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Study implicates neural stem cell defects in smooth brain syndrome

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Research led by scientists at UC San Francisco and Case Western Reserve University School of Medicine has used brain "organoids"—tiny 3-D models of human organs that scientists grow in a dish to study disease—to identify root causes of Miller-Dieker Syndrome (MDS), a rare genetic disorder that causes fatal brain malformations.

MDS is caused by a deletion of a section of human chromosome 17 containing genes important for neural development. The result is a brain whose outer layer, the neocortex, which is normally folded and furrowed to fit more brain into a limited skull, instead has a smooth appearance (lissencephaly) and is often smaller than normal (microcephaly). The disease is accompanied by severe seizures and intellectual disabilities, and few infants born with MDS survive beyond childhood.

In the new study—published online January 19, 2017 in *Cell Stem Cell*—the research team transformed skin cells from MDS patients and normal adults into induced pluripotent stem cells (IPSCs) and then into neural stem cells, which they placed in a 3 dimensional culture system to grow organoid models of the human neocortex with and without the genetic defect that causes MDS.

Closely observing the development of these MDS organoids over time revealed that many neural stem cells die off at early stages of development, and others exhibit defects in cell movement and cell division. These findings could help explain how the genetics of MDS leads to lissencephaly, the authors say, while also offering valuable

insights into normal brain development.

"The development of cortical organoid models is a breakthrough in researchers' ability to study how human brain development can go awry, especially diseases such as MDS," said Tony Wynshaw-Boris, MD, PhD, chair of the Department of Genetics and Genome Studies at Case Western Reserve University School of Medicine, and co-senior author of the new study. "This has allowed us to identify novel cellular factors that contribute to Miller-Dieker syndrome, which has not been modeled before."

'Smooth Brain' Organoids Reveal Defects

Previous research on the causes of lissencephaly has relied on mouse models of the disease, which suggested that the main driver of the disorder was a defect in the ability of young neurons to migrate to the correct location in the brain. But Arnold Kriegstein, MD, PhD, professor of neurology, director of the Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research at UCSF, and co-senior author, says there are significant drawbacks to this approach.

"Unlike the human brain, the mouse brain is naturally smooth," Kriegstein said. "If you are studying a disease that leads to a smooth brain in humans, it's a challenge to study it in an animal that normally has a smooth brain."

The mouse brain also lacks a type of neural stem cell called outer radial glia, which were discovered by Kriegstein's group in 2010. These cells are thought to have played a crucial role in the massive expansion in size and complexity of the primate brain relative to other mammals over the course of evolution.

In order to more accurately model the progression of MDS in the

embryonic human brain, study first author Marina Bershteyn, PhD, a postdoctoral researcher in the Wynshaw-Boris and Kriegstein labs, spearheaded the development of MDS cortical organoids and techniques to observe how stem cells within these organoids developed in the laboratory into the different cell types seen in first-trimester embryonic human brains.

Bershteyn and her team found using time-lapse imaging that outer radial glia cells that grew in patient-derived organoids had a defect in their ability to divide—potentially contributing to the small, smooth brains seen in MDS patients.

"There are just fundamental differences in how mouse and human brains grow and develop," said Bershteyn, who is now a scientist at Neurona Therapeutics, a company founded by Kriegstein and colleagues to develop stem cell therapies for neurological diseases. "Part of the explanation for why these observations were not made before is that outer radial glia cells are quite rare in mouse."

In addition, the team found that early neural stem cells called neuroepithelial cells – which are present in both mice and humans – die at surprisingly high rates in MDS organoids, and when they do survive, divide in an abnormal way—as if they are prematurely transforming into neurons, cutting short important early stages of brain development.

Consistent with prior mouse studies, time-lapse imaging also revealed that newborn neurons are unable to migrate properly through developing brain tissue, which potentially contributes to the failure of MDS brains to properly form outer brain structures.

Organoid Research Opens Doors to Studying Human Brain Diseases in Lab

Together, these observations helped the team pinpoint developmental stages and specific neural cell types that are impaired in MDS. The next step to understanding lissencephaly more broadly, the authors say, will be to test cells from patients with different genetic forms of the disease, so researchers can begin to link specific mutations with the cellular defects that drive brain malformation.

The study is also a demonstration of the utility of patient-derived brain organoids as a way to bridge the gap between animal models and human disease, the authors say. In particular, the finding that human outer radial glia cells readily grow in organoid models opens the door for scientists worldwide to study the role of these cells in both normal human brain development and disease.

"Patient-derived cortical organoids are creating a huge amount of excitement," Kriegstein said. "We are now able to study human brain development experimentally in the lab in ways that were not possible before."

More information: Marina Bershteyn et al. Human iPSC-Derived Cerebral Organoids Model Cellular Features of Lissencephaly and Reveal Prolonged Mitosis of Outer Radial Glia, *Cell Stem Cell* (2017). DOI: 10.1016/j.stem.2016.12.007

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