

Human Cerebral Organoids Reveal Secrets of Lissencephaly

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Editorial

In vitro organoid models have been a major technical breakthrough in biological research. Organoids are miniature versions of complex organs derived from stem cells obtained from animals, including humans that can be grown and studied in culture. This has made organoids an attractive tool to study underlying mechanisms of normal biology and disease [1]. In their recent publication, Bershteyn et al. have used stem cells derived from Lissencephaly, Miller-Dieker syndrome (MDS) patients to make cerebral organoids for the study of the disease phenotype and uncover the underlying mechanism of the disease [2]. These patients derived organoids have incredible potential for research in the disease mechanism and drug trials for treatment of Lissencephaly patients.

Lissencephaly is a disease in which the child's brain does not develop the cerebral folds characteristic of normal human cortex. This condition impairs cognitive and mental development, and is also associated with intractable epilepsy. As obtaining live cerebral samples from live patients is not practical, until now the cellular and molecular mechanism of this disease could only be studied in postmortem human tissue and mouse genetic models. However, there are limitations to the applications of finding from the postmortem tissue and mouse models to living MDS patients. MDS is a developmental disease and postmortem brain does not allow us to study early stages of the disease and has potential fixation artifacts. Mice cerebral tissue does not have folds like human cerebral tissue and thus mice are inherently not a good model to study cerebral fold diseases such as MDS. Though MDS occurs due to deletion of an entire region of human chromosome 17p13.3, harboring several potential genes, mouse models of the disease have focused on deletion of one gene PAFAH1B1 (Lissencephaly-1 Protein, LIS1 protein) from the chromosome [3]. These limitations were overcome by Bershteyn et al. who utilized cerebral organoids derived from MDS patient cells, which allowed for study of early stages of the disease and contained the entire chromosome 17p13.3 deletion as they came directly from patients. Bershteyn et al. prepared cerebral organoids from Miller-Dieker syndrome (MDS) patient derived induced-pluripotent stem cells (iPSCs) adapting previously established methods of making cerebral organoids from embryonic stem cells (ESCs) [4]. Thus, this study sets a

paradigm for modeling other human developmental diseases associated with deletion of chromosome regions.

Organoid technology is new and fast evolving, but faces challenges with regards to high variability and poor cellular health [5]. To address these concerns and to show the validity of their cerebral MDS organoid as disease model, Bershteyn et al. showed that these MDS mini-brain show several known key phenotypic features of the disease. The MDS organoids recapitulated the decreased brain size due to increased apoptosis and increase in number of deep cortical neurons at the expense of outer radial glia (oRG) progenitor cells. Bershteyn et al. performed single cell RNA-sequencing (scRNA-seq) on the oRG cells from both MDS and normal organoids, and in both found known markers of oRGs further validating that the cerebral organoids mimic the developing brain at the molecular level. This scRNA-seq dataset is a valuable resource that is available now in the public domain. The scRNA-seq technology can allow for the transcriptome analysis of individual cells to decipher the heterogeneity and complexity of oRGs in MDS [6]. Bershteyn et al. show that RG cells in different spatial locations, vRGs (located in the ventricular zone) are normal in MDS unlike the oRG (located in the sub-ventricular zone). Thus, it will not be surprising, if future exploration of the scRNA-seq data from oRGs reveal that even within oRGs there are subtypes that are normal and abnormal in MDS. The ability to identify oRGs subtypes defective in MDS, opens the possibility of finding abnormal oRGs cell type specific drug targets without targeting normal oRGs.

Cellular signaling pathways, molecular interactions and cellular processes are dynamic in nature [7]. The cells themselves are flexible changing shape and position in response to extrinsic and intrinsic cues. This spatiotemporal aspect is well exemplified by stem and progenitor cells, which undergo quick turnover of signaling molecules, undergo interkinetic movement during cell division and have well timed lengths of cell cycle phases. Utilizing time-lapse imaging and immunostaining techniques, Bershteyn et al. have explored the spatiotemporal aspects of cellular changes and biological processes occurring in the MDS patient organoids. During development, they found that the key progenitor cells, the oRG cells, spent upto 7 hours longer in mitotic phase before cell division and the deep-layer cortical neurons produced from them took longer to migrate to their final location or

remained static in intermediate locations. During development, cell cycle length directly influences cell fate decisions and differentiation [8]. It remains to be seen if cortical deep neuronal defects in the MDS organoids are due to the altered cell cycle length of oRGs or are these cell cycle independent defects in MDS patients. These results open up the possibility to target these dynamic properties of oRG progenitor cells and deep neurons for therapeutic intervention in MDS.

In conclusion, organoids technology in combination with iPSC technology, time-lapse technology and next generation sequencing technology, has the potential to transform personalized medicine and drug discovery. As we cannot study live humans during development, the mouse models will play an integral role to provide a point of reference for the organoid disease models as demonstrated by Bershteyn et al. who reference the mouse model phenotypes several times in the paper for comparison. It can be envisioned that with increased patient participation, reduced costs of culturing organoid from patient derived iPSC made from patient fibroblast and reduced genomic sequencing costs, organoids and omic may become a regular part of healthcare. The present study on organoids from MDS patients has well demonstrated the potential of organoids in understanding human disease to discover novel routes for therapeutic intervention. To take full advantage of this promise and potential, we must not only celebrate the success of these technologies but work toward improving them to enable applications in healthcare where accuracy of decisions determine treatment outcome.

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