Deciphering structure of a toxic matter that destroys the nerves in the brain

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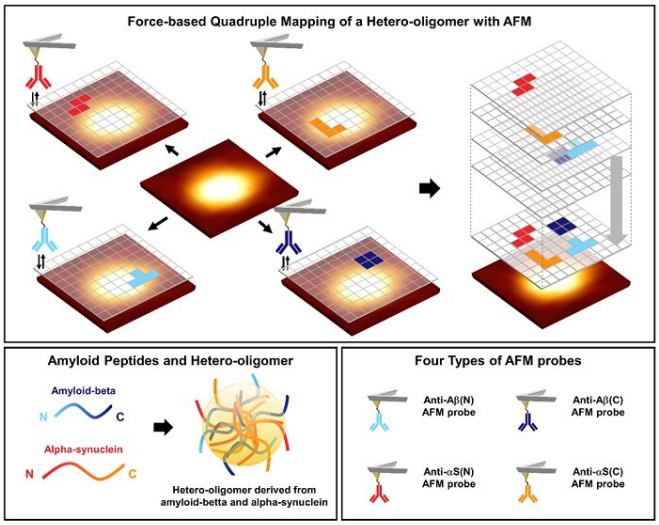

Schematic diagram of quadruple force mapping of hetero-oligomers derived from amyloid-beta and alpha-synuclein. Hetero-oligomers were characterized by the four types of AFM probes tethering an antibody recognizing each end of peptides.

Credit: Pohang University of Science & Technology (POSTECH)

Alzheimer's disease—also called dementia—where memory and cognitive functions gradually decline due to deformation and death of neurons, and Parkinson's disease, that causes tremors in hands and arms impeding normal movement—are major neurodegenerative diseases. Recently, a research team at POSTECH has identified the structure of the agent that causes Alzheimer's and Parkinson's diseases to occur together.

A research team led by Professor Joon Won Park and Ph.D. candidate Eun Ji Shin of the Department of Chemistry at POSTECH investigated the surface structure of hetero-oligomers found in the overlap of Alzheimer's disease and Parkinson's disease, using an atomic force microscopy (AFM) to reveal their structural identity. This study was featured as the front cover paper in the latest issue of *Nano Letters*.

It is known that the pathological overlap of Alzheimer's disease and Parkinson's disease is associated with the formation of hetero-oligomers derived from amyloid-beta and alpha-synuclein. However, it was difficult to study the treatment due to technical limitations in observing their structure.

To this, the researchers used the AFM to observe the surface characteristic of the hetero-oligomer nano-aggregates derived from amyloid-beta, known as the biomarker of Alzheimer's disease, and alpha-synuclein, known as the biomarker of Parkinson's disease, at the single-molecule level.

When the research team investigated with four AFM tips immobilized with antibodies that recognize N-terminus or C-terminus of each peptide, it was confirmed that all aggregates were hetero-oligomers. In addition, in the case of hetero-oligomer, it was confirmed that the probability of recognizing the end of the peptide is higher than that of the homo-oligomer.

This result indicates that the end of each peptide has a larger tendency to be located on the surface of hetero-oligomers than homo-oligomers, or that the ends of the peptides located on the surface have more degrees of freedom. That is, it can be confirmed that the aggregation between peptides is more loosely packed in the hetero-oligomer than in the homo-oligomer.

This study is the first study to observe the structure of protein disordered nano-aggregates, which has never been identified before, using the quadruple mapping with four AFM tips. It serves as experimental grounds to verify the hypothesis of hetero-oligomer aggregation. It can also be used in studies related to the overlapping phenomena of various neurodegenerative diseases other than Alzheimer's and Parkinson's.

"Until now, there was no adequate method to analyze the nano-aggregates, making it impossible

to elucidate the structural identity of heterogeneous aggregates," explained Professor Joon Won Park. "As the analysis method developed in this study is applicable to other amyloid protein aggregates, it will help to identify the cause of diseases such as Alzheimer's or the mad cow disease."

More information: Eun Ji Shin et al, Nanoaggregates Derived from Amyloid-beta and Alpha-synuclein Characterized by Sequential Quadruple Force Mapping, *Nano Letters* (2021). DOI: 10.1021/acs.nanolett.1c00058

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