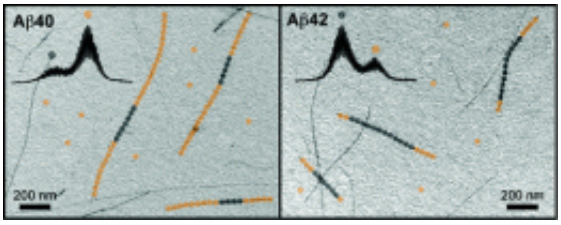
Recycling of Alzheimer's proteins could be key to new treatments

May 25 2011



The formation of abnormal strands of protein called amyloid fibrils -- associated with two dozen diseases ranging from Alzheimer's to type-2 diabetes -- may not be permanent and irreversible as previously thought, scientists are reporting in the *Journal of the American Chemical Society*. Rather, protein molecules are constantly attaching and detaching from the fibrils, in a recycling process that could be manipulated to yield new treatments for Alzheimer's and other diseases.

In a study that focused on the fibrils associated with Alzheimer's disease (AD), Natàlia Carulla and colleagues explain that scientists once believed that the fibrils themselves caused the memory loss and other symptoms of AD. During the last 10 years, however, suspicion has fallen on some toxic intermediate of the process through which those fibrils form in the brain. This study suggests that fibrils could be a source of those toxic intermediates.

The new study used laboratory techniques to detail molecular recycling within fibrils formed by two proteins, Aβ40 and Aβ42, which is most associated with AD. After monitoring recycling for 40 days, they found that both Aβ40 and Aβ42 molecules recycle within the fibril population, although to different extents. After 40 days, 80 percent of the molecules making up Aβ40 fibrils underwent recycling while only 30 percent did so in Aβ42 fibrils. These observations imply that Aβ42 recycles more slowly.

"In the context of AD, demonstrating that recycling occurs in the fibrils is a step forward but it is also crucial to identify the recycling species involved; whether they are individual Aβ units or small aggregates made of several units," explains Carulla. "It will be important to address if differences in the recycling species within Aβ40 and Aβ42 fibrils are relevant in the development of Alzheimer's disease. We are now working towards this aim. Once we have this information, we will be in a position to devise new therapeutic strategies that can modulate recycling."

More information: Aβ40 and Aβ42 Amyloid Fibrils Exhibit Distinct Molecular Recycling Properties, *J. Am. Chem. Soc.*, 2011, 133 (17), pp 6505–6508. DOI: 10.1021/ja1117123

Abstract
A critical aspect to understanding the molecular basis of Alzheimer's disease (AD) is the characterization of the kinetics of interconversion between the different species present during amyloid-β protein (Aβ) aggregation. By monitoring hydrogen/deuterium exchange in Aβ fibrils using electrospray ionization mass spectrometry, we demonstrate that the Aβ molecules comprising the fibril continuously dissociate and reassociate, resulting in molecular recycling within the fibril population. Investigations on Aβ40 and Aβ42 amyloid fibrils reveal that molecules making up Aβ40 fibrils recycle to a much greater extent than those of Aβ42. By examining factors that could influence molecular recycling

and by running simulations, we show that the rate constant for dissociation of molecules from the fibril (koff) is much greater for Aβ40 than that for Aβ42. Importantly, the koff values obtained for Aβ40 and Aβ42 reveal that recycling occurs on biologically relevant time scales. These results have implications for understanding the role of Aβ fibrils in neurotoxicity and for designing therapeutic strategies against AD.

Provided by American Chemical Society