Human cerebral organoids in neurodegenerative disease: Promise, prospects, problems

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Abstract

Human cerebral organoids (hCOs) are three-dimensional cell-culture based simulacra of the human brain, derived from human induced pluripotent stem cells. While initially useful for studying early brain development, there are now at least four promising types of applications of hCOs in neurodegenerative disease research. In reviewing the ethical and scientific prospects for hCOs in this domain, we base our analysis in the mundanity of scientific practice, avoiding esoteric sensationalism about these models. 1. They may be useful as models of neurodegeneration and neurodegenerative disorders such as Parkinson Disease (PD) and Alzheimer's Disease (AD). *To what extent do hCOs faithfully replicate these processes and disorders as compared with native tissues?* 2. As potential therapeutics for transplantation. *How could hCOs help solve outstanding challenges with cell-based transplants?* 3. As assay systems for potential therapeutics. *Do hCOs improve upon other novel approaches, such as clinical-trials-on-a-chip?* 4. As models of human brain evolution, especially regarding the apparent uniqueness of PD and AD amongst humans. *Could hCOs shed light on these key issues while moving us beyond ethical concerns in research with non-human primates?* In this presentation, we outline these applications and the various methodological and ethical problems they pose - and help to resolve.

Promise

Derived from human (induced) pluripotent stem cells, human cerebral organoids (hCOs) are three-dimensional cell-culture based simulacra of the human brain. Over the past decade, researchers have made significant progress in refining hCOs, whether whole-brain or region-specific. hCO research promises to facilitate the study of neurodevelopment, dys/function, and neurodegeneration, improve modeling of human brain disorders, ameliorate the challenges of cell-transplant therapies, and expedite drug development and accurate assessment of neurotoxicity.

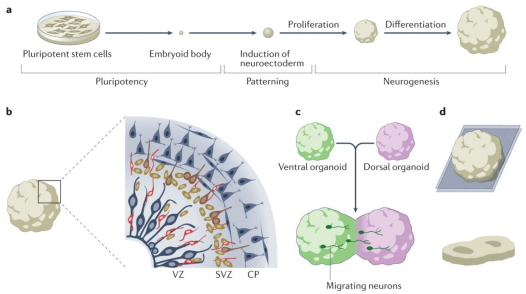

Figure 1. Production and use of organoid models. a | Organoids are generated from pluripotent stem cells, either embryonic or induced, that are grown in adherent 2D culture. These cells are aggregated in low-attachment plates to produce embryoid bodies, after which induction of neuroectoderm occurs. Organoid progenitors proliferate symmetrically in the first weeks, followed by neuron production and differentiation. During the initial culture period, organoids can be patterned to develop into representations of specific brain regions. Various protocols enable patterning for dorsal or ventral forebrain, thalamus, hypothalamus, midbrain, hindbrain and cerebellum. **b** | Mature organoids recapitulate developmental hallmarks of the human brain, including ventricular zone (VZ) structures that contain apical radial glia, subventricular zone (SVZ) areas that contain intermediate progenitors and outer radial glia, and an emerging cortical plate (CP) that contains neurons. **c** | Restricted organoids can be fused to model interactions between distinct brain areas; for example, the tangential migration of interneurons from ventral to dorsal areas, the striatal or thalamic projections to the cortex, hypothalamic projections to the pituitary gland or the connection of cortical neurons to muscle via the spinal cord. **d** | To overcome difficulties such as restricted nutrient supply, sliced organoids — so-called air–liquid interface cerebral organoids — can be cultured. (Reproduced from Eichmüller and Knoblich (2022).)

Prospects

While hCO research is most obviously a boon to the study of the early human brain and its development, the sheer variety of hCOs available (and, recently, hCO assembloids and chimeras) has demonstrated their potential to shed light on the processes of neurodegeneration. Accordingly, hCOs may be useful in studying neurodegenerative diseases that manifest uniquely in humans.

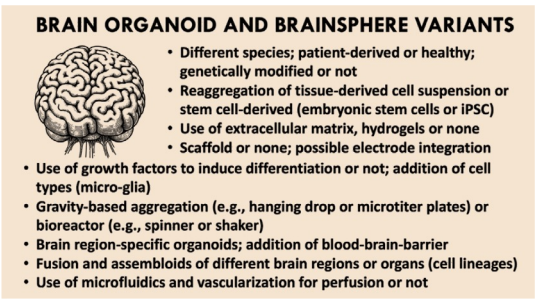

Figure 2. Brain organoid and brainsphere variants. (Reproduced from Smirnova and Hartung (2024).)

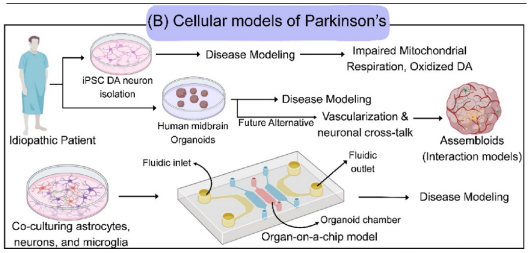

Figure 3. Schematic representations of experimental models of PD. (Reproduced from Lal *et al.* (2024).)

Problems

Many of the innovations required to realize the potential of hCOs for the study and eventual treatment of neurodegenerative diseases remain to be developed. In addition to persistent technological challenges, familiar ethical issues involving consent, biobanking, commercialization, and contexts of use, *inter alia*, endure. Moreover, other ethical issues have arisen, including concerns about the moral status of hCOs and, more recently, about the ways in which hCOs may be integrated with emerging technologies in artificial intelligence, biological design, and synthetic biology.

Early and ongoing collaboration with ethicists may prove useful in maximizing the prospects of hCOs at minimal moral expense.

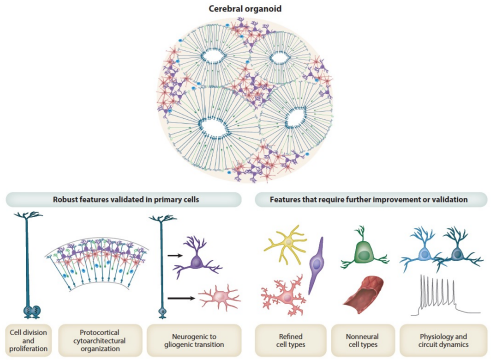

Figure 4. Features of cerebral organoids. Organoids robustly replicate proliferation and division programs and spontaneously organize into a rudimentary radial scaffold. Neural progenitors generate neurons and later differentiate into astroglial cells. However, cerebral organoids still require validation for certain applications and continued refinement to better replicate neurodevelopmental features. Currently, organoids are impaired in gene expression programs that define robust cell type specification. They lack specific nonneural cell types that are vital for brain health and function, including vascular endothelial and mural cells and immune microglia. Organoids also may not replicate complex physiological dynamics that define intracortical and subcortical circuitry. (Reproduced from Andrews and Kriegstein (2022).)

References

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