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Understanding the role of Wingless (Wg) signaling pathway in Amyloid-beta 42 (Aβ42) mediated neurodegeneration in Alzheimer's Disease

Understanding the Role of Wingless(Wg) Signaling Pathway in Amyloid-beta 42 (Aβ42) mediated neurodegeneration in Alzheimer's Disease

Ankita Sarkar[1],Madhuri Kango-Singh[1,2,3]

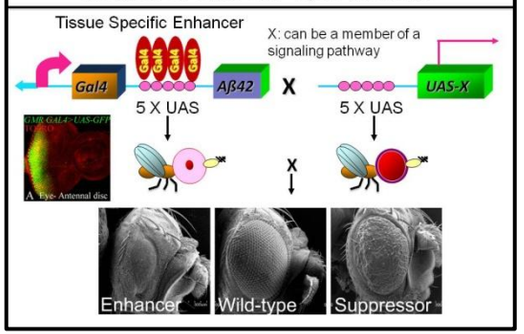
Amit Singh[1,2,3,4]

1) Department of Biology, University of Dayton, 300 College Park Drive, Dayton, OH. 2) Premedical Program, University of Dayton,300 College Park Drive, Dayton, OH. 3) Center for Tissue Regeneration and Engineering at Dayton (TREND), University of Dayton, Dayton, OH. 4) Center for Genomic Advocacy (TCGA), Indiana State University, Terre Haute, IN, USA.

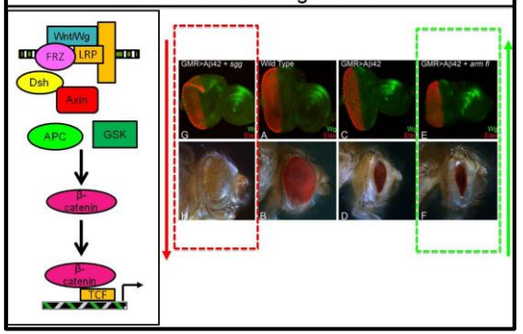
Abstract

Alzheimer's disease (AD), a common form of dementia and an age related progressive neurodegenerative disorder, manifests as memory loss and reduced cognitive ability. One of the hallmarks of AD is formation of the Amyloid-beta 42 (hereafter Aβ42) plaques, which triggers oxidative stress due to aberrant signaling and finally results in the death of neurons. However, the exact mechanism causing cell death is still not well understood. We misexpressed high levels of human Aβ42 protein in the developing fly retina, which mimics AD like neuropathology. In a forward genetic screen, we identified members of highly conserved Wingless (Wg) signaling pathway as modifiers of the Aβ42 mediated neurodegeneration. Misexpression of negative regulator of Wg like Shaggy kinase (sgg) or a dominant negative form of Drosophila T-cell factor (dTCF^{DN5}) or blocking Wg transport specifically by downregulating Porcupine (using porcupine^{RNAi}) rescued Aβ42 mediated neurodegeneration by reducing the number of dying cells and restoring the axonal targeting from the retina to the brain. In order to determine the role of Wg in early vs late onset of AD, we have modulated our transgenic expression system to activate at different time points and will assess whether Wg is activated in all stages. It is also known that Wg induces cell death in the early eye developmental stage of *Drosophila*. We therefore want to understand by what mechanism and in which cells the Wg signaling is triggering cell death, whether it's the Aβ42 misexpressing cells or the neighboring wild type cells. In order to approach this question we have developed a two clone system in our lab to understand the crosstalk between the two cell populations, where we have shown that the wild type neighboring cells are undergoing cell death compared to the Aβ42 misexpressed cells.

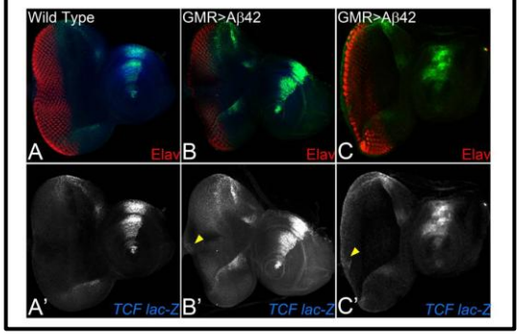
Strategy for the forward genetic screen to identify modifiers of GMR-Gal4>Aβ42 phenotype

