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Self-replicating amyloid-beta oligomers open doors to new molecular mechanisms in Alzheimer disease

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Aggregates of amyloid-β (Aβ) peptides have been implicated in the etiology of Alzheimer disease (AD). Among the different forms of Aβ aggregates, low molecular weight species ranging between 2- and 50-mers, also called "soluble oligomers," have emerged as the species responsible for early synaptic dysfunction and neuronal loss. Emerging evidence suggests that the neurotoxic oligomers need not be formed along the obligatory nucleation-dependant fibril formation pathway. In our earlier work, we reported the isolation of one such "off-pathway" 12–18-mer species of Aβ42 generated from fatty acids called large fatty acid-derived oligomers (LFAOs) (Kumar, A., Bullard, R. L., Patel, P., Paslay, L. C., Singh, D., Bienkiewicz, E. A., Morgan, S. E., and Rangachari, V. (2011) PLoS One 6, e18759). Here, we present the physiochemical aspects of LFAOmonomer interactions and its implications to AD. We discovered that LFAOs are a replicating strain of oligomers that recruit Aβ42 monomers and quantitatively convert them into LFAO assemblies at the expense of fibrils, a mechanism similar to prion propagation. These results further support the hypothesis that low molecular weight oligomers can be generated via non-fibril formation pathways. Furthermore, the unique replicating property of off-pathway oligomers may hold profound significance for Alzheimer disease pathology.

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