Activation of JNK signaling in Aβ42-expressing neurons triggers cell death in wild-type neurons in a *Drosophila* eye model of Alzheimer's disease

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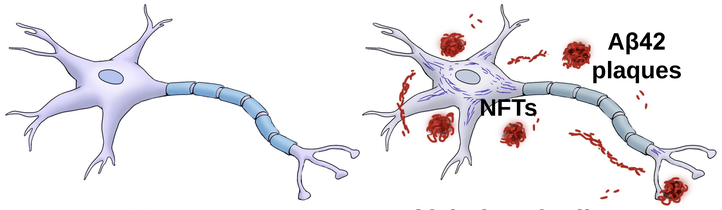
Introduction

Alzheimer's disease (AD) is a debilitating neurodegenerative disorder with no cure and few effective treatments

One process underlying the pathology of AD is the accumulation of amyloid beta 42 (Aβ42) plaques, which leads to aberrant activation of cell signaling pathways and neurodegeneration

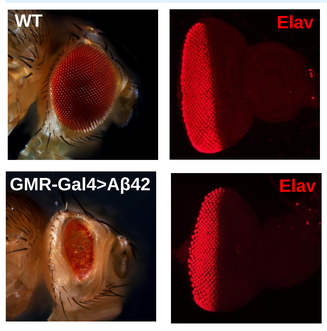
Many transgenic models use the expression of human Aβ42 throughout an entire tissue or field

We use a *Drosophila* eye model of AD to investigate interactions between wild-type and Aβ42-expressing neurons



Two characteristics of AD are intracellular neurofibrillary tangles (NFTs, blue) and extracellular amyloid beta (red). AD can be modeled in flies by expressing Aβ42 in developing retinal neurons using the Gal4/UAS transgenic expression system.

Modeling Alzheimer's disease in *Drosophila*

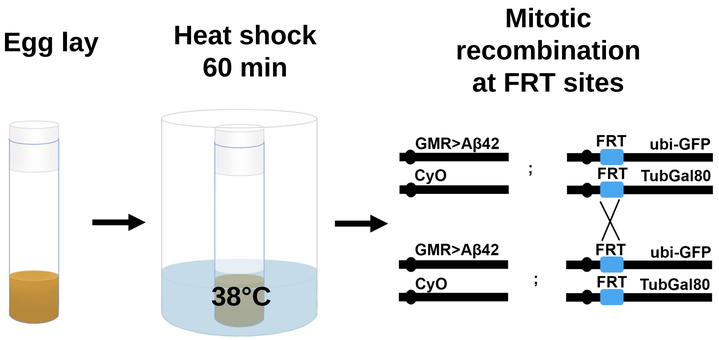


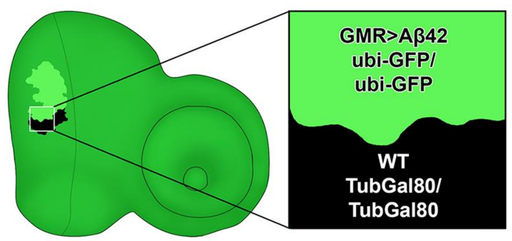
Comparison of wild-type (WT) flies with flies expressing Aβ42 in retinal neurons using the Gal4 driver, GMR-Gal4. Aβ42-expressing flies show small, glassy eyes. Neurons (shown by Elav staining) of eye-antennal imaginal discs of larvae show early neurodegeneration in Aβ42-expressing animals.

Goal

To understand how interactions between wild-type and Aβ42-expressing neurons contribute to the progression of Alzheimer's disease

Two clone system to study interactions between Aβ42-expressing and WT neurons

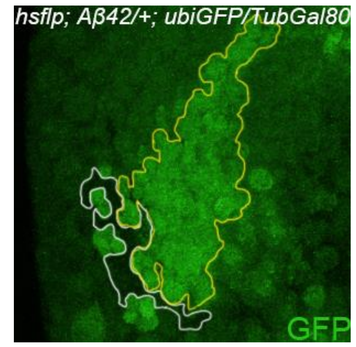


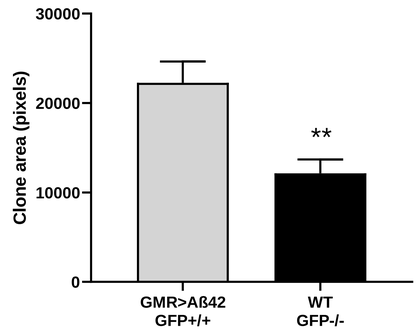


Traditional models require comparing two different animals, one WT and one expressing Aβ42

We have developed a two-clone system using the FLP/FRT and Gal4/UAS/Gal80 approaches. Heat shock mediated mitotic recombination at FRT sites results in animals with GFP-negative WT neurons adjacent to GFP-positive Aβ42-expressing neurons in the same tissue

WT clones are reduced in size compared to Aβ42-expressing clones





WT cells are eliminated leading to a significant decrease in clone size compared to Aβ42-expressing clones

Conclusions

Crosstalk between Aβ42-expressing neurons and neighboring WT neurons leads to the death of WT cells

Genetic manipulations can be introduced in Aβ42-expressing cells to understand what signaling pathways trigger this cell death

Future Directions

Determine how changes to cell-cell signaling between Aβ42-expressing and WT neurons lead to to the preferential death of WT neurons

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