Human iPSC-Derived Cerebral Organoids Model Cellular Features of Lissencephaly and Reveal Prolonged Mitosis of Outer Radial Glia

Graphical Abstract

Highlights
- Cortical organoids from control and MDS patient-derived iPSCs model lissencephaly
- Neural stem cells in MDS organoids show increased apoptosis and horizontal divisions
- Deep-layer neurons are more abundant in MDS organoids than in controls
- Outer radial glia-like cells forming in MDS organoids show a mitotic delay

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In Brief
Bershteyn and colleagues show that cerebral organoid modeling of lissencephaly using iPSCs derived from Miller-Dieker syndrome patients can characterize cellular and neurodevelopmental disease phenotypes and identify a mitotic defect in outer radial glia, a cell type that is particularly important for human cortical development.

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Human iPSC-Derived Cerebral Organoids Model Cellular Features of Lissencephaly and Reveal Prolonged Mitosis of Outer Radial Glia

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SUMMARY

Classical lissencephaly is a genetic neurological disorder associated with mental retardation and intractable epilepsy, and Miller-Dieker syndrome (MDS) is the most severe form of the disease. In this study, to investigate the effects of MDS on human progenitor subtypes that control neuronal output and influence brain topology, we analyzed cerebral organoids derived from control and MDS-induced pluripotent stem cells (iPSCs) using time-lapse imaging, immunostaining, and single-cell RNA sequencing. We saw a cell migration defect that was rescued when we corrected the MDS causative chromosomal deletion and severe apoptosis of the founder neuroepithelial stem cells, accompanied by increased horizontal cell divisions. We also identified a mitotic defect in outer radial glia, a progenitor subtype that is largely absent from lissencephalic rodents but critical for human neocortical expansion. Our study, therefore, deepens our understanding of MDS cellular pathogenesis and highlights the broad utility of cerebral organoids for modeling human neurodevelopmental disorders.

INTRODUCTION

The human cerebral cortex develops from a pseudostratified layer of neuroepithelial stem cells (NESCs) into a functionally complex, six-layered structure with a folded (gyrencephalic) surface. The molecular underpinnings of brain size and topology are encoded by the genome and distinguish us from species with a small and smooth (lissencephalic) brain surface, such as mice. Although brain folding in the human does not begin until the end of the second trimester (after gestation week [GW] 23) (Chi et al., 1977; Martin et al., 1988; Hansen et al., 1993; Armstrong et al., 1995), many of the key cellular events that influence this process, including expansion of the progenitor population and neuronal migration, occur starting around GW4 (Lui et al., 2011; Sidman and Rakic, 1973; Stiles and Jernigan 2010). Genetic and infectious diseases that disrupt these processes underlie a number of cortical malformations and cause mental retardation, mortality, and morbidity (Guerrini and Dobyns 2014; Hu et al., 2014). Despite the prevalence and societal burden of cortical malformations, our understanding of how disease-linked mutations disrupt brain development is still limited.

Miller-Dieker syndrome (MDS) is a severe cortical malformation characterized by nearly absent cortical folding (lissencephaly) often associated with reduced brain size (microcephaly), craniofacial dysmorphisms, mental retardation, and intractable epilepsy (Dobyns et al., 1983, 1991; Nagamani et al., 2009). MDS is caused by large heterozygous deletions of human band 17p13.3, harboring dozens of genes, including PAFAH1B1 (LIS1 protein) and YWHAE (14-3-3ε protein) (Dobyns et al., 1983; Reiner et al., 1993; Hattori et al., 1994; Chong et al., 1997; Cardoso et al., 2003). Smaller deletions or mutations in PAFAH1B1 are the major cause of isolated lissencephaly sequence (ILS), which exhibits less severe degrees of lissencephaly (Ledbetter et al., 1992; Lo Nigro et al., 1997; Pilz et al., 1998; Barkovich et al., 1991; Cardoso et al., 2003). Insight into lissencephaly pathogenesis is largely derived from mouse models and limited analyses of postmortem human brains. Reduction in LIS1 levels in Pafah1b1 mutant mice leads to defects in neuronal migration (Iriotsume et al., 1998; Smith et al., 2000), consistent with the disrupted cortical layering and neuron dispersion seen in the postmortem MDS brain (Sheen et al., 2006b; Saito et al., 2011). LIS1 is an atypical microtubule-associated protein that regulates microtubule dynamics and nuclear-centrosomal coupling during neuronal migration (Faulkner et al., 2000; Gambello et al., 2003; Shu et al., 2004; Tanaka et al., 2004; Youn et al., 2009). Collectively, these studies led to the prevailing model that lissencephaly is due to defective neuronal migration (Kato and Dobyns, 2003). However, the mouse brain is naturally lissencephalic,
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