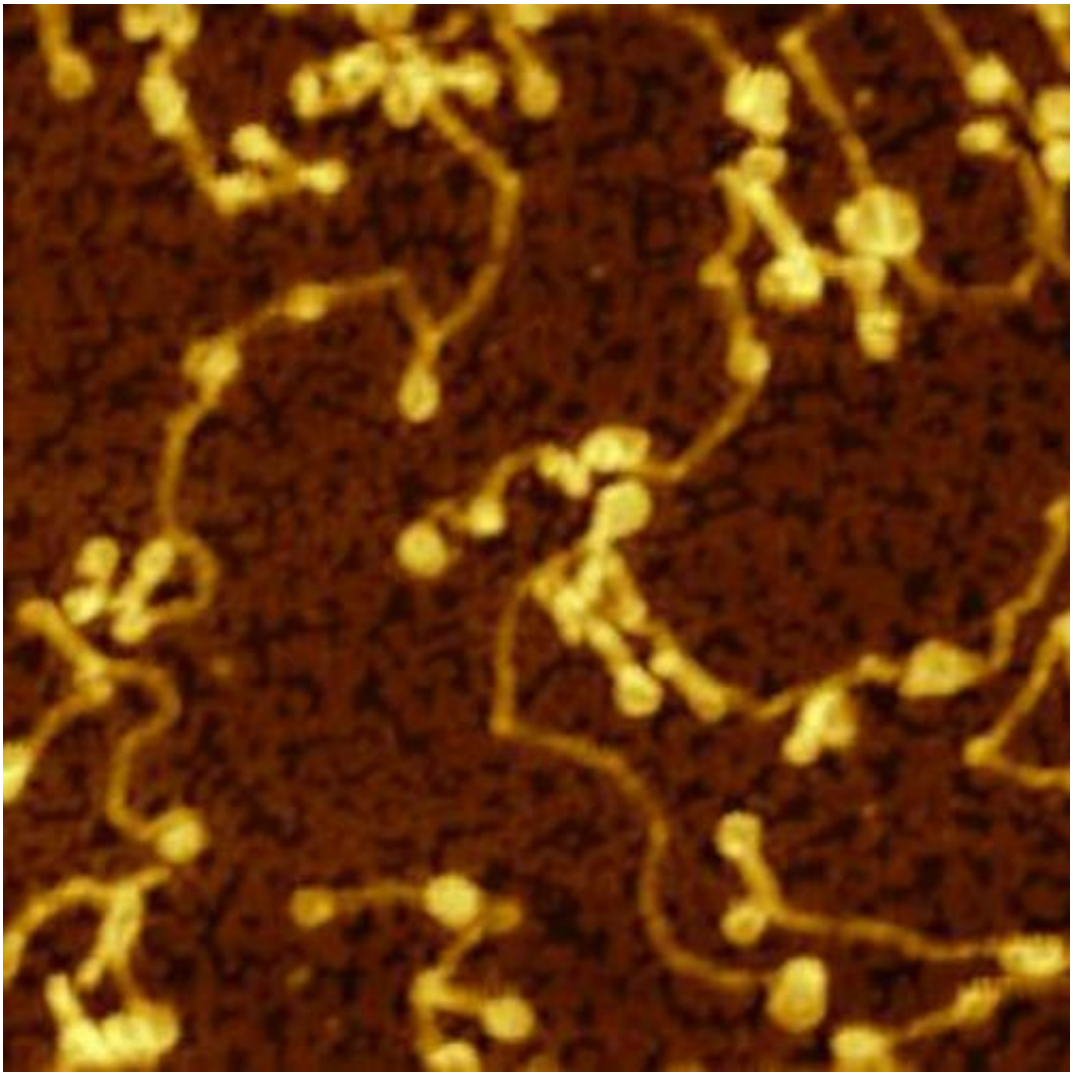
# Protein threshold linked to Parkinson's disease

February 2 2015



A detail of an atomic force microscopy image which shows amyloid fibrils of alpha-synuclein grown out of synthetic lipid vesicles. Credit: A.K. Buell

The circumstances in which a protein closely associated with Parkinson's Disease begins to malfunction and aggregate in the brain have been pinpointed in a quantitative manner for the first time in a new study.

The research, by a team at the University of Cambridge, identified a critical threshold in the levels of a protein called alpha-synuclein, which normally plays an important role in the smooth flow of chemical signals in the brain.

Once that threshold is exceeded, the researchers found that the chances that alpha-synuclein proteins will aggregate into potentially toxic structures are dramatically enhanced. This process, known as nucleation, is the first, critical step in the chain of events that scientists think leads to the development of Parkinson's Disease.

The findings represent another important step towards understanding how and why people develop Parkinson's. According to the charity Parkinson's UK, one in every 500 people in the UK - an estimated 127,000 in all - currently has the condition, but as yet it remains incurable.

Dr Celine Galvagnion, a Research Associate at St John's College, University of Cambridge, and the lead author of the study, said: "Finding a cure for Parkinson's depends on our ability to understand it. For the first time, we have been able to provide a mechanistic description of the initial, molecular events that can ultimately result in the development of the disease."

The study suggests that the likelihood of an individual developing Parkinson's is related to a delicate balance between the protein, alpha-synuclein, and the number of synaptic vesicles in their brain. Synaptic vesicles are tiny, bubble-like structures that help to carry neurotransmitters, or chemical signals, between nerve cells. The cell

constantly reproduces the vesicles to enable this.

Under normal circumstances, alpha-synuclein plays a pivotal role in the release of these neurotransmitters from one nerve cell to another. It does this by attaching itself to a thin membrane around the synaptic vesicle, known as the lipid bilayer.

When alpha-synuclein binds to lipid vesicles, it folds into a helical shape in order to perform its function. In certain circumstances, however, the proteins on the vesicle surface misfold and stick together. Once this nucleation process has begun, there is then a danger that free protein molecules within the brain cell will come into contact with the misshapen nucleus on the lipid surface. As these combine, they form thread-like chains, called amyloid fibrils, and start to become toxic to other cells. These amyloid deposits of aggregated alpha-synuclein, also known as Lewy-bodies, are the hallmark of Parkinson's Disease.

Previous research has suggested that overexpression of alpha-synuclein in the brain is somehow associable with the onset of Parkinson's, and that the interaction of alpha-synuclein with the lipid bilayer could play a role in modulating the development of the disease, but until now it was not clear why this might be the case.

In the new study, the research team simulated the process by which the proteins attach themselves to the vesicles by creating synthetic vesicles in the lab. These were then incubated with different quantities of alpha-synuclein.

The results showed that when the ratio of protein molecules to vesicles exceeds a level of about 100 (a level 10 times higher than that typically found in a human brain), the proteins attaching themselves to the lipid bilayer around a vesicle are too highly concentrated and bunch together on the surface. As a result, the chances of proteins nucleating on the

lipid surface are, remarkably, at least a thousand times higher than the chances of two proteins randomly binding together in solution.

"It became clear in our experiment that there are specific conditions in which you can see the aggregation happening, and other conditions in which you don't," Galvagnion added. "It turns out that the ratio determines the ability of alpha-synuclein proteins to nucleate. This provides us with a likely explanation of how the initial steps leading to Parkinson's occur."

Together, the results provide, for the first time, a mechanistic description of the key role that membrane interactions can play in the initiation of neurodegenerative diseases, including Parkinson's Disease.

The full report appears in the new issue of *Nature Chemical Biology*.

**More information:** Lipid vesicles trigger alpha-synuclein aggregation by stimulating primary nucleation, DOI: 10.1038/nchembio.1750

Provided by University of Cambridge