Modifiers of Amyloid-beta Toxicity in Alzheimer’s Disease

Mayida Azhar

Department of Genetics

Alzheimer’s disease and Dementia, 2014
Is there an interaction between two pools of Aβ?
We secrete Aβ peptides from the neurons of fly brain and study toxicity
Secreted Aβ is toxic in Drosophila

Reduced Longevity

![Graph showing percent survival over days for wild type and Aβ expressing Drosophila. The Aβ expressing group shows a significantly reduced survival rate compared to the wild type group.](image)
Locomotor deficit

- **Wild type**
- **Aβ expressing**
Plaque like deposits in the brain
Without SSP, Aβ is expressed in cytoplasm
...but Cytoplasmic Aβ is non-toxic

![Graph showing percent survival over time for Wild type and Aβ expressing cells. The graph indicates that Aβ expressing cells have a higher survival rate compared to wild type cells, especially after 60 days.](Image)
No plaque like deposits
What happens if we co-express these constructs?

Median Survival (days)

Wild type, NSP Aβ, SSP Aβ, NSP+ SSP Aβ

Stanislav Ott, 2013
Increase in plaque deposition
Which pathways are facilitating this synergy?
An example......CG1824 siRNA
RNAi screen outcome

- **13 Genes** (Extracellular toxicity)
- **4 Genes** (Combined toxicity)
Conclusion

- There is a synergistic relationship between extracellular and Cytoplasmic Aβ.
- Gene knockdown at interface of the cells, modifies Aβ toxicity.
- We are trying to replicate this effect in mammalian cells and study the pathways involved.
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