Huntington's Disease iPSC-Derived Brain Microvascular Endothelial Cells Reveal WNT-Mediated Angiogenic and Blood-Brain Barrier Deficits.

Journal: Cell Rep

Publication Year: 2017

Authors: Ryan G Lim, Chris Quan, Andrea M Reyes-Ortiz, Sarah E Lutz, Amanda J Kedaigle, Theresa A Gipson, Jie Wu, Gad D Vatine, Jennifer Stocksdale, Malcolm S Casale, Clive N Svendsen, Ernest Fraenkel, David E Housman, Dritan Agalliu, Leslie M Thompson

PubMed link: 28514657

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

Public Summary:
Brain microvascular endothelial cells (BMECs) are an essential component of the blood-brain barrier (BBB) that shields the brain against toxins and immune cells. While BBB dysfunction exists in neurological disorders, including Huntington's disease (HD), it is not known if BMECs themselves are functionally compromised to promote BBB dysfunction. Further, the underlying mechanisms of BBB dysfunction remain elusive given limitations with mouse models and post-mortem tissue to identify primary deficits. We undertook a transcriptome and functional analysis of human induced pluripotent stem cell (iPSC)-derived BMECs (iBMEC) from HD patients or unaffected controls. We demonstrate that HD iBMECs have intrinsic abnormalities in angiogenesis and barrier properties, as well as in signaling pathways governing these processes. Thus, our findings provide an iPSC-derived BBB model for a neurodegenerative disease and demonstrate autonomous neurovascular deficits that may underlie HD pathology with implications for therapeutics and drug delivery.

Scientific Abstract:
Brain microvascular endothelial cells (BMECs) are an essential component of the blood-brain barrier (BBB) that shields the brain against toxins and immune cells. While BBB dysfunction exists in neurological disorders, including Huntington's disease (HD), it is not known if BMECs themselves are functionally compromised to promote BBB dysfunction. Further, the underlying mechanisms of BBB dysfunction remain elusive given limitations with mouse models and post-mortem tissue to identify primary deficits. We undertook a transcriptome and functional analysis of human induced pluripotent stem cell (iPSC)-derived BMECs (iBMEC) from HD patients or unaffected controls. We demonstrate that HD iBMECs have intrinsic abnormalities in angiogenesis and barrier properties, as well as in signaling pathways governing these processes. Thus, our findings provide an iPSC-derived BBB model for a neurodegenerative disease and demonstrate autonomous neurovascular deficits that may underlie HD pathology with implications for therapeutics and drug delivery.