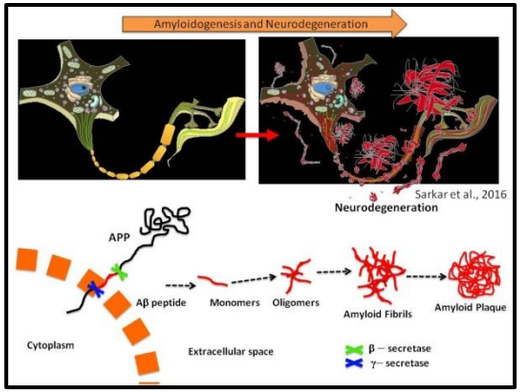


Blocking Wg Signaling suppresses the Aβ42 mediated neurodegeneration

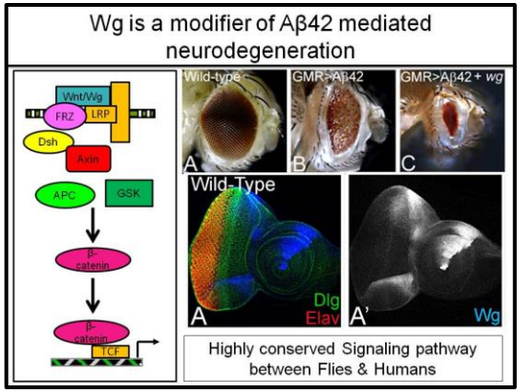


wg transcription is affected in Aβ42 background

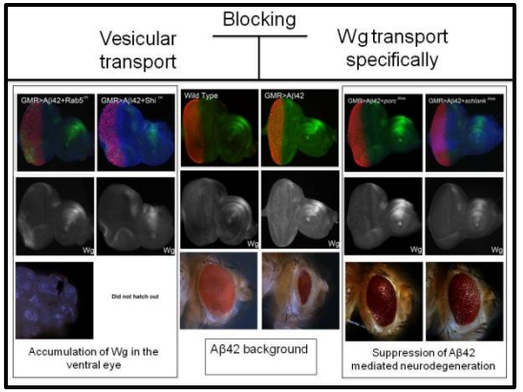




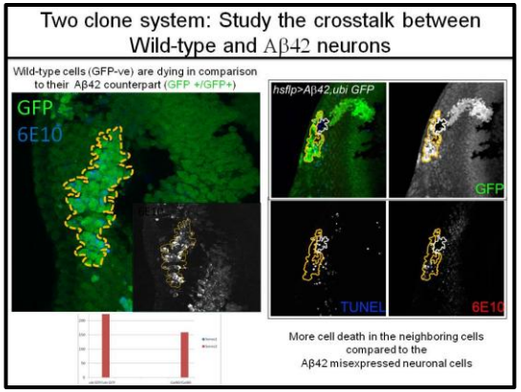
Wg is a modifier of Aβ42 mediated neurodegeneration



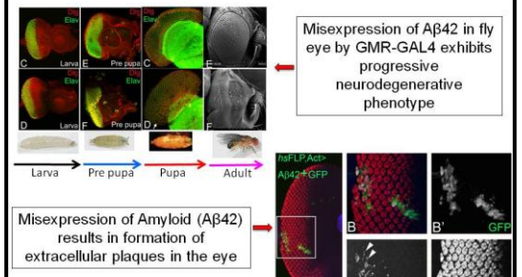
Blocking Wg transport specifically



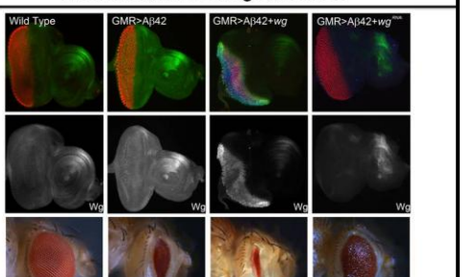
Two clone system: Study the crosstalk between Wild-type and Aβ42 neurons



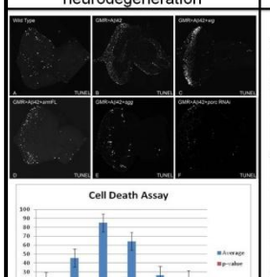
Proof of concept for our *Drosophila* eye model



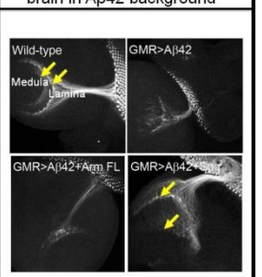
Altering Wg levels modulates the Aβ42 mediated neurodegeneration



Wg signaling triggers cell death in Aβ42 mediated neurodegeneration

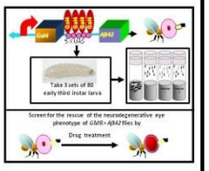


Wg signaling affects axonal targeting from the retina to the brain in Aβ42 background



Conclusion

1. Our transgenic eye model exhibits neurodegenerative phenotypes similar to AD.
2. We have identified Wg as a genetic modifier of Aβ42 mediated neurodegeneration.
3. We have developed a two clone system to study crosstalk between the Wild type and Aβ42 accumulating neurons.
4. Preliminary Data: Wild-type cells are affected more.



Wnt Inhibitors to be tested in our *in vivo* model

No	Name	Effect
1	XAV-939	selectively inhibits Wnt/β-catenin-mediated transcription through tankyrase, regulates axin levels and does not affect CRE, NF-κB or TGF-β.
2	IWR-1-endo	induces Axin2 protein levels & promotes β-catenin phosphorylation by stabilizing Axin-scaffolded destruction complexes
3	ICG-001	antagonizes **Wnt/β-catenin**/TCF-mediated transcription

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