Drosophila Eye Model to Investigate the Role of Mitochondrial Dysfunction as a Trigger for Neurodegeneration in Alzheimer's disease

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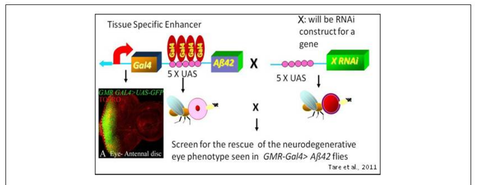
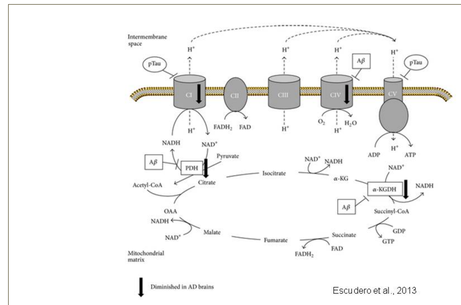
Abstract

Alzheimer's disease is a progressive neurodegenerative disorder that affects cognitive function and memory of the patient. It results from plaques formed by the abnormal cleavage of the Amyloid Precursor Protein (APP). Accumulation of this peptide triggers cell death in the neuronal cell population of central nervous system. The role of mitochondrial dysfunction as the trigger for neurodegeneration is investigated, as its malfunction or loss could lead to loss of dendritic branches and alteration of dendritic spines. The Drosophila melanogaster eye serves as a model of Alzheimer's disease, and the GAL4/UAS system is utilized to misexpress the gene in the photoreceptor neurons of the fly retina. My proposed studies will shed light on how certain mitochondrial genes can affect the survival of Drosophila photoreceptor neurons where high levels of the human Alzheimer's gene are expressed.

Drosophila as a Model: The Gal4/UAS Technique

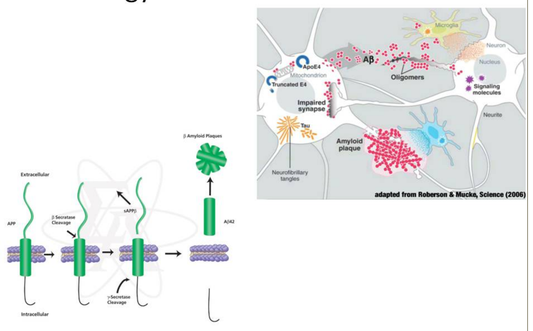


Gal4/UAS Technique Schematic. In the Gal4/UAS system, the GAL4 (DNA binding domain), restricts the expression of target transgenes that are cloned downstream to the Upstream activating sequence (UAS). The gene of interest, known as the responder, can be controlled by the presence of the UAS element. In the presence of GAl4, transcription is initiated, and the responder will be expressed.

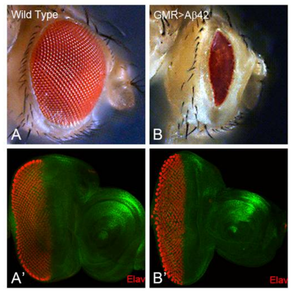


Schematic Presentation of AD-related alterations of mitochondrial respiratory chain, tricarboxylic acid cycle, and protein levels found in Alzheimer disease brains as well as the targets of amyloid-β (Aβ) and phosphorylated Tau (pTau).

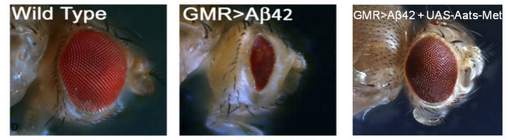
Neurology Behind Alzheimer's Disease



Drosophila Model: Expression of Aβ42 by GMR/GAL4



Upregulating Mitochondrial Ribosomal Protein S31 Rescues Aβ42-Mediated Neurodegenerative Phenotype



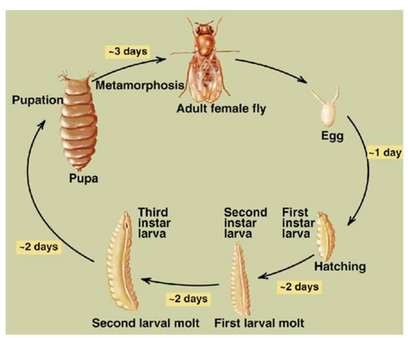
Phenotype Description

- Highly organized ommatidial structure
- Even pigmentation
- Functioning photoreceptor neurons
- Round and crystalline appearance

- Lack of ommatidial organization
- Degeneration of photoreceptor neurons and appearance of necrosis
- Dark, uneven pigmentation
- Small, flat shape, lacking functional characteristics

- Rescue of ommatidial structure and organization
- Widened anterior and posterior regions
- Dark pigmentation
- Round and crystalline appearance

Drosophila Melanogaster Life Cycle



Role of Mitochondria in Neurodegeneration

- Mitochondria assume central functions in the cell, including ATP production, calcium homeostasis, reactive oxygen species generation, and apoptotic signaling. Mitochondrial dysfunction, abnormal mitochondrial dynamics and degradation by mitophagy occur during the disease process, contributing to the onset and progression of Alzheimer's disease.
- In AD, alterations in enzymes involved in oxidative phosphorylation, oxidative damage, and mitochondrial binding of Aβ and amyloid precursor protein have been reported.

Conclusion

The upregulation of the mitochondrial ribosomal protein S31 allowed for successful rescue of the Aβ42-mediated neurodegenerative phenotype. This promising data pushes the aim of the project to identify other components of mitochondrial function that are affected by the expression of the Aβ42 gene.