Integrative Organoid and Genomic Approaches Illuminate FOXP1 Function in Human Neurogenesis

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Abstract:

Precise regulation of gene expression during human neurogenesis is essential for cortical development and the formation of functional neuronal circuits. Disruptions in this critical window can lead to neurodevelopmental disorders. FOXP1 is a transcription factor essential from early development and plays a key regulatory role. Heterozygous mutations in this gene cause FOXP1 syndrome, a rare disorder characterized by language impairment, intellectual disabilities, and autistic traits. Notably, mouse models of FOXP1 deficiency do not reveal major cortical phenotypes, suggesting human-specific pathogenic mechanisms.

To study FOXP1 functions in a human context, we use human pluripotent stem cell (hPSC)-derived brain organoids (hBOs), 3D models that recapitulate key steps of human brain development. In this system, FOXP1 is highly expressed in human neural progenitor cells (NPCs), highlighting its critical role in regulating their development and function.

We applied CUT&RUN on human NPCs to map the genome-wide binding profile of FOXP1. Analysis of its targets reveals a central role in orchestrating multiple NPCs processes, including progenitor maintenance, regional specification, initiation of differentiation programs, and responsiveness to extracellular signals. Bulk RNA sequencing at multiple differentiation stages further captured the activation and repression dynamics of FOXP1 target genes. Integration of CUT&RUN and RNA-seq data provides a comprehensive view of FOXP1's regulatory functions during human neurogenesis.

To understand which of these processes may be disrupted in pathological contexts, we are also generating FOXP1 knockout hPSC lines using the CRISPR-Cas9 system. We have already obtained lines with reduced nuclear FOXP1 expression while retaining pluripotency and the ability to form hBOs. This tool will enable functional investigation of pathogenic phenotypes arising from FOXP1 loss and offers insights into its contribution to human neurodevelopmental disorders.

Overall, our study demonstrates the power of combining hPSC-derived brain organoids with genomic and functional approaches to dissect the role of FOXP1 in human brain development and its link to neurodevelopmental disease.