Schizophrenia originates early in pregnancy, 'mini-brain' research suggests

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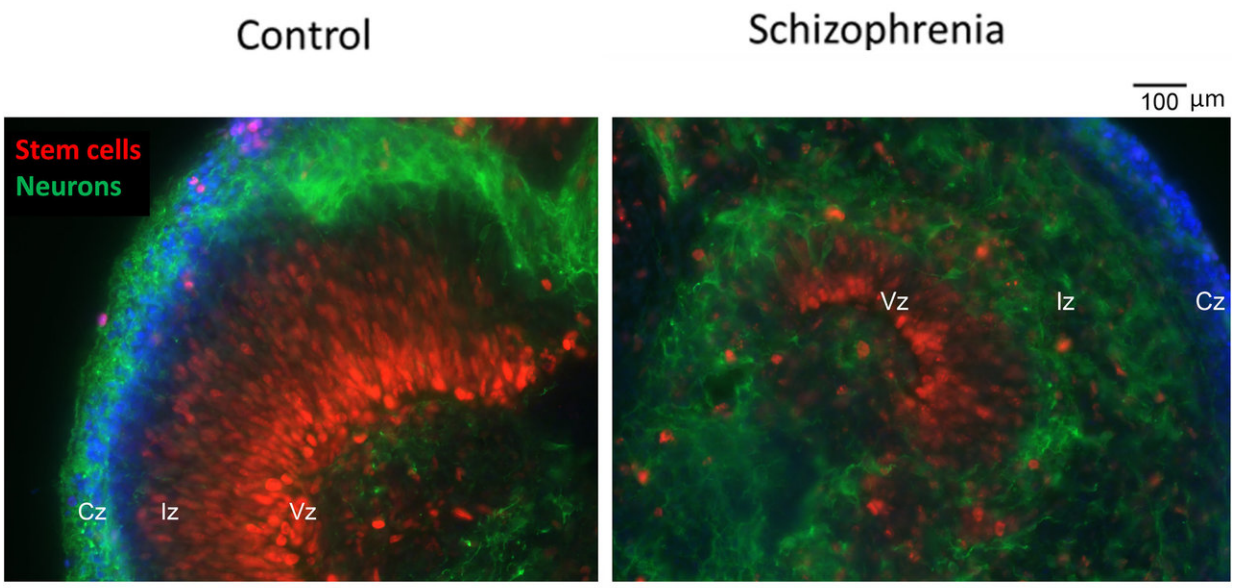

VZ – ventricle zone; Cz – cortex zone

In cerebral organoids generated from stem cells of patients with schizophrenia, (image on the right), disruption in the layers of stem cell (red) surrounding the brain-like ventricles was evident as early as two weeks into the development of the organoids – roughly comparable to the first trimester of pregnancy. Formation of neurons (green) is clearly impaired compared to the control figure. Credit: M. Stachowiak

Symptoms of schizophrenia usually appear in adolescence or young adulthood, but new research reveals that the brain disease likely begins

very early in development, toward the end of the first trimester of pregnancy. The finding opens up a new understanding of this devastating disease and the potential for new treatment possibilities in utero.

A paper describing the research was published today in *Translational Psychiatry* by scientists at the Jacobs School of Medicine and Biomedical Sciences at the University at Buffalo and other institutions.

Fetal beginnings

The findings provide powerful evidence that schizophrenia begins early in fetal development, said Michal K. Stachowiak, PhD, lead author and professor in the Department of Pathology and Anatomical Sciences at UB. "This disease has been mischaracterized for 4,000 years," he said, referring to the first time a disease believed to be schizophrenia was described in the 1550 BC Egyptian medical text, the Ebers Papyrus.

"After centuries of horrendous treatment, including even the jailing of patients, and after it has been characterized as everything from a disease of the spirit or moral values or caused by bad parental influence (a concept that appeared in psychiatric textbooks as recently as 1975) we finally now have evidence that schizophrenia is a disorder that results from a fundamental alteration in the formation and structure of the brain ," Stachowiak said.

The research builds on previous work by Stachowiak and his colleagues showing that although hundreds of different genetic mutations may be responsible for schizophrenia in different patients, they all converge in a single faulty genomic pathway called the Integrative Nuclear FGFR 1 Signaling (INFS) pathway, which the UB researchers reported on earlier this year. But when and how dysregulation of that pathway occurred and how it affected brain development was unknown.

