Growing Brains from Stem Cells

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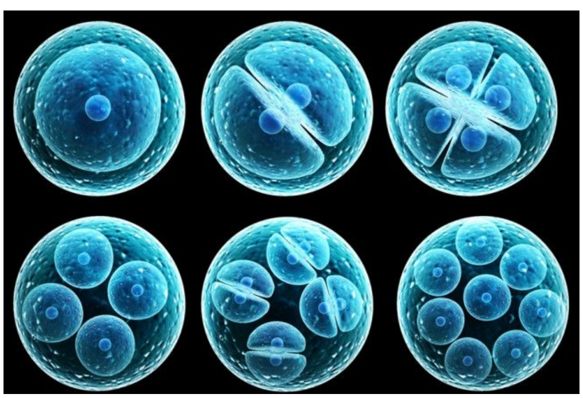
The study of stem cells is often said to be the most revolutionary field of research in medicine since the discovery of antibiotics. Their best known practical application is arguably stem cell therapy, yet that seems to be only one of their applications in the broad spectrum of their potential. These days, stem cells are key in repairing damaged tissue, but who could have ever assumed that they might lead us towards the era of growing organ-like structures in laboratories?



Stem cells and the controversy

It was nearly forty years ago when embryonic stem cells were derived from mouse embryos for the first time. This was a starting point for a cascade of research projects that built upon this discovery. Intriguingly, it was in 1998 when the detailed study of the biology of mouse stem cells led to the discovery of a method used to derive human embryonic stem cells from human embryos and grow the cells in the laboratory. The embryos used for research purposes were donated with informed consent of the donor, in case they became unnecessary for *in vitro* fertilization, which usually is their primary purpose.

Nevertheless, this procedure raised several ethical questions, which spurred a crucial debate regarding the morality of using human embryonic stem cells in research. Fortunately, the issue was resolved by the 2012 Nobel Prize-winning Japanese researcher Shinya Yamanaka who, in collaboration with other scientists, changed stem cell research forever by discovering a technique whereby even specialized adult cells could be reprogrammed to gain the same properties as embryonic stem cells. These properties included pluripotency, which is the ability of a cell to give rise to any somatic cell type in the body. Therefore, these cells were named induced pluripotent stem cells (iPSCs) and are nowadays frequently used for *in vitro* research.

From sponge cells to cerebral organoids

One of the first attempts to create organs *in vitro* was carried out more than a hundred years ago by Henry Van Peters Wilson, whose experiments on sponges demonstrated that dissociated sponge cells are capable of giving rise to a whole new organism. This showed that dissociated cells tend to spontaneously reaggregate. The discovery of this property was later on used by multiple laboratories across the world and resulted in attempts to generate organs *in vitro*.

Malcolm Steinberg proposed a so-called differential adhesion hypothesis (DAH), which explained the phenomenon of mechanically dissociated cells being prone to aggregate and reorganize themselves into tissues. The DAH relies heavily on thermodynamic properties, thus treating tissues as liquids, whose varying degrees of surface adhesion cause them to spontaneously reorganize. Furthermore, the thermodynamics behind this states that this behavior is fueled by the need to minimize the interfacial free energy between the mobile cells. In other words, cells move towards cells with similar adhesive strength to form stronger bonds and consequently become more thermodynamically stable.

The aspirations to grow organs in Petri dishes started with tissues grown from stem cells in 2D media, yet the shift to 3D media allowed us to explore the possibility of generating complex organ-like structures, also known as organoids. Advances were made in many different fields of organogenesis. The researchers succeeded in generating liver organoids, renal organoids, or even cardiovascular organoids in 2014.

An important milestone for neuroscience occurred in 2013 when a young researcher at the Austrian Academy of Sciences, Madeline Lancaster, developed a protocol for culturing cerebral organoids derived from stem cells, thus immensely directing the future research of brain development and neural diseases.

Mini brains, research, and bioethical quandaries

Mini brains, more formally known as cerebral organoids, have once been mere science fiction; yet, by reprogramming human skin cells into iPSCs and differentiating them into neural stem cells by exposing them to the right environmental conditions, we can now create extremely rudimentary versions of an actual human brain. This offers us a range of opportunities to approach the core of several neurological disorders or even mental illnesses that have proven to be too problematic to be tackled by research on model organisms. Cerebral organoids have already managed to prove their desirability in scientific advances when they were used in researching how the Zika virus disrupts normal brain development. However, this is only the start of the mini brain era. A few of the many challenging targets that scientists aim towards include the development of therapies for conditions such as autism, schizophrenia, or Alzheimer's disease.

Cerebral organoids are not only about science; the application of cerebral organoids constitutes a leap towards the unknown, an ethical problem which was recognized by a group of biologists, ethicists, and lawyers who published commentaries on the ethics of mini-brains in *Nature* in 2018. One of the prospects they addressed was the idea of conscious cerebral organoids. These days, cerebral organoids reach the size of peas, they lack structures and connectivity necessary to receive sensory inputs. In the future, however, if we manage to cultivate more complex neural structures, they may develop such a high-level sensitivity to stimuli that we might arguably ascribe consciousness to them, although the debate on how to define consciousness is contentious territory. In the commentary, the team of experts worked with the premise that a being with highly-developed connectivity has welfare interests, thus there might be some bioethical considerations to navigate in the case of the development of such an advanced type of neural structure. Some believe that because of our limited understanding of what consciousness means, the progress of developing complex brain structures should be slowed down.

Moreover, another interesting aspect brought up by the commentary was the idea of chimeras, also known as human-animal hybrids. Cerebral organoids have already been vascularised by being transplanted into mice. This step seems radical and unethical to some individuals, as it presumably crosses the imagined sacred line between being an animal and being a human. But who is to decide where to set the limits?

It remains to be seen whether solving these issues will become inevitable and the research still has a long way to go; nowadays we are working with more primitive brain representations, the use of which is nothing else but crucial.

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