Asia Pacific Nano Congress 2019: Critical role of membranes in nanoassembly of amyloid proteins

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Abstract

Statement of the Problem: The amyloid cascade hypothesis is currently considered as the main model for a vast number of neurodegenerative diseases including Alzheimer's, Parkinson's, and Huntington's diseases. Numerous studies have shown that amyloidogenic proteins are capable of spontaneous assembly into aggregates, and eventually form fibrillar structures found in amyloid or amyloid-like deposits. However, there is a serious complication with translating current knowledge on amyloid aggregation in vitro to understand the aggregation process in vivo. If the critical concentration for the spontaneous aggregation of Aβ peptide in vitro is in the micromolar range, physiological concentrations of Aβ are in the low nanomolar range making impossible amyloids to assemble.Methodology & Theoretical Orientation: We discovered a novel on- surface aggregation pathway that allows for spontaneous assembly of amyloid beta peptides at the physiological concentration range. We combined experimental studies involving single-molecule time-lapse AFM imaging with all-atom molecular dynamics simulations to characterize the on-surface self-assembly process of amyloid proteins. Experimental data demonstrate that onsurface aggregation occurs in the physiological range of concentrations of the proteins. Our combined experimental and computer modeling approaches demonstrate that the onsurface aggregation is a dynamic process, so the assembled aggregate can dissociate from the surface to the bulk solution.

As a result, the dissociated oligomers can play roles of seeds for aggregation in the bulk solution, or start a neurotoxic effect such as phosphorylation of the tau protein to initiate its misfolding and aggregation. Both processes can lead to neurodegeneration. Conclusion & Significance: We posit that on-surface aggregation is the mechanism by which neurotoxic amyloid aggregates are produced under physiological conditions. A change in membrane properties leading to an increase in affinity of amyloid proteins to the membrane surface facilitates the assembly of stable oligomers. The proposed model is a significant departure from the current model as it directs the development of treatments and preventions towards approaches that control the cell membranes composition to prevent the on-surface aggregation process.

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