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The promises of brain organoids in the context of bioethical redefinition. Embryo status, consent and animal research

La promesa de los organoides celulares en el contexto de una redefinición de la bioética. El estatuto del embrión, el consentimiento y la investigación con animales

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Resumen

Algunas de las mayores inversiones en el área de investigación en salud están asociadas con la investigación en el campo de las neurociencias, especialmente en enfermedades neurodegenerativas. Una de las más prometedoras innovaciones en investigación es la proporcionada por las células madre, que pueden usarse para producir organoides cerebrales en el laboratorio. El desarrollo del uso de organoides, así como de células madre adultas, es la expresión de que el origen de la relación entre la ética y las ciencias es la complementariedad. El desafío ético de los organoides radica en el hecho de que sus células en su desarrollo difieren y forman estructuras relacionadas con las observadas en los tejidos embrionarios. Uno de los desafíos a los que se enfrenta la bioética en esta área es el hecho de que hoy podemos usar las células de formas que no hubiéramos podido imaginar hasta hace unos años. Las consecuencias de usar esta técnica en el modelo animal es la necesidad de cambiar el grado de compromiso ético en el uso del modelo animal. En conclusión, el progreso científico en el área de la medicina regenerativa y la ingeniería de tejidos utilizando organoides cerebrales, plantea desafíos éticos que no se ven en otras formas de investigación con células madre. En este artículo afirmamos que es urgente establecer un marco moral para los organoides cerebrales que pueda abordar inquietudes éticas relevantes sin obstaculizar indebidamente esta importante área de investigación.

Palabras clave: Bioética; Ética médica; Medicina regenerativa; Organoides cerebrales; Células madre.

Abstract

Some of the largest investments in the area of health research are associated with research in the field of neurosciences, especially in neurodegenerative diseases. One of the most promising innovations in research is provided by stem cells, which can be used to produce brain organoids in the laboratory. The development of the use of organoids, as well as adult stem cells, is proof that the origin of the relationship between ethics and science lies in their complementarity. The ethical challenge of organoids lies in the fact that their cells in their development differ and form structures related to those seen in embryonic tissues. One of the challenges that bioethics faces in the area of organoids is the fact that we are now able to use cells in ways that we might not have imagined until a few years ago. The consequences of using this technique in the animal model are the need to change the degree of ethical commitment in using the animal model. In conclusion, scientific progress in the area of regenerative medicine and tissue engineering, using brain organoids, raises ethical challenges not seen in other forms of stem cell research. In this article we claim that it is urgent to establish a moral framework for brain organoids that can address relevant ethical concerns without unduly impeding this important area of research.

Keywords: Biothethics; Medical Ethics; Regenerative medicine; Brain organoids; Stem cells.

Introduction

Some of the largest investments in the area of health research are associated with research in the field of neuroscience, especially in neurodegenerative diseases (Lewis-Fernández et al., 2016).

Following the ethical issues associated with his large investment, a theme takes on special relevance: the delicate character of cerebral morphology, associated with the core function of identity, implies a delicate invasive intervention. In view of these difficulties, an alternative source to the difficulty of intervening invasively in the human brain has always been sought. For centuries, the use of the animal model has presented itself as a safe, inexpensive and very effective possibility (Ericsson et al., 2013).

Despite this, the “sentient” condition of the animals has always been an obstacle to their use in research. This obstacle helped to identify a set of challenges no less problematic than the intervention of the human brain in vivo. European standards in animal protection legislation, associated with the ethical debate, did the rest[i]. The consequence was the development of alternatives based on the developments of regenerative medicine (Levin et al., 2019).

One of the most innovative forms is provided by stem cells, which can be used to produce brain organoids in the laboratory. Brain organoids are small collections of brain cells that organize themselves into structures that resemble parts of the human brain.

Some of the largest investments in the area of health research are associated with research in the field of neurosciences, especially in neurodegenerative diseases. One of the most promising innovations in research is provided by stem cells, which can be used to produce brain organoids in the laboratory.

The ethical challenge of organoids lies in the fact that their cells in their development differ and form structures related to those seen in embryonic tissues. As the similarities between organoids and brains increase, researchers need to pay close attention to the potential for ethical issues. This innovative research tool thus poses a set of ethical challenges not seen in other forms of stem cell research (Koplin & Savulescu, 2019). We can easily sense that the evolution of the complexity of brain organoids is substantially more problematic at the ethical level than other forms of organoid evolution.

Since 2013, the team of researchers led by Lancaster (Lancaster et al., 2013) built the first human brain organoids from human pluripotent stem cells, demonstrating the ability to synthesize specific characteristics of human cortical development with an increased density of glial stem cells.

