A cerebral organoid model for Tuberous sclerosis identifies human-specific aspects of brain development

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The human brain is unique in size and complexity, but also the source of some of the most devastating human diseases. Cerebral organoids derived from patients suffering from neuro-developmental disease can recapitulate the developmental defects leading to those diseases and allow us to disentangle the mechanistic complexity of disorders like Epilepsy and Autism. We were able to recapitulate the histological characteristics of Tuberous sclerosis, a severe form of epilepsy caused by genetic upregulation of mTOR signaling. We show that different culture conditions can be used to recapitulate either tumor formation or generation of giant neurons, both features that are diagnostic of TSC patient brains. Unlike all mouse models, organoid models display those features even in heterozygous patients without the need for loss of heterozygosity. Using single cell transcriptomics, we identify the CLIP cells (caudal late interneuron progenitors), a previously unknown human specific progenitor cell located in the caudal ganglionic eminences. Our data suggest that CLIP cells are responsible for the massive postnatal migration of interneurons into the prefrontal cortex that is seen in humans but not in rodents, adding functional relevance to this recently discovered phenomenon. Our results indicate that organoid models can fundamentally change widely accepted human disease concepts and lead to fundamental insights into the human-specific aspects of brain development.