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Protein-protein interaction and amyloid cascade hypothesis for Alzheimer's disease

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. We have discovered a novel on-surface aggregation pathway that allows for spontaneous assembly of amyloid beta peptides at the physiological concentration range. Our combined experimental and computer modeling approaches demonstrate that the on-surface 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 lead to neurodegeneration. Importantly, in most of cases, we found that aggregates formed on the surface are oligomers, which are considered to be the most neurotoxic amyloid aggregates. Therefore, 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 properties and composition preventing the on-surface aggregation process.

Biography

Yuri L Lyubchenko is Professor of Pharmaceutical Sciences at the University of Nebraska Medical Center, Omaha, NE, USA. His research focuses on understanding fundamental mechanisms underlying health and disease, which are key to developing new and more effective diagnostics and medications. This primarily basic research allows him not only to identify new drug targets for small molecule drugs, it also leads to the development of nanotools and methods to discover novel approaches for diagnostic, treatment, disease prevention and to rapidly determine their efficacy at the molecular level.

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