Structural and Molecular Basis of Age-Related Memory Impairment

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How transient events create persistent memories is a yet unsolved question. Although synapses have been established as the basic units of memory, the molecular processes behind long term memory formation and persistence are poorly understood. Among such processes, the experience-dependent self-assembly of the cytoplasmic polyadenylation element-binding (CPEB) protein is a plausible physical storage unit of long-term memories. While CPEB monomer functions as a translation repressor, its aggregate version activates the translation of synaptic mRNAs involved in memory. Through electron cryo-microscopy as well as functional and biochemical tests, we have recently revealed the atomic structure and biochemical activity of aggregated CPEB from 3-7-day old *Drosophila* brains. CPEB in *Drosophila*, known as Orb2, adopts a hydrophilic amyloid state which boosts the translation of mRNA targets associated with memory. Using this knowledge, we may now delve further into the molecular sources of memory decline. Humans and *Drosophila* alike suffer from age-related memory impairment (AMI). In this talk, I will introduce our preliminary experiments showing that hydrophilic Orb2 amyloid is susceptible to changes with AMI. We identified three major and distinct Orb2 amyloid polymorphs - from young flies with effective memories (“young polymorph”), adult flies with slight AMI (“adult polymorph”), and old flies with extreme AMI (“aged polymorph”). Differences in the prevalence of the three major Orb2 amyloid polymorphs found in each group of flies show that as age increases, so does the presence of the aged polymorph - which has a decreased capability to enhance the translation of mRNA related to memory. We believe these changes between a biochemically active (young polymorph) and inactive (aged polymorph) state of Orb2 amyloid could be one factor leading to AMI. Thus, we hope to further understand the correlation between the conformational state of Orb2 amyloid and AMI by examining the functional and atomic-level structure of Orb2 isolated from *Drosophila* brains during ageing. In the long term, the understanding of the molecules behind memory decline and how we can create structure-based strategies to ameliorate AMI could benefit from this research.