Protein released from cells triggers chain reactions that could cause Alzheimer's disease

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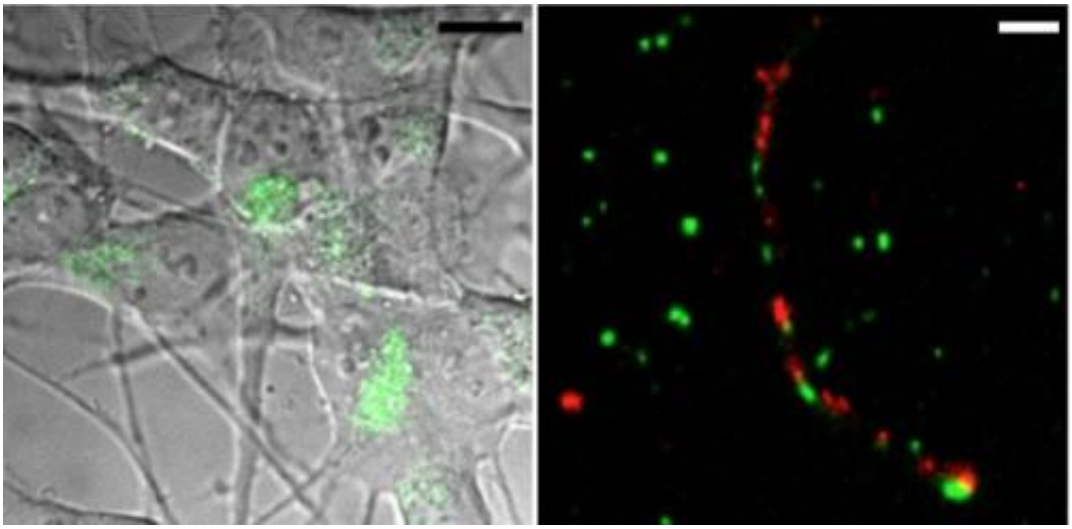

Credit: University of Cambridge

Researchers have shown that tiny quantities of the protein tau can be enough to kick-start an aggregation process which may explain the onset of Alzheimer's in the brain.

A powerful laser imaging technique has been used by researchers to show how minute quantities of a protein associated with Alzheimer's Disease trigger a process which may be crucial to its onset and spread.

The study also potentially links neuronal damage – for example, through brain injury, or head injuries sustained in contact sports – to the onset of Alzheimer's.

The researchers involved, however, are urging caution about the results, stressing that the study used a model cell culture and that the processes, which enable the disease to take root and develop in the brain could be far more complicated.

"These are molecular-level glimpses of what may be going on," Clemens Kaminski, Professor of Chemical Physics at the University of Cambridge, who led the research, said. "We are just beginning to see the molecular steps that may provide an explanation for what we see in the brains of patients who have died of Alzheimer's."

The study, reported in The *Journal Of Biological Chemistry*, focused on tau, a protein normally found inside healthy brain cells. In the brains of people who have died of Alzheimer's, however, clusters of malfunctioning tau are also found, and these appear to play a critical role in preventing their brain cells from working properly.

In the new study, researchers investigating how this happens added tiny quantities of normal tau to the outside of brain cells. To their surprise, the cells immediately started to ingest the protein. The ensuing uptake process, called endocytosis, kick-started aggregation of the protein into clumps. These clumps were then observed to cause "healthy tau" inside cells to misbehave and also aggregate.

Although seen in model cell cultures, the observations may show how the events that cause Alzheimer's begin. If so, there are practical implications: tau can be released into fluid around the brain, and therefore become a candidate for ingestion by other cells, through repeated head injuries, such as those suffered in contact sports. This,

however, is only one process by which the protein is released.

The aggregation process which forms clusters of tau is also linked to other diseases, including certain forms of brain cancer and Parkinson's. By drawing attention to a potential root cause of Alzheimer's, the research could eventually enable the development of therapies targeting the underlying problems in the brain, which stimulate its spread.

"The study underlines how significant the uptake of small quantities of tau might be as an initiator for the conditions that then prevail in the brains of Alzheimer's sufferers," Kaminski added. "It is one piece in the puzzle that could provide us with an explanation as to why head injuries may be connected to the disease. It's not necessarily correct – but it is plausible."

Tau – an abbreviation of Tubulin Associated Protein Unit – has long been linked with Alzheimer's, and researchers trying to find a cure have focused on attempting to understand how dysfunctional tau emerges and how it spreads.

To do this, however, they need to be able to observe events at a molecular level. The Cambridge Laser Analytics Group, to which Kaminski and his colleagues belong, is a team of physicists, biologists, chemists and engineers who, over many years, have developed laser-based imaging techniques to watch these basic chemical processes and study the molecular mechanisms that lie behind diseases like Alzheimer's.

During the new study, normal, monomeric tau protein was placed into a model system of neuronal cell lines and then watched through super-high resolution microscopes as the team tracked the effects. For the first time, this enabled them to watch monomeric tau form dysfunctional clumps which infected healthy tau and caused it to malfunction.

The ingestion process appeared to be caused by fat droplets, used by the cell to take on nutrients. As foreign tau enters the cell, a nucleation event takes place, during which the first clumps are formed. The tau already inside the cell then aggregates with these, causing the protein to misbehave. The newly-formed polymer then emerges from the cell and can potentially infect others.

"What is striking is that small concentrations of healthy tau form clumps when ingested into cells. We would never have thought that this could lead to the formation of potentially harmful aggregates," Dr Claire Michel, who performed the experiments, said. "The processes during ingestion could be crucial in the context of the disease."

The team's future research will focus on identifying how and where a molecule of tau entering a neuronal cell meets the tau already inside it, and also on how the aggregated clusters of tau emerge. This could pinpoint targets for future treatments.

While a lot of research into therapies has focused on how to remove clusters of tau from the brain, this latest investigation suggests that preventing individual monomers from entering cells might be just as essential.

"Our priority now is to connect what we have observed to the pathology of the disease," Dr Gabriele Kaminski-Schierle, who led biological aspects of the research, said. "We still do not know if we can stop cells from ingesting tau, or whether we can somehow wash tau out of the brain fluid. Answering these questions is key to developing future therapies to treat what remains, at the moment, a terrible and incurable disease."

Dr Simon Ridley, Head of Research at Alzheimer's Research UK, said: "The state-of-the-art technology used by this research team allows a

unique insight into the molecular events that occur in Alzheimer's. Investigating how the tau protein spreads between nerve cells can help researchers better understand what causes the disease and offer new approaches for treatments. It is unclear from this study whether head injury could trigger this molecular process, but it is a risk factor for dementia that needs to be investigated further."

More information: www.jbc.org/content/early/2013 … M113.515445.abstract

Provided by University of Cambridge