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Cortex in a dish: new brain organoid model replicates human cortical domains

Brain organoids provide unique insights into the human brain. Now, the group of Jürgen Knoblich at the Institute of Molecular Biotechnology (IMBA) of the Austrian Academy of Sciences, developed a new method that allows scientists to cultivate brain organoids with distinct cortical areas and front-to-back patterning. Together with collaborators at the Human Technopole and the University of Milan-Bicocca, they reported a method that gives scientists a deeper look into human-specific brain development and disorders. The new method is reported in Nature Methods on September 18.

Brain organoids are extensively used to study human brain development. Derived from human pluripotent stem cells, the 3D models allow scientists to study unique properties of the human brain. Recently, the group of Jürgen Knoblich at IMBA used cortical organoids to answer fundamental questions such as how the human brain can grow to its large size or how the human brain's long-range connections form. However, cortical organoids used so far are fairly uniform spherical cultures – like miniature footballs. This ball-shaped structure is quite unlike the oblong human cortex, which is structured into distinct domains from back to front, each with a distinct function. Therefore, the team now developed a new protocol to generate cerebral organoids organized into distinct domains along the longitudinal axis. The work was spearheaded by Camilla Bosone, Veronica Krenn and Davide Castaldi.

Experimental platform to understand brain disorders

During development, the forming brain is patterned by different signaling molecules, so-called morphogens. In the newly presented method, the researchers first produced long linear organoids which were then patterned through fusion with a clump of cells producing a factor called FGF8. This single asymmetric source of FGF8 establishes gene expression and cell segregation along the organoids' longitudinal axis, similar to the pattern observed in the human cortex. "We are able to generate this polarity consistently along the organoid's entire longitudinal axis", corresponding author Jürgen Knoblich says.

The scientists then demonstrated how patterned cortical organoids can be used to study brain disorders. In achondroplasia patients, the temporal lobe – an area of the cortex – forms incorrectly. These malformations are linked to a mutation in FGFR3, a receptor for the FGF8 signal. In the patterned cortical organoids, this mutation in FGFR3 also leads to changes in patterning and cell proliferation along the longitudinal axis. "Patterned organoids are a model for studying patterning defects that underlie developmental disorders", Knoblich adds. The organoids may even be an experimental platform to test the hypothesis that early patterning defects are responsible for transcriptional changes in the brains of autistic individuals. "Organoids offer a means to connect genetic and environmental alterations relevant to neuropsychiatric disorders with specific early cortical patterning events."

A new model for cortex development

Using patterned cerebral organoids, the scientists also gained insights into human development. During human brain development, multiple morphogens and signaling pathways interact, and so it's hard to tease out how each component

contributes to development individually. In the patterned brain organoids, by contrast, FGF8 is the only signal that specifies the different domains. Analyzing the brain organoids, the scientists conclude that the FGF8 source in the developing human brain, the so-called anterior neural ridge, plays a primary role in patterning the cortex. "By fusing organoids that produce distinct morphogens and precisely controlling the timing and quantity of morphogen-producing cells in these fusions, polar cortical assembloids (PolCAs) serve as an optimal in vitro model for introducing and studying individual signaling pathways in isolation", says Camilla Bosone, one of the study's first authors. "Patterned brain organoids will be a useful model to further study how neurons acquire their identity during development", Knoblich adds.

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