Establishing Disease Modeling of CADASIL Using Human Induced Pluripotent Stem Cell-Derived Pericytes

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Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is an extremely rare neurological small vessel disease, affecting about 2-5 people every 100,000 globally, defined by the NOTCH3 mutation (Khan, et al., 2020). The aim of this study was to establish a disease model for CADASIL using human induced pluripotent stem cells (hiPSC)-derived pericytes to represent the disease pathogenesis of CADASIL through validation of hiPSC-derived pericytes and functional analysis. Validation of hiPSC-derived pericytes (PC) were performed through qPCR and Immunofluorescence. There was a significantly lower expression of PDGFRß and NG2 in CADASIL cell lines ($p < 0.0001$), suggesting dysregulation in pericyte function, compromised angiogenic potential, and impaired vascular development in CADASIL. To examine the calcium influx of CADASIL vs. Non-CADASIL cell lines, the brightness intensity was quantified, followed by the addition of ionomycin to accentuate the calcium signal. The system showed significantly more calcium influx in CADASIL cell lines ($p < 0.05$), indicating elevated levels of Ca^{2+} due to the vasocontraction. Cell migration rates of pericytes were compared using the Scratch assay. The Scratch assay also demonstrated that PC from Non-CADASIL exhibited a faster proliferation rate compared to CADASIL ($p < 0.05$). Through the MTT Assay, the healthy control pericytes exhibited significantly higher absorbance compared to CADASIL pericytes ($p < 0.001$), indicating reduced proliferation rate in CADASIL-derived pericytes. As the hiPSC-derived PC provided an effective model for CADASIL, the research has implications for future drug development and improved diagnosis, allowing further investigation of CADASIL pathogenesis.

Awards Won:
Third Award of $1,000