Examining the Effects of Tau-mediated Neurodegeneration on CircRNA Formation

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Alzheimer's Disease Background

- Alzheimer's disease is characterized by intracellular neurofibrillary tangles composed of aggregates of the tau protein, placing it under the broader category of tauopathies.

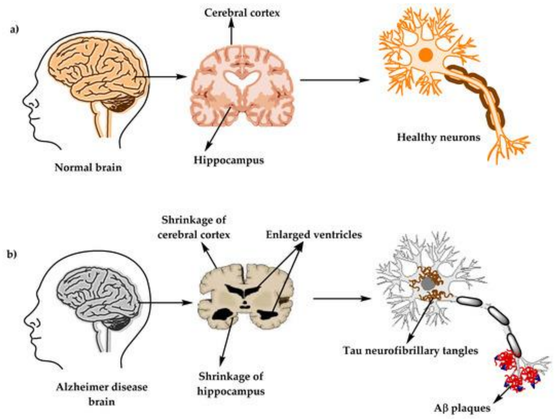

Figure 1. *Alzheimer's Brains and Neurons contain Tau Neurofibrillary Tangles (Breijyeh and Karaman 2020).*

Tau aggregates cause neurodegeneration through effects on RNA splicing

- Tau aggregates act as "sinks" that sequester proteins and factors essential to RNA splicing

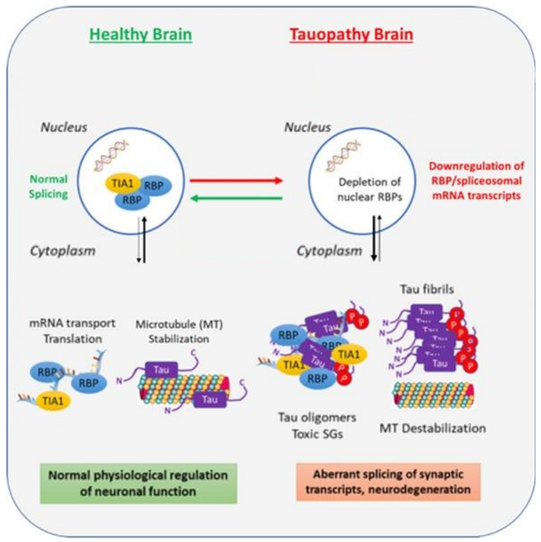

Figure 2. *Tau Aggregates Sequester Essential Splicing Factors (Apicco et al., 2019)*

RNA splicing is a key step in gene expression

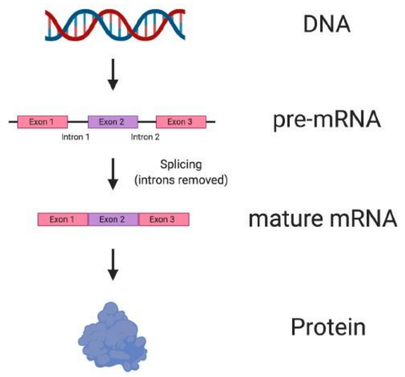

Figure 3. *The General Process of Gene Expression (Spinal Muscular Atrophy UK)*

Alternative splicing results in different proteins from the same gene based on exon combination

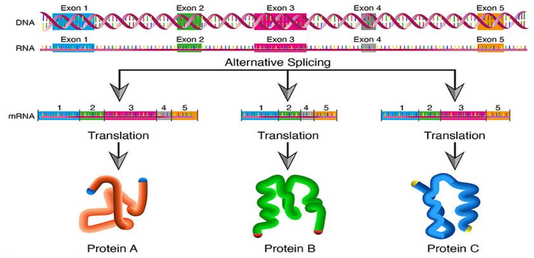

Figure 4. *Alternative Splicing of the Same Gene Results in Multiple Different Proteins. (Sharp, 2023)*

CircRNA's are Upregulated in Tauopathies via Back-splicing Events

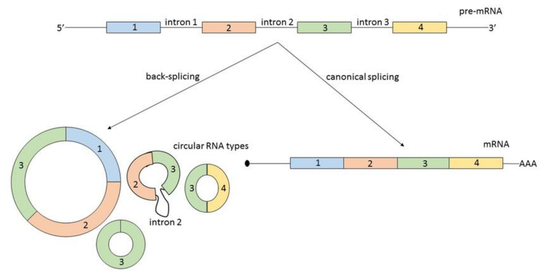

Figure 5. *Formation of Types of circRNA and Linear RNA from the Same Gene (Dragomir & Calin, 2018).*

Hypothesis:

The overexpression of tau (formation of tau aggregates) disrupts RNA splicing leading to an increase in circRNA formation

Overexpressing Tau in *Drosophila* through the GAL4 system

- Our study used *Drosophila melanogaster,* fruit flies, to test the effects the overexpression of tau had on circMbl levels.
- Fruit flies are widely used to model human neurological disorder due to their cheap cost, ease of genetic manipulation, and high genetic similarity in neuronal pathways compared to humans.
- Our circRNA of interest, circMbl, is genetically identical between humans and fruit flies.

