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Comparative transcriptome and gene regulation in human iPSC-derived organoids and donor-identical brain tissue

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Modeling human brain development *in vitro* is critically important to understand the pathophysiology of neuropsychiatric disorders. As part of the PsychENCODE project, we generated human induced pluripotent stem cells (hiPSCs) from skin fibroblasts of three human specimens at 15, 16 and 17 postconceptional weeks. These hiPSC were differentiated into telencephalic organoids to study early genetic programs in forebrain development. By using RNA-seq and histone chromatin immunoprecipitation (ChIP-seq), we compared transcriptomes and epigenomes of hiPSCs-derived organoids to donor-identical cortical brain tissue. Immunocytochemical characterization of the organoids over a time course (TD0, TD11 and TD30) showed expression of radial glial markers and mature cortical neurons confirming telencephalic fate. Hierarchical clustering of the organoids' transcriptomes demonstrated stage-specific patterns of gene expression during *in vitro* development. Mapping organoids' transcriptomes against the BrainSpan dataset suggested highest correlations with neocortex and showed their correspondence to post-conceptional weeks 8-16 of human fetal development. We then inferred transcriptional alterations, by differential gene expression, between organoids and the two brain regions analyzed. We found ~5000 of differentially expressed genes (DEG) between TD0 and fetal cortex and a decreasing number of DEG at TD11 and TD30 suggesting a stronger, albeit incomplete similarity of the organoids to the cortex at later time points. ChIP-seq experiments identified H3K27ac and H3K4me3 peaks (putative promoters and enhancers) differentially active at different organoids developmental stages and between organoids and fetal brain. Overall, however, hierarchical clustering of H3K27ac and H3K4me3 peaks demonstrated clustering of organoids with human fetal brain samples from various databases, whereas neonatal and adult brain samples formed separate clusters. These data suggest that organoids recapitulate in part transcriptome and epigenome features of fetal human brain.

Keywords
Cortical development, human iPSCs, organoids, fetal brain