A Drosophila Model for Alzheimer’s Disease with Amyloid Plagues and Neurofibrillary Tangles

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Clinical Image

The study of cognition is one of the most challenging subjects of neuroscience in this century. Memory is the most vital cognitive faculty of the human mind and much of the information we have obtained has been drawn from studying disorders, such as the cognitive symptom of memory loss in Alzheimer’s disease. About 100 years ago, Alois Alzheimer described this cognitive disease as a mental illness of dementia with neuropathological hallmarks of neurofibrillary tangles and senile plagues in 1907 [1]; and “Alzheimer’s disease” was historically termed by Emil Kraepelin in 1910. Currently, Alzheimer’s disease is still a medical and social challenge without cure.

A complete understanding of the molecular and neuronal mechanism of brain diseases will be valuable for constructing effective strategies to optimize clinical prevention or diagnosis and therapeutic treatments of these specific cognitive diseases such as Alzheimer’s disease. The human genome projects and genome-wide association studies [2] have identified numerous genes for hereditable Alzheimer’s disease. However, our understanding of how these diverse functions of AD genes conjoin to maintain healthy post mitotic neuronal function in memory of brains remains incomplete. In order to maximize the advantageous accessibility of fly genetics and fly brains, we along with many other researchers have established fly models for Alzheimer’s disease [3,4]. Here, we attempt to describe a fly model for AD which could fill the gap between fly genetic models and mouse models for AD that give a strong neuropathology which recapitulates the plague and neurofibrillary tangle like phenotypes in the animal model of Drosophila.

Our first effort was to co-express Aβ42 and GFP in glutamatergic neurons and several other types of neurons and observe Aβ42’s effect on these neurons over time. As shown in Figure 1, it appears that the expression of Aβ42 formed “AD plague-like” protein accumulations by whole mount fly brain staining with monoclonal antibody, 6E10 against Aβ amino acid 1-16 where it located to outside of neuron surface labeled with membrane CD8-GFP using confocal microscopy. We notably observed that the formation of AD plague like neuropathology is a risk combination of neuronal vulnerability and time-dependent process (not shown).

Figure 1: Expression of Aβ42 recapitulated plague-like pathology in fly brains. A confocal micrograph of a fly brain with co-expression of CD8-GFP and Aβ42 in glutamatergic neurons stained using anti- Aβ42 antibody. Scale bar, 20 μm. Note Aβ plaque-like pathology, the 6E10-staining pattern (red) is abnormal extracellular protein accumulation that is not co-localization to the glutamatergic neuronal expression pattern of CD8-GFP (green) as an age-dependent process.
The second neuropathological hallmark of AD is the neurofibrillary tangle. Many groups have modeled tau pathology in fly brains; this previous paper [5] specifically described expression of tau caused neurofibrillary tangle-like pathology by Congo red staining and its filament ultrastructure shown in Figure 2. We anticipate that this fly model for AD with amyloid plaques and neurofibrillary tangles is clinically and pathologically similar to AD patient brains. This will be suitable for the study of how the diverse function of AD genes can cooperate to maintain a healthy neuron in aging brains and to understand how their dysfunction contributes to age-dependent cognitive diseases, such as AD, the first step toward to find the potential neuron repair genes for this cognitive brain disease.

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References