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Monomeric structures of the disordered amyloid-beta protein: an all-atom computational study.[1]

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The aggregation of disordered peptides into oligomers and amyloid fibrils is a hallmark of several neurodegenerative diseases including Alzheimer's and Parkinson's. The interaction of these aggregates with the cell membrane accounts for an important mechanism of cell toxicity wherein annular shaped oligomers can form pores in the lipid bilayer and amyloid fibrils can induce lipid loss through a detergent-like mechanism. As monomeric amyloid peptides have been found to be mostly non-toxic, the development of strategies to inhibit aggregation has a strong potential to translate into new preventive treatments for diseases. These efforts require, however, a deep understanding of the atomic interactions and pathways accounting for amyloid aggregation. Here, I will discuss ongoing efforts in my lab to determine the set of structures adopted by monomers of the disordered amyloid-beta (Aβ) protein and to identify the ones preceding aggregation. This protein is the main component of plaques in Alzheimer's disease and the existence of monomeric structures that are precursor to aggregation could have important implications in the development of new treatments. In particular, these structures could serve as targets for drugs aimed at reducing aggregation before the irreversible formation of fibrils. If time permits, I will also discuss efforts in my group to understand pathways of aggregation of small amyloid-like peptides. These efforts make use of enhanced sampling methods and very long all-atom computer simulations in explicit solvent.

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