

Cerebral Organoid as a Model System in the Study of Microcephaly

Scientists use cerebral organoids, which are artificially produced miniature organs that represent embryonic or fetal brains and have many properties similar to them, to help them study developmental disorders like microcephaly. In human embryos, cerebral tissue in the form of neuroectoderm appears within the first nine weeks of human development, and it gives rise to the brain and spinal cord. In the twenty-first century, Juergen Knoblich and Madeleine Lancaster at the Institute of Molecular Biotechnology in Vienna, Austria, grew cerebral organoids from pluripotent stem cells as a model to study developmental disorders in embryonic and fetal brains. One such disorder is microcephaly, a condition in which brain size and the number of neurons in the brain are abnormally small. Scientists use cerebral organoids, which they've grown in labs, because they provide a manipulable model for studying how neural cells migrate during development, the timing of neural development, and how genetic errors can result in developmental disorders.

Lancaster and her team developed the cerebral organoid as a model to study the genetic basis of conditions such as microcephaly and fetal alcohol syndrome. Genetic microcephaly affects one in 30,000 to one in 250,000 infants worldwide and was common in northern Pakistan, where one in 10,000 infants were affected. Children with microcephaly display a smaller than normal skull size, and some also have a reduced overall body size. Symptoms of the condition include seizures, a delay in motor function and speech, hyperactivity, and intellectual disability. By 2015, there was no cure for microcephaly, but doctors had developed ways to treat symptoms of the condition.

Genetic microcephaly is an autosomal recessive disorder, meaning that both parents must pass on a copy of the mutated gene to their offspring to result in the offspring being affected. Microcephalin is a gene expressed in humans during fetal brain development that enables neurons to migrate and form the cerebral cortex. Knoblich and Lancaster found that when the gene had specific kinds of mutations, the expression of the mutated gene during development caused genetic microcephaly.

In 2013, Lancaster, Knoblich, and their team published their paper "Cerebral Organoids Model Human Brain Development and Microcephaly", in which they detail how skin stem cells from a patient with genetic microcephaly developed into neurons when put into a nutrient rich solution. Once the neurons developed, Lancaster surrounded them with gel for structural support and let them grow in a spinning chamber so they could better absorb oxygen and nutrients. Under these conditions the clusters of neurons assembled into clumps, and formed definite regions that corresponded to specific areas in the human brain. However, the cerebral organoid, unlike a naturally formed brain, did not develop neuronal networks, and it was less functional but still useful for assessing how drugs affect a developing embryonic brain.

The cerebral organoid provides researchers with a model to study human brain development when features of that development cannot be modeled in other organisms, such as mice, because their brains develop differently than do human brains. This difference is relevant with microcephaly, which researchers often studied in mice, even though the microcephalin gene is not expressed as severely in mice as it is in humans. Although the cerebral organoid provides a model by which to study human brain development, its small size and lesser complexity as compared to a fully-grown brain limits its role as a model.

Sources

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