Growing "mini-brains"

To find out, Stachowiak and colleague and spouse, Ewa Stachowiak, PhD, assistant professor of pathology and anatomical sciences, adapted mini-brain technology, growing in vitro miniature brain structures called cerebral organoids. "The goal was to, in a sense, recapitulate important stages in brain formation that take place in the womb," said Stachowiak.

The mini-brain structures were reprogrammed into induced pluripotent stem cells (iPSCs) using skin cells removed from three controls and four patients with schizophrenia as described in earlier publications by the UB researchers and Kristen J. Brennand of the Icahn School of Medicine at Mt. Sinai. In the developing embryo, Stachowiak explained, surface cells develop tissues and organs such as skin and brain structures.

"We mimic this process in the laboratory with stem cells, focused specifically on developing the cerebral organoids that resemble the developing human brain in its earliest stages of growth," he said. The UB approach modifies a recently developed protocol for developing early brain structures in vitro.

For a few weeks, the researchers fed the stem cells nutrients, glucose, acids and growth factors that enabled the development and formation of so-called embryoid bodies, which contain the first recognizable stage where tissues begin to differentiate. With the addition of new composition media, nutrients and growth factors, they grew large enough to eventually develop the tissue out of which the brain forms, called the neuroectoderm.

After being removed, placed on a different substrate and provided with other chemicals and nutrients, these neuroectoderm cells grow under kinetic (constantly moving) conditions, eventually developing into organoids, or mini-brains, containing brain ventricles, a cortex, and a

region similar to the brain stem.

Pinpointing malformations in the cortex

"At this stage, we discovered critical malformations in the cortex of the mini-brains formed from the iPSCs of the patients with schizophrenia," said Stachowiak. That made sense, he added, since increasing evidence has recently linked schizophrenia to abnormal functioning in the cortex, the largest part of the brain, which is responsible for such critical functions as memory, attention, cognition, language and consciousness.

They found that certain kinds of neural progenitor cells (which later become neurons) were abnormally distributed in the cortex of the mini-brains developed from patients. And while maturing neurons were plentiful in regions outside of the cortex, they were rare in the cortex, Stachowiak explained.

"Our research shows that the disease likely starts during the first trimester and involves accelerated cell divisions, excessive migration and premature differentiation of the neuroectodermal cells into neurons," he continued. "Neurons that connect different regions of the cortex, the so-called interneurons, become misdirected in the schizophrenia cortex, causing cortical regions to be misconnected, like an improperly wired computer.

"We now can state that schizophrenia is a disorder of faulty brain construction that occurs early in development, corresponding to the first trimester, and involving specific malformation of neuronal circuits in the cortex," he said. The experiments implicate the dysregulation of the INFS mechanism as a trigger for deconstructing gene networks in the developing brain cells of individuals who will later develop the disease.

"The next step is to investigate how to target the INFS pathway and even

other pathways that interact with INFS using drugs or even dietary supplements that could prevent the dysregulation from taking place," he continued, noting that this kind of supplementation has been effective with disorders such as spina bifida, for example.

Brain-machine interfaces

Stachowiak noted that the brain organoid model he and his colleagues have developed is already proving applicable to other diseases. The National Science Foundation has funded Stachowiak and Josef M. Jornet, PhD, assistant professor in the Department of Electrical Engineering in the UB School of Engineering and Applied Sciences, to use these models to explore what he calls brain-machine interfaces, treatments that would be useful in eventually guiding the regeneration of brain tissue after trauma or a stroke.

"We are working on combining the organoid research with smart nanophotonic devices to develop a new generation of brain-machine interfaces," explained Stachowiak. "With this technology, one may eventually be able to control and correct development of cells in complex tissue of the developing brain. An important step toward developing such technologies will be testing them in cerebral organoids or mini-brains to see if they can actually direct and modify the developing brain in real time."

More information: E. K. Stachowiak et al. Cerebral organoids reveal early cortical maldevelopment in schizophrenia—computational anatomy and genomics, role of FGFR1, *Translational Psychiatry* (2017). DOI: 10.1038/s41398-017-0054-x

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