Aberrant Development Corrected in Adult-Onset Huntington's Disease iPSC-Derived Neuronal Cultures via WNT Signaling Modulation.

Journal: Stem Cell Reports

Publication Year: 2020

Authors: Charlene Smith-Geater, Sarah J Hernandez, Ryan G Lim, Miriam Adam, Jie Wu, Jennifer T Stocksdale, Brook T Wassie, Maxwell Philip Gold, Keona Q Wang, Ricardo Miramontes, Lexi Kopan, Iliana Orellana, Shona Joy, Paul J Kemp, Nicholas D Allen, Ernest Fraenkel, Leslie M Thompson

PubMed link: 32109367

Funding Grants: CIRM Stem Cell Research Biotechnology Training Program at CSULB

Public Summary:
Aberrant neuronal development and the persistence of mitotic cellular populations have been implicated in a multitude of neurological disorders, including Huntington's disease (HD). However, the mechanism underlying this potential pathology remains unclear. We used a modified protocol to differentiate induced pluripotent stem cells (iPSCs) from HD patients and unaffected controls into neuronal cultures enriched for medium spiny neurons, the cell type most affected in HD. We performed single-cell and bulk transcriptomic and epigenomic analyses and demonstrated that a persistent cyclin D1(+) neural stem cell (NSC) population is observed selectively in adult-onset HD iPSCs during differentiation. Treatment with a WNT inhibitor abrogates this NSC population while preserving neurons. Taken together, our findings identify a mechanism that may promote aberrant neurodevelopment and adult neurogenesis in adult-onset HD striatal neurons with the potential for therapeutic compensation.

Scientific Abstract:
Aberrant neuronal development and the persistence of mitotic cellular populations have been implicated in a multitude of neurological disorders, including Huntington's disease (HD). However, the mechanism underlying this potential pathology remains unclear. We used a modified protocol to differentiate induced pluripotent stem cells (iPSCs) from HD patients and unaffected controls into neuronal cultures enriched for medium spiny neurons, the cell type most affected in HD. We performed single-cell and bulk transcriptomic and epigenomic analyses and demonstrated that a persistent cyclin D1(+) neural stem cell (NSC) population is observed selectively in adult-onset HD iPSCs during differentiation. Treatment with a WNT inhibitor abrogates this NSC population while preserving neurons. Taken together, our findings identify a mechanism that may promote aberrant neurodevelopment and adult neurogenesis in adult-onset HD striatal neurons with the potential for therapeutic compensation.