

Orb2/CPEB amyloid: similarities and differences with pathological amyloids

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Ordered proteinaceous aggregates called “amyloids” are typically associated with neurodegenerative diseases and cognitive impairment. Contrasting to this, the amyloid-like state of the neuronal RNA binding protein Orb2/CPEB in *Drosophila* was recently implicated in memory consolidation, but it remains unclear what makes this functional amyloid-like protein to behave in such a diametrically opposed way. By means of an array of biophysical, cell biological and behavioural assays we have characterized the structural features of Orb2 from the monomer to the amyloid state. Remarkably, we found that Orb2 shares many structural traits with pathological amyloids, including the intermediate toxic oligomeric species, which can be sequestered in vivo in hetero-oligomers by pathological amyloids. Nevertheless, unlike pathological amyloids, Orb2 rapidly forms amyloids and its toxic intermediates are extremely transient, which indicates that kinetic parameters differentiate this functional amyloid from pathological amyloids. Furthermore, we also observed that QBP1, a well-known anti-amyloidogenic peptide, interferes with long-term memory in *Drosophila*. Our results provide structural insights into how the amyloid-like state of the Orb2 protein can stabilize memory and be nontoxic. Furthermore, they provide a mechanism for how memory processes are often affected in amyloid-based diseases.