ALPHA-SYNUCLEIN AFFECTS DIFFERENTLY THE INTERNAL AND EXTERNAL LEAFLET OF THE LIPID MEMBRANES

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ABSTRACT

Peptides and proteins possess an inherent tendency to convert from their native functional states into intractable amyloid aggregates. This phenomenon is associated with a range of increasingly common human disorders, including Alzheimer's and Parkinson's diseases, type II diabetes, and several systemic amyloidosis [1]. Several experimental evidences indicated that amyloid toxicity is associated with the interaction between the aggregates of protein and cell membranes [2]. In particular, the lipid part of the cell membrane seems to play a crucial role in the toxicity cascade. By simplifying the system, i.e., by using model membranes, it is possible to systematically study the interaction of such protein aggregates with lipid membranes.

Atomic Force Microscopy (AFM) allows the study of topographical and biomechanical changes at the nanoscale. In the current work, we used a protocol developed for preparing defect-free supported lipid bilayers (SLBs) with the coexistence of both fluid and gel lipid phases [3]. In particular, we employed two different lipid mixtures, mimicking the composition of both the external and internal leaflet of the neuronal cell membranes. An essential difference between the two mixtures is the localization of the negatively charged lipid head-group, confined in the gel phase in the external leaflet composition, and the fluid phase in the internal leaflet composition. Among all the possible protein misfolding diseases, here we focus on Parkinson's disease (PD). We found that the interaction with α-synuclein, the principal peptide involved in PD, induced significant damages in SLBs with different extents in the two investigated lipid mixtures. These results highlighted the fine interplay between protein aggregates characteristic and membrane composition and organization as a key factor in the cytotoxicity of amyloid aggregates. Furthermore, the result presents biological importance, being α-synuclein localized both at both the cytosol and at the extracellular level.

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