Drosophila eye model to demonstrate the role of microRNA-277 in Alzheimer's disease

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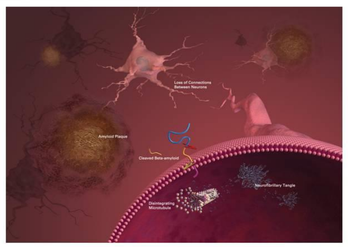
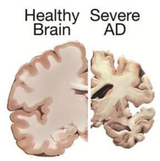
Abstract

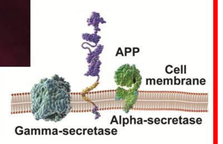
Alzheimer's Disease (AD) is a progressive neurodegenerative disorder associated with gradual cognitive impairment and memory decline. As the most common form of dementia, AD currently affects more than 5 million Americans and is expected to affect over 16 million Americans by 2050, according to the Alzheimer's Association. This disease is characterized by the accumulation of Amyloid-beta 42 (Aβ-42) polypeptides, resulting from the hydrophobic nature of an improperly cleaved transmembrane protein called the amyloid precursor protein (APP). When the APP is cleaved to be 42 amino acids long instead of 40, plaques are formed that alter cellular pathways, inhibit synaptic activity, and initiate neuronal death. Using Drosophila melanogaster as a transgenic model system, we misexpressed Aβ-42 in the differentiating photoreceptors of the developing Drosophila eye. Misexpression of Aβ-42 in the eye results in a strong neurodegenerative phenotype. This project focuses on the impact of a specific microRNA, mir-277, on amyloid-beta-42 mediated neurodegeneration. MicroRNAs act as post-transcriptional regulators of gene expression and work by binding to complementary sequences of mRNA to induce effects such as target degradation, or translational repression. By doing so, microRNAs are capable of preventing protein assembly associated with specific mRNA targets. The results from our studies will be presented.

Alzheimer's disease: a progressive disorder

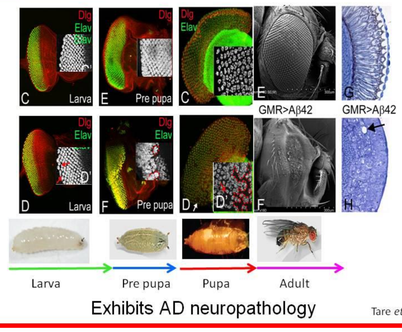




1.Amyloid Plaques
2.Neurofibrillary Tangles
3.Oxidative Stress
4.Neuronal Loss



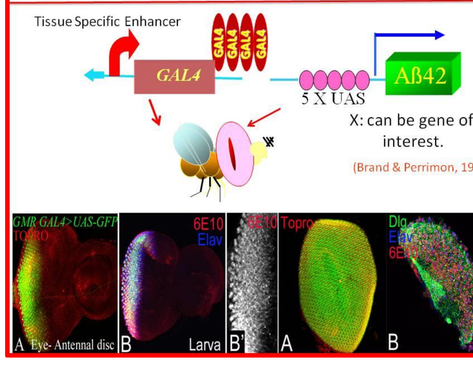
Misexpression of Aβ42 in fly eye by GMR-GAL4 exhibits progressive neurodegenerative phenotype



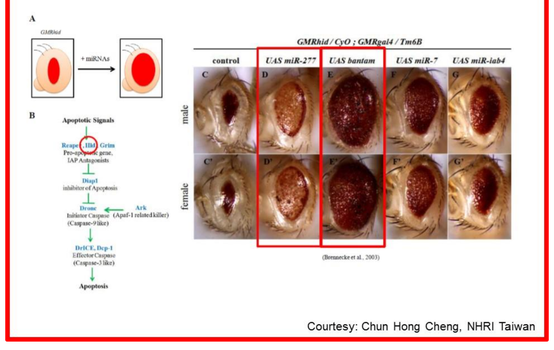
Exhibits AD neuropathology

Tare *et al.*, 2011

Gain of-function approach: GAL4/UAS- System

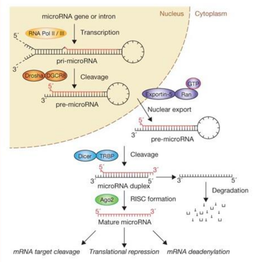


Screening for anti-apoptotic microRNAs



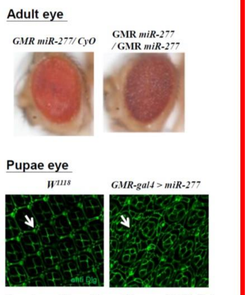
Courtesy: Chun Hong Cheng, NHRI Taiwan

MicroRNA plays a role in target repression



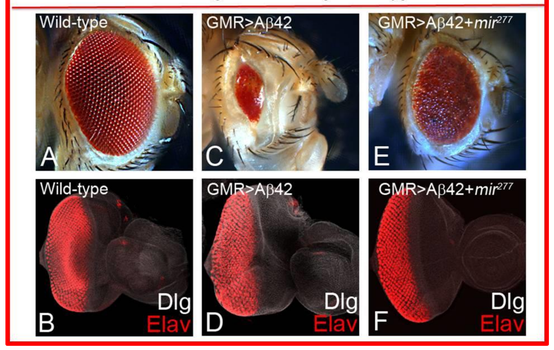
Vector Biolabs

mir-277 inhibits apoptosis

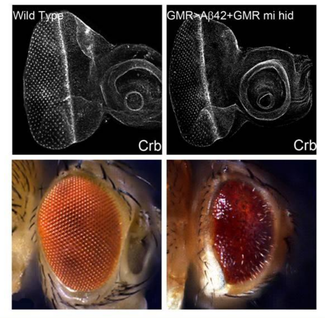


Courtesy: Chun Hong Cheng, NHRI Taiwan

Misexpression of microRNA 277 rescues the Aβ42 neurodegenerative phenotype



Downregulation of mi-277 target hid also rescues Aβ42 mediated neurodegeneration



Conclusion: Mi-277 is a genetic modifier of Aβ42 mediated neurodegeneration.
We have identified activation of hid as an outcome of misexpression of Aβ42 in the eye.

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