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Spatial structure of amyloid fibrils linked to Parkinson's disease highly dependent on salt concentration

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By combining two-dimensional infrared spectroscopy and atomic force microscopy, Amsterdam researchers have established that the spatial structure of amyloid fibrils related to Parkinson's disease is highly dependent on salt concentration during protein aggregation. The results, published recently in Nature's open access journal 'Scientific Reports', can contribute to an explanation of observed differences in fibril-related pathologies.

The research was carried out by PhD students Steven Roeters (Van 't Hoff Institute for Molecular Sciences, UvA, under the supervision of Prof. Sander Woutersen) and Aditya Iyer (AMOLF, under the supervision of Prof. Vinod Subramaniam, VU). They studied the aggregation of the intrinsically disordered protein alpha-synuclein (αS) into amyloid fibrils, a process known to be involved in neuronal cell death in Parkinson's disease. Using a combination of techniques, among which atomic force microscopy, UV-circular dichroism CD, X-ray diffraction and sophisticated 2D infrared spectroscopy, they were able to show that the structure of these αS fibrils is highly sensitive to the salt concentration (ionic strength) during the aggregation process.

Currently approximately fifty disorders are known to be related to amyloid fibril formation, including Alzheimer's and Parkinson's disease, and type-II diabetes. Since recent studies show that subtle difference in fibril structure can have varied effects on cell death, the researchers argue that the observed high sensitivity to ionic strength can have significant physiological implications. They also anticipate that the observed high sensitivity of αS to aggregation conditions can contribute to the relatively frequent occurrence of contradicting findings in the research field. They expect that their proposed mechanism will be relevant to other amyloid forming proteins.

The authors explain the salt sensitivity by its influence on the monomer structure of the αS protein. In the absence of salt the interaction between the oppositely charged tails can stabilise a folded conformation of the protein. A salt environment strongly reduces this Coulombic interaction, leading to an

unfolded conformation which exposes the previously shielded hydrophobic central region of the protein. In order to minimize the hydrophobic exposure, the protein folds into an antiparallel β-sheet conformation with a relatively high aggregation propensity.

Source:

http://www.uva.nl/en/news-events/news/uva-news/uva-news/uva-news/content-2/folder-10/2017/02/formation-of-amyloid-fibrils-susceptible-to-salt-concentration.html

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