APOE Genotype Impacts Mitochondrial Dynamic Response to Insulin in Induced Pluripotent Stem Cells

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Introduction. Variants of the apolipoprotein E (APOE) gene impact the risk of developing late onset Alzheimer's disease (AD), insulin resistance, and influence mitochondrial dynamics. A single nucleotide variant (SNV) of the APOE gene (APOE E4) results in an increased risk for these pathologies, while another SNV, APOE Christchurch (APOE Ch) is protective, yet there is little data on how insulin and APOE genotypes interact to influence mitochondrial dynamics. This study found that in Crispr edited induced pluripotent stem cells (iPSCs) with different APOE SNVs, mitochondrial dynamic protein levels differ at baseline and in response to insulin treatment.

Methods. Utilizing iPSCs from the same cell line and changing only APOE genotype, we compare mitochondrial dynamic protein levels at baseline and in response to physiologically relevant levels of insulin. Specifically, we investigate iPSCs that are homozygous for detrimental (E4/E4) and protective (Ch/Ch) mutations, as well as cells that are considered a baseline genetic risk (E3/E3) for these diseases. We measure the relative abundance of protein levels using nano liquid chromatography tandem mass spectrometry.

Results. In response to insulin, mitochondrial fusion protein OPA1 increased in Ch/Ch iPSCs, decreased in E3/E3s, and had no effect on E4/E4s. Regardless of insulin treatment, fission protein Drp-1 was higher in E4/E4s compared to E3/E3s.

Conclusions. This data suggests that APOE SNVs differentially impact mitochondrial dynamics and responses to insulin treatment in iPSCs. However, further studies are needed to determine post translational modifications or epigenetic changes that may mediate relevant differences in mitochondrial dynamics.