy brain cells intact [7].

To model network conditions, it is necessary to have a protocol that mimics pre-and-postnatal human neural network development [3]. An optimized cortical organoid protocol was tested using micro-electrode arrays [8]. Interestingly, the electrical activity starts to increase by 4 months, showing signs of neural oscillatory waves for the first time. The oscillations behave quite differently by 8 to 9 months, when they become more complex [8]. However, the question arises—how similar are these oscillations to the natural human brain? Using a machine learning algorithm, it was possible to create an unbiased regression model to test how similar the human electroencephalograms are compared to the signal from the human brain organoids. Surprisingly, the similarities were remarkable, showing that human brain organoids have an indistinguishable...
The emergence of oscillatory behavior in human brain organoids is a significant milestone because it is the first step toward bridging basic biology to human cognition [9]. Moreover, organoids with excitation (E) and inhibition (I) can be used to model several conditions of E/I imbalance, such as epilepsy. One of such conditions is called CDKL5 deficiency disorder (CDD), which is characterized by severe seizures early in life. Cortical organoids derived from CDD patients showed increased hyperexcitability at early time points [10]. Another condition called focal cortical dysplasia was modeled using this protocol, showing early alterations in neural rosettes and the presence of balloon cells that might contribute to the cortical malformation and proper network wiring [11].

**Discussion: moving towards novel applications**

The human brain receives chronic stimulation during neurodevelopment, but brain organoids grow inside incubators without input and output. Previous protocols could generate brain organoids with spurious photoreceptors, but no one has specifically engineered the circuits related to a human visual cortex.

Another idea for input and output for brain cortical organoids is to use a mechanical interface. Here, the goal is not to mimic human biology but to artificially challenge the organoids. This experiment is currently being done with the Center for Engineered Natural Intelligence at University of California San Diego. The goal is to create a close stimulation loop between the robot and the organoid. We hope that these simple experiments will allow us to confirm if these human organoids can store memories or even learn how to adapt to a different environment. Perhaps even more critical would be applications in artificial intelligence (AI). These experiments can influence current AI algorithms to become more human-like.

Biomedical applications using functional cortical organoids are another hot area. Our lab is working with several neurological conditions caused by either copy number variations or mutations in single genes. Once a screenable phenotype is found, one can use both pharmacological treatments and gene therapy (in the case of single-gene driver conditions) for proof-of-principle, paving the way for a robust pre-clinical set of experiments [2,3].

Brain organoids can also be used to understand human evolution. To identify the unique genomic variants in modern human genomes, a genomic comparison was performed, contrasting modern human genomes against those of Neanderthals and Denisovans. We found 61 genetic variants in protein-coding genes unique to modern humans [12]. Among them, there is an interesting single-base pair substitution in the NOVA1 gene. The archaic version of NOVA1 was placed into 2 human induced pluripotent stem cells using genome editing technologies. Intriguingly, the archaic version of NOVA1 changed gene expression and splicing isoforms during neurodevelopment. Such alterations lead to changes in cell populations, affecting the morphology and resultant electrophysiology of the neural networks.

Finally, another exciting application is to explore the impact of the space environment on the human brain. By growing brain organoids on the International Space Station, we hope to understand how this environment affects brain cells. The information can mitigate eventual problems for astronauts on long flights, such as Earth-Mars. Moreover, we also plan to leverage the accelerated telomerase activity in human cells to speed up organoid maturation on Earth. That strategy might improve the modeling of late-onset neurological disorders, such as Alzheimer’s disease and dementia.

**Concluding remarks**

In summary, the brain model technology using stem cells had several incremental improvements since the original description by Dr. Sasai [1]. We now know that brain organoids can mimic several aspects of human neurodevelopment despite the limitations previously described. Thus, the next generation has an opportunity to achieve new milestones in our understanding of human brain health and disease.

**Notes**

**Conflict of interest**

Dr. Muotri is a co-founder and has an equity interest in TIS-MOO, a company dedicated to genetic analysis and brain organoid modeling focusing on therapeutic applications customized for autism spectrum disorder and other neurological disorders with genetic origins. The terms of this arrangement have been reviewed and approved by the University of California San Diego per its conflict-of-interest policies.

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