Modular approach found to improve consistency of organoids

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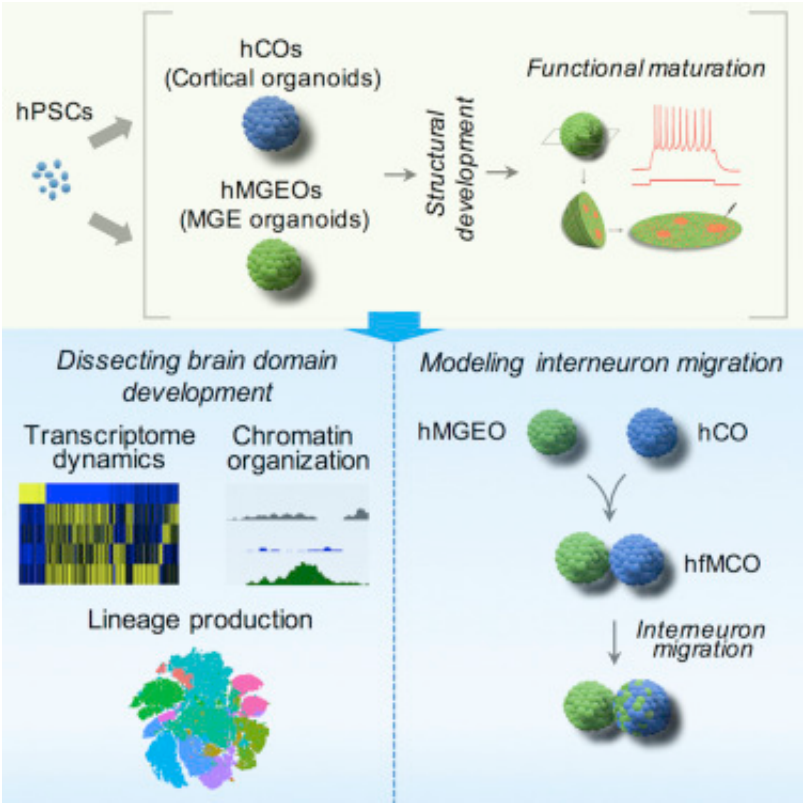

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(Medical Xpress)—A team of researchers from the U.S. and Australia working at the Yale Stem Cell Center report that they have met with some success in improving the usefulness of organoids. In their paper published in the journal *Cell Stem Cell*, the team describes their work using a modular approach to building more useful organoids.

Organoids are very small balls of living human cells that have grown to resemble in some ways the human brain. They are grown for research purposes and get their start with stem cells. Unfortunately, as the researchers note, getting the organoids to grow in useful ways has proved to be extremely challenging. Since 2013, when the first organoid was created by Madeline Lancaster, many other organoids have been created by many other teams, but they all suffer from inconsistencies—each organoid is different from every other. In this new effort, the researchers have taken a new approach—growing smaller, more functionally oriented sub-organoids and then fusing them together to create a whole organoid that is more consistent.

The new approach is based on prior research yielding the creation of the more functional sub-organoids. One of them mimics a human medial ganglionic eminence (MGE). Its purpose is to produce inhibitory neurons that play a role in normal human brain development. Another sub-organoid was designed to play the role of the cortex.

The researchers report that allowing the two sub-organoids to grow together after initial formation resulted in the two fusing together, forming one larger organoid. But more importantly, they found that inhibitory interneurons that had grown in the MGE migrated to the cortex and mixed with its network, mimicking action in the real brain.

The researchers plan to continue their research, building other types of sub-organoids to see if their approach can lead to better organoids overall. They acknowledge that there is still a long way to go—organoids are still not shaped properly, nor do they grow blood vessels or other brain tissue. They also do not have glial cells, which means they have no white matter. But work will continue because the payoff could be enormous—the development of a powerful tool for studying how the brain works and possibly testing medicines to treat brain ailments.

More information: Yangfei Xiang et al, Fusion of Regionally Specified hPSC-Derived Organoids Models Human Brain Development and Interneuron Migration, *Cell Stem Cell* (2017). DOI: 10.1016/j.stem.2017.07.007

Abstract

Organoid techniques provide unique platforms to model brain development and neurological disorders. Whereas several methods for recapitulating corticogenesis have been described, a system modeling human medial ganglionic eminence (MGE) development, a critical ventral brain domain producing cortical interneurons and related lineages, has been lacking until recently. Here, we describe the generation of MGE and cortex-specific organoids from human pluripotent stem cells that recapitulate the development of MGE and cortex domains, respectively. Population and single-cell RNA sequencing (RNA-seq) profiling combined with bulk assay for transposase-accessible chromatin with high-throughput sequencing (ATAC-seq) analyses revealed transcriptional and chromatin accessibility dynamics and lineage relationships during MGE and cortical organoid development. Furthermore, MGE and cortical organoids generated physiologically functional neurons and neuronal networks. Finally, fusing region-specific organoids followed by live imaging enabled analysis of human interneuron migration and integration. Together, our study provides a platform for generating domain-specific brain organoids and modeling human interneuron migration and offers deeper insight into molecular dynamics during human brain development.