Use Drosophila as Model to Study Alzheimer's Disease

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INTRODUCTION

- Alzheimer's disease(AD) is the most common neurodegenerative disease, which is marked by extracellular deposition of the amyloid β-peptide (Aβ) in the senile plagues.
- "Amyloid cascade" hypothesis: Aβ arise from the sequential cleavage of the Amyloid Precursor Protein (APP), which is cleavage by β-secretase and γ-secretase. APP intracellular domain(AICD) can contribute to a transcriptional regulatory complex. (Fig.1)(Ming Guo et al,2008)
- Transgenic flies: In order to identify factors that regulate APP levels or APP cleavage by γ-secretase, we introduce transgenic fies (GAMAREP).(Fig.2)

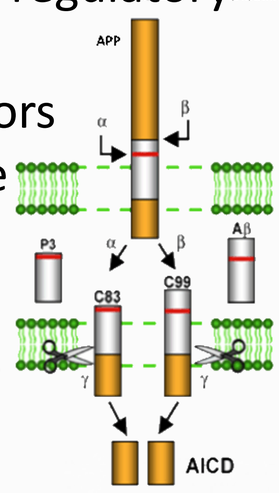
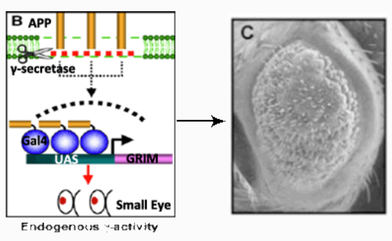


Fig.1



The system contains two components: GMR-APP-Gal4; UAS-GRIM.

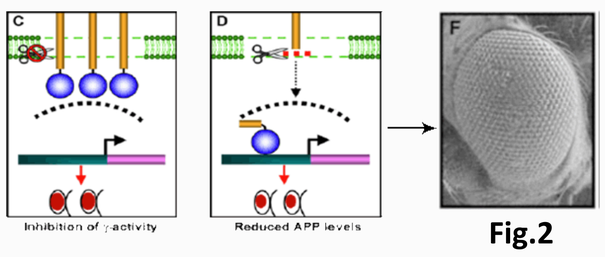


Fig.2

When APP-Gal4 cleaved by γ-secretase, AICD-Gal4 will translocate to nuclei, bind to UAS, and start the transcription of GRIM-an apoptotic gene. Any factor that would rescue the GAMAPEP phenotype could be a very important suppressor to AD.

DESIGN

- Genetic modifier: By genetic screen, our lab identified several genetic modifiers. By crossing them with GAMAREP, we can test its sensitivity.
- Chemical modifier: Humanin is a well known neuroprotective peptide, HNG is a derivative of HN(S14G), and it is reported that HNG is more effective than HN.(Cohen et al, 2013)We want to know if it plays a role in this process.
- Experiment design:
  - I. Phenotype scan: I will use GAMAREP cross with GMR-modifier gene flies to see the eye size.(or feed GAMAREP with HNG)
  - II. Western-blot： APP tagged with myc in C-terminal will be expressed in eyes. By western-blot of these flies' tissue with anti-myc antibody, we can examine the fate of APP.

RESULTS

- HNG cannot change GAMAREP phenotype at 10,20,40μM(Fig.3)

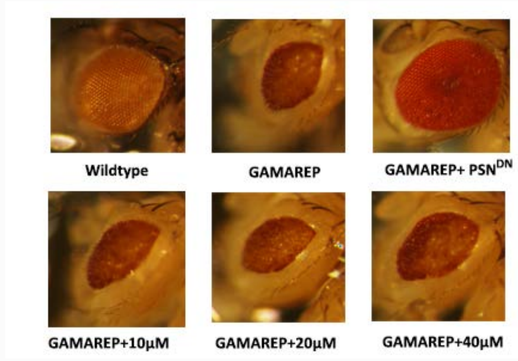


Fig.3

- Candidate gene1,2,3 can suppress GAMAREP phenotype. PSN^{DN} and RNAi-nct are reported γ-activity suppressors(Fig.4)

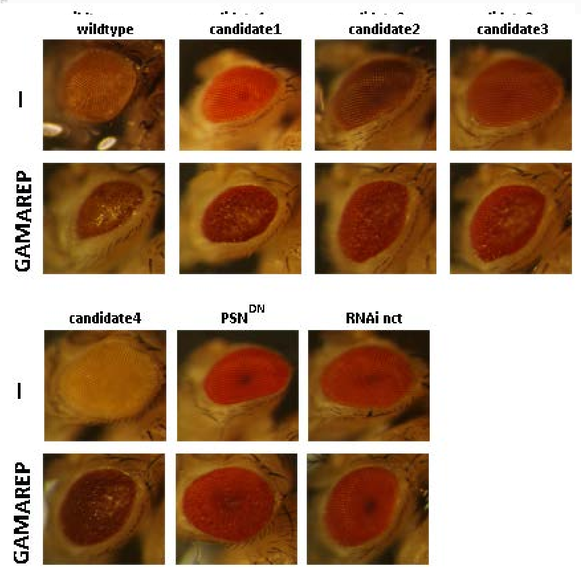


Fig.4

DISCUSSION

- GAMAREP could sensitively testify the genes that can suppress the Aβ-forming APP processing.
- HNG could protect the cell from AD-relevant gene insults in neuronal cell line. It possess both intra- and extra-cellular modes of action. One hypothesis is that HNG can suppress Aβ-forming APP processing. Our GAMAREP would be a good model to testify the hypothesis.
- Our experiments show that HNG doesn't suppress GAMAREP phenotype at 10,20,40μM, which suggests that HNG may not suppress APP process at this level. There are possibilities that it may play it role at higher concentration, or derivatives of HNG(such as HNG-F6A) may change GAMAREP phenotype, which I am working on right now.

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