What does make an amyloid toxic: morphology, structure or interaction with membrane?

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The toxicity of amyloids is a subject under intense scrutiny. Many studies link this toxicity to the existence of various intermediate structures prior to the fiber formation and/or their specific interaction with membranes. Membranes can also be a catalyst of amyloidogenesis and the composition or the charge of membrane lipids may be of particular importance. Despite intensive research in the field, such intermediates are not yet fully characterized probably because of the lack of adapted methods for their analyses, and the mechanisms of interaction with the membrane are far to be understood.

For 7 years, our researches allowed to highlight some in vitro characteristics that seem to be convergent to explain the toxicity observed for some amyloids. Based on a comparison between the behavior of a model non-toxic amyloid (the Prion Forming Domain of HET-s) and its toxic mutant (M8), we could establish that short oligomers and/or fibers assembled in antiparallel β-sheets strongly interact with membrane leading to its disruption. Many recent evidences are in favor of the formation of antiparallel toxic oligomers assembled in β-helices able to form pores. We may also propose a new model of amyloid interaction with membranes by a “raft-like” mode of insertion that could explain important destabilization of membranes and thus amyloid toxicity. Our recent works on the peptide αβ1-42, involved in the Alzheimer disease, confirm these results.