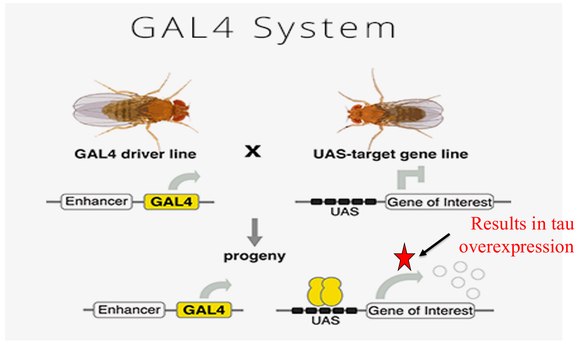

Figure 6. *GAL-4 System Used to Overexpress Tau in Drosophila (Caygill and Brand, 2016)*

Detection of circMbl through Quantitative Reverse Transcription PCR

- qRT-PCR was used to measure the levels of circMbl in young female and male *Drosophila* head tissue

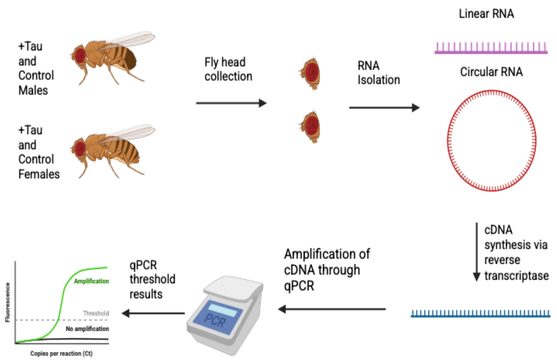

Figure 7. *Experimental Workflow Showcasing Fly Head Collection, RNA isolation, cDNA Synthesis and qPCR (Biorender)*

Tau overexpression had no impact on circMbl formation

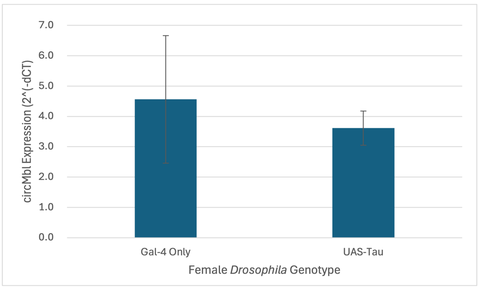

Figure 8. *Tau Overexpression Had No Significant Impact on the Levels of circMbl in Female Drosophila Head Tissue. circMbl .*

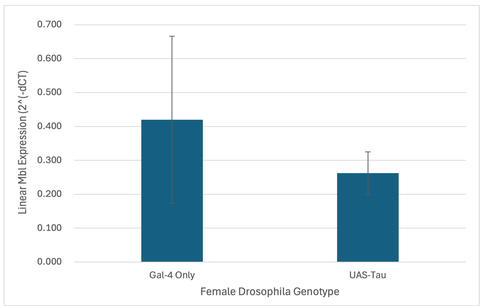

Figure 9. *Tau Overexpression Had No Significant Impact on the Levels of Linear Mbl in Female Drosophila Head Tissue.*

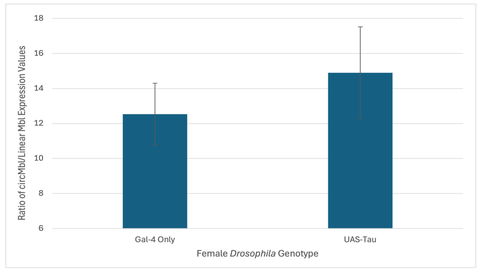

Figure 10. *Tau Overexpression Had No Significant Impact on the Ratio of circMbl Expression to Linear Mbl Expression in Female Drosophila .*

Conclusion and Future Directions

- Our study did not find significant differences in circMbl expression between the overexpressing tau groups and controls, which did not support the past literature on circRNA formation in tauopathies.
- However, investigating the impact of tau aggregates on RNA splicing could lead to identifying the cause of the neurodegeneration seen in Alzheimer's.
- Future studies should compare the levels of circRNA formation across multiple age points in *Drosphila* due to circRNA's quality of accumulating over time.