Role of Relish/NF-kB Apoptosis Pathway in Amyloid-beta 42 Mediated Neurodegeneration in Alzheimer's Disease

Authors: Steven G. Borchers, Neil William Glenn, Neha Gogia
Advisor: Dr. Amit Singh

Abstract

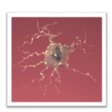
Alzheimer's disease (hereafter AD) is a progressive neurodegenerative disorder which affects the cognitive functioning of patients. This disease does not have a cure at this point. One of the reasons for the manifestation of AD is the accumulation of amyloid-beta-42 (Aβ42) plaques. We have developed a Drosophila eye model where human Aβ42 is misexpressed in the differentiating eye, which triggers neuronal death in the retinal neurons. Our lab has identified that a soy based protein, Lunasin, can be employed to block Aβ42 mediated cell death. There is evidence to support that Lunasin can block inflammation through downregulating the NFkB pathway. This pathway leads to the activation of apoptotic mechanisms including in the jun-N Terminal Kinase (JNK) pathway. We have developed transgenic flies which can produce both human Aβ42 and soy protein Lunasin in the Drosophila eye. These flies have closer to normal eyes as Lunasin blocks Aβ42 mediated neurodegeneration. I want to test how Lunasin prevents neuronal death observed in our Aβ42 model. I propose to genetically change the activity of NFKB pathway kinases Relish and Cactus in transgenic flies where we have introduced human Aβ42 and Lunasin. I have generated transgenic and mutant flies which can be used for gain-of-function as well loss-of-function of these pathway members to observe their effect on Aβ42 neurodegenerative phenotype. I will observe these interactions at three developmental time points of larval eye imaginal disc, pupal retina and the adult eye. These studies will have significant bearing on use of NFKB members as therapeutic targets for AD in the future.

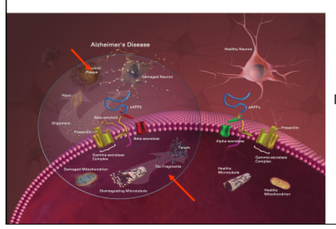
Alzheimer's Disease

1. Amyloid Plaques
2. Neurofibrillary Tangles
3. Oxidative Stress due to ROS
4. Neuronal loss (Secondary)
5. Genetic Basis of ApoE

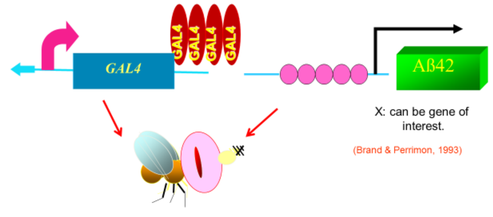
Healthy neuron + Aβ42

Dying neuron



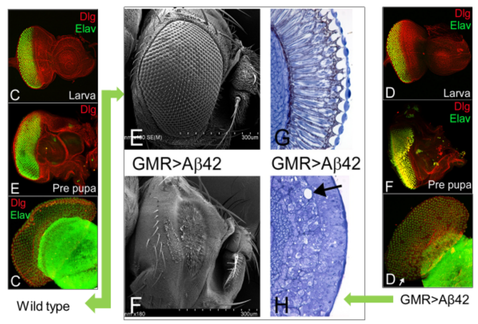


Gain of-function approach: GAL4/UAS-System

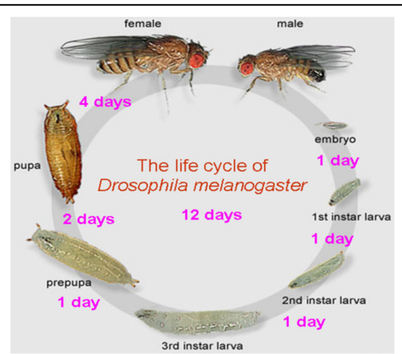


Tare et al., 2011

Drosophila eye model to study Aβ42 mediated neurodegeneration



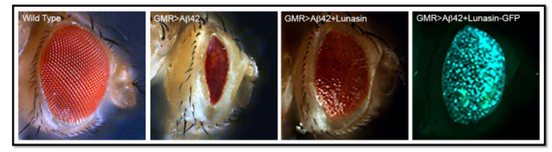
Drosophila melangaster Life Cycle



Lunasin

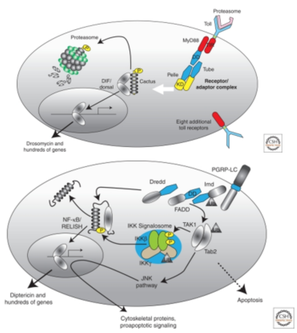
- Soy albumin bioengineered protein
- Disrupts cell mitosis, causes chromosomal fragmentation and apoptosis in unregulated cell proliferation
- Poly-Aspartic tail allows for direct chromatin binding
- Caused eye rescue in Aβ42 model

Lunasin's effects on Alzheimer's Model



Adult phenotypes show a cell rescue in the fly retina indicating neuroprotective function of Lunasin

Cactus and Relish



Hetru, C. & Hoffmann, J.A. NF-κB in the Immune Response of Drosophila. Cold Spring Harbor Perspectives in Biology 1, a000232 (2009).

Conclusion

If Lunasin, UAS Cactus, or UAS Relish show less loss-of-function than the Aβ42 model, then Lunasin is negatively regulating NF-kB activity. With this knowledge, drugs can be synthesized to help combat Alzheimer's disease. Future projects can include other protein and protein complexes in the NF-kB pathway as other targets.