A Drosophila-based genetic screen reveals new modifiers of Abeta and Tau co-pathology

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Alzheimer's disease (AD) is an incurable neurodegenerative brain disorder that causes progressive memory loss and cognitive decline and is the No.1 cause of dementia. It is characterized by the coexistence of extracellular amyloid plaques, mainly formed by the amyloid beta-42 (Abeta) peptide, and intracellular neurofibrillary tangles containing aggregates of abnormal tau. Abeta and tau were considered disconnected culprits for many years, but in view of recent studies, it is clear that they are intimately related and possess synergistic activities. Sadly, very little is known about how Abeta and tau interactions trigger AD pathogenesis, which significantly hinders the development of effective treatments. To address this, we generated a new fly model of AD that genetically produces both human Abeta and tau, resulting in synergistic pathology. These flies display extracellular deposits of thioflavin-S-positive Abeta, intracellular aggregation and phosphorylation of wild-type tau, and progressive loss of neuronal cells. These robust phenotypes represent a unique opportunity for gene discovery efforts. Thus, we performed a massive loss-of-function RNAi screen in the fly eye, which provides a useful and easy-to-score phenotype. Out of 6,000 RNAi stocks tested, we identified 31 suppressors and 119 enhancers, including multiple genes not previously known to be associated with AD. Most suppressors are linked to protein modification or cleavage, ribosomal function, cell metabolism, transcription, chromatin modulation, and transport. We are currently assessing the role of these modifiers in the fly CNS to better understand their functional involvement. This work will help uncover new molecular pathways and potential therapeutic targets for this devastating disorder

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