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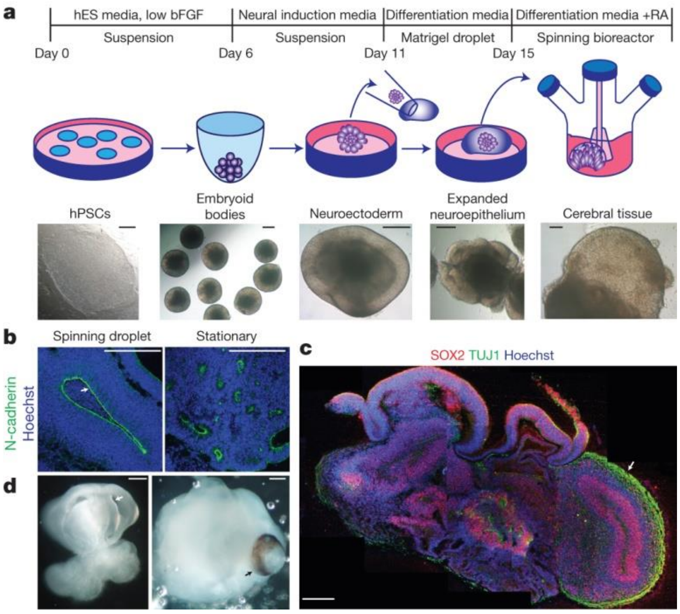

MA Lancaster et al. Nature 000, 1-7 (2013) doi: 10.1038 / nature12517

One of the main promises of this tool in brain research was that, as brain organoids behave similarly to the real brain, they can be studied without the need to test treatments and therapies in living patients. To be a good model, the organoid will have to match an archetype as human as possible. This is precisely the central issue in the current ethical dilemma (Henry et al., 2018).

I. Good science that produces good ethics

The development of the use of organoids, as well as adult stem cells, is the expression that the origin of the relationship between science ethics is complementarity.“The most recent discovery in the area of stem cells, the so-called STAP cells, pluripotency cells induced by environmental stimulus, illustrate, once again, how the bringing of doubts and challenges to science, in an ethical way, resolving objections or ethical uncertainties has become a healthy exercise in good ethics and good science. Perhaps this evolution should be welcomed as promising for the future relationship between ethics and research, proving the stimulus (and not the block) that ethical reflection can bring to the researcher's ingenuity” (Carvalho, 2014).

> The development of the use of organoids, as well as adult stem cells, is proof that the origin of the relationship between ethics and science lies in their complementarity.

Instead of embryonic stem cells, brain organoids are created using induced pluripotency cells. That is, by making the adult cells developed from a donor revert to the pluripotential stage making it possible to produce brain cells or neurons in the laboratory.

This pluripotential cell reversal method is not ethically innocuous, since in this way it relieves the ethical tension caused by the use of embryonic stem cells and the consequent ethical wound of embryo destruction.

When placed in laboratory culture, neurons replicate and grow, and with the help of a 3D scaffold-like artificial support structure, they begin a process of mutating into shapes similar to parts of the human brain, each modeling a region different from the human brain; the anterior brain, cerebellum and cerebral cortex[ii].

Brain organoids respond to chemicals and pharmaceuticals in the same way as real human brains and are therefore a promising technique in the possible treatments of diseases such as Alzheimer's, Parkinson's disease and even brain cancer.

> The ethical challenge of organoids lies in the fact that the cells in their development differ and form structures related to those seen in embryonic tissues.

Bearing in mind the specificity of these elements, ethical evaluation does not fit into a clear category for the supervision of ethics commissions: they are not exclusively research with human beings; they are not investigations with animals or stem cells ex vivo. There is not necessarily a regulatory framework for organoids. This is not a terrible thing at the moment. But it is a gap that should probably be filled if organoids develop in such a way that concerns are more realistic. Ethics and science are working together to see if this specificity justifies the development of more targeted rules. Ethical discussions are progressing rapidly, well ahead of science (Ramos et al., 2019).

II. Organoids, Bioethics and futurology

Despite the growing number of articles related to this technique, the ethical debate has not followed it (Lavazza & Massimini, 2018), having even suffered from a form of futurological contamination brought by the promises of scientific development (Attiah & Farah, 2014). Eric Racine draws attention to the need to distinguish between long, medium- and short-term challenges (Sample & Racine, 2017). One of the first concerns is to think that we are growing small brains in a petri dish. This assumption frees our imagination to the idea of creating brains capable of thinking and feeling. However, this should not be the bioethical focus. We are not yet at that stage of the investigation. Even the most complex brain organoids lack the size, structure and interconnectivity of real human brains. Important cell types and blood vessels are needed to keep tissues nourished and healthy. They are extremely immature: a technique to stimulate their developmental age matched a fetus brain in the following quarters. In addition, they lack the ability to receive sensory information (Hostiuc et al., 2019).

> One of the challenges that bioethics faces in the area of organoids is the fact that today we are able to use cells in ways that we might not have imagined until a few years ago.

Brain organoids, like small clumps of cells, are only able to respond physiologically and molecularly to drugs or signals similarly to parts of the brain, but they are not brains.

The ethical focus should therefore be on other issues, such as the use of human cells to produce these organoids. We know that the evolution of the technique of induced pluripotentiality has meant that the question of the exclusive use of embryonic cells is no longer asked (Hostiuc et al., 2019) in regenerative medicine or chromosomal mutation.

