Investigation of the Role of Mitochondrial Dysfunction as a Trigger for Neurodegeneration in Alzheimer’s disease

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**Drosophila** Eye Model to Investigate the Role of Mitochondrial Dysfunction as a Trigger for Neurodegeneration in Alzheimer’s Disease

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**Abstract**

Alzheimer’s disease (AD) is a progressive neurodegenerative disorder that affects the cognitive function and memory of those affected. It results from plaques formed by the abnormal cleavage of the Amyloid Precursor Protein (APP), which result in the formation of a β-amyloid peptide, also known as amyloid beta (Aβ). Accumulation of these hydrophobic Aβ plaques triggers neuronal cell death in the central nervous system. However, the reason for the neuronal cell death still remains unknown. A possible explanation involves the role of mitochondrial dysfunction, as mitochondria carry out many vital cellular functions in a cell, including ATP production, reactive oxygen species production, and apoptosis. This study uses Drosophila melanogaster - the fly – as the model organism, as 75% of the genetic machinery is conserved between flies and humans and much of the information generated using this model can be extrapolated to humans. This study uses an AD fly model in which human Aβ42 peptides can be misincorporated into the Drosophila eye using the GAL4/UAS system. In our study, we have identified (1) alpha-ketoglutarate dehydrogenase and (2) pyruvate dehydrogenase as potential synaptic modulators of the human Aβ42 neurodegeneration. To investigate their effect on Alzheimer’s, we used the GAL4/UAS system, and misexpressed the AαKDH and αKDHC genes in the eye arms along with human Aβ42 in the fly eye and checked the resultant phenotypes in both wild-type and transgenic discs and in adults. Our results showed partial rescue in the LOF of alpha-ketoglutarate dehydrogenase, which clearly indicates that the enzyme plays a major role in AD progression. In the future, we will test the EOH of both synaptic modulators in further experiments. This study has significant bearing in understanding how certain synaptic mitochondrial machineries are involved in AD progression.

**Components of Gluconeogenesis and Krebs Cycle to be Investigated**

Two enzymes of interest –

1. Pyruvate Carboxylase (PC) plays a key role in energy-related memory impairment.
2. Alpha-Ketoglutarate Dehydrogenase (A-KDH)

**Gain of Function Approach: GAL4/UAS-System**

**Axonal Targeting is Strengthened in LOF forms of Modifiers**

1. Axonal targeting in the wild type is strong and penetrates two layers of the brain lobe.
2. GMR-Aβ42 axonal targeting is severely weakened and almost absent.
3. LOF forms of modifiers strengthens connection between the photoreceptors and brain lobes.

**Mitotimer: A Tool to Monitor Mitochondrial Turnover**

1. RNA interference of Alpha-Ketoglutarate Dehydrogenase and Pyruvate Carboxylase causes an eye rescue phenotype.
2. Numerous dark necrotic spots in GMR-Aβ42 mice.

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