This issue is relevant to our discussion of the measure. Organoid research defies the so-called "14-day rule", according to which no investigation with complete human embryos should use embryos older than 14 days[iii]. Some Ethics Commissions identified this period as relevant mainly due to its close temporal connection with the beginning of neural development and with the embryo's distinct identity. The Warnock Committee specifies three elements: the human origin of the embryo, the possibility of suffering and the possibility of generating individualized human beings (Hurlbut, 2017).

Researchers, like Insoo Hyun or Appleby, question the moral relevance of this rule for organoids (Hyun, 2017; Appleby & Bredenoord, 2018). If moral status is explicitly linked to the neural development of incomplete embryos, one can easily question the morality of the development and use of brain organoids in clinical investigation (Bredenoord, 2017).

Another set of questions arises: who owns these cells? Who are they for? What are we going to do with these organoids? Growing them in a petri dish is one thing, but the possibility of transplanting them to humans or animals is another. What will the consequences be?

a. The challenges to informed consent

One of the challenges that bioethics faces in the area of organoids is the fact that today we are able to use cells in ways that we might not have imagined until a few years ago. Stem cells are a proven valuable resource that cannot be left unused.

Given this assumption, it is necessary for science to exercise its full potential so that society can understand the use of human tissues in a way that individual consent for all possible uses is not necessary. It is a matter of trust. A position of trust in the work of scientists is urgently needed. This process cannot be one-sided, but scientists need to be trusted.

Consent cannot only be limited to research with biomaterials but must extend to genetic information. The question is how we ensure that people have sufficient control over the use of their fabrics and are protected.

Several models have been proposed, from the most comprehensive, such as general consent, in which all uses in research are authorized, to the most restrictive and dynamic, where the agreed terms continue to be discussed and negotiated, passing through general consent, but with specific exceptions.

Taking these models into account, the one that ethically best promotes autonomy is, in our view, the one that sustains continuous governance and supervision. According to this model, the donor is not approached about each research in which his genetic material is being used, but about what type of research is being carried out. It is a consent model in which each tissue donor consents, but there are checks and balances on the use of that tissue.

> The consequences of using this technique in the animal model are the need to change the degree of ethical commitment in using the animal model.

One of the main areas of therapeutic application of brain organoids is their use as test beds to understand how our larger and much more complex brains can react in a molecular way to different chemicals and pharmaceuticals. This possibility implies innovation in health and in the way new products are launched on the market, particularly in some other areas of stem cell science.

b. Cognitive improvement of the animal model and animal welfare

Until now, organoids in the human brain have been widely cultivated and studied in vitro. The novelty is that they are being transplanted into the brains of some animal species, especially mice.

Contrary to what one would expect, there was a peculiar form of synapses between human and animal cells. This discovery ends a pressing ethical question, since these animals have human and animal parts. Would human neurons implanted in a rat's brain cause it to become human?

Scientific progress in the area of regenerative medicine and tissue engineering, using brain organoids, raises ethical challenges not seen in other forms of stem cell research.

So far, we know that mice have actually become smarter when looking at cognitive processing and memory tests. Obviously, we cannot conclude at the moment that this improvement means that they become more human, but there is a data that can have incalculable potential: through this technique we can make animals more intelligent, and, through that, facilitate the communication and the use of animals for the benefit of our lives.

It is urgent to establish a moral framework for brain organoids that can address relevant ethical concerns without unduly impeding this important area of research.

One of the most challenging consequences of using this technique in the animal model is the need to change the degree of ethical commitment in using the animal model. The enhancement of animal faculties, associated with suffering, for example, could lead to reconsider ethical attitudes preparing the way for a better consideration of animal ethics.

Conclusion

Scientific progress in the area of regenerative medicine and tissue engineering, using brain organoids, raises ethical challenges not seen in other forms of stem cell research. Given that brain organoids partially reproduce the development of the human brain, it is plausible that brain organoids may one day achieve superior cognitive skills. This technique raises difficult questions about the moral status of these organoids - issues that are currently outside the scope of existing regulations and guidelines.

It is urgent to establish a moral framework for brain organoids that can address relevant ethical concerns without unduly impeding this important area of research.

The balance between the benefits of research using brain organoids is clearly positive. Although the concerns associated with biosafety, if brain organoids are ever used directly in therapies as a form of tissue transplantation, we will have to think again about the risks of introducing these cells in specific ways.

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[i]The protection of the animal model in research is conditioned in Portugal by Decree-Law No. 113/2019, which establishes the rules for the use of the animal model.
http://www.dgv.min-agricultura.pt/portal/page/portal/DGV/genericos?actualmenu=61974&generico=15470&cboui=15470

[ii]By implanting the organoids of the human brain in the rat brain, they grow faster and survive longer. (Yuen et al., 2018; Hostiuc et al., 2019)

[iii]The embryo's moral status is one of the most important ethical concepts in reproductive and regenerative medicine. (Hyun, 2016; Wilkerson& Johnston, 2016)