New toxic pathway identified for protein aggregates in neurodegenerative disease

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Led by professor Ludo Van Den Bosch (VIB-KU Leuven), scientists from Belgium, the UK and the US have identified new processes that form protein "clumps" that are characteristic of amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). How these proteins, which can bind RNA in normal cells, stick together has remained elusive until recently, when scientists demonstrated that they demix from the watery substance inside cells, much like oil separates from water. Prof. Van Den Bosch's team sheds light onto the molecular interactions behind the process in patients with defects in the C9orf72 gene. Their results are featured on the cover of the leading journal *Molecular Cell*.

Clumps of RNA-binding proteins occur naturally in normal neurons under times of stress in the form of stress granules (SGs), which precipitate from the water inside cells. However, in normal cells, the process of stress granule formation is tightly controlled, reversible and does not lead to disease. Scientists previously believed that hydrophobic interactions – or the protein's inability to mix with water – caused the formation of stress granules. However, Dr. Steven Boeynaems and colleagues under guidance of Prof. Van Den Bosch showed that in patients with defects in the C9orf72 gene, a different process can also cause this demixing, which precedes the formation of these toxic protein aggregates.

Mutation makes it easier for proteins to aggregate

Stress granules normally behave as liquid protein droplets within in a cell, while protein aggregates do not. The C9orf72 mutation causes neurons to produce small, abnormal and highly-charged toxic proteins, or peptides. Yet, precisely how these peptides are toxic was not well-understood. The research team was able to observe in vitro that these peptides cause RNA-binding proteins to spontaneously stick together and change the dynamics of stress granules in cells, making them more like solids than liquids.

Prof. Ludo Van Den Bosch (VIB-KU Leuven): "These observations give us more insight into the molecular process that leads to the clumping of RNA-binding protein in familial ALS and FTLD. It is believed that this process is an important step that occurs before the irreversible 'sticking-together' of the proteins, which is a pathological hallmark of these diseases. When enough of these clumps form, the neuron is unable to function and dies."

Protein clump 'antifreeze'

A multidisciplinary approach was vital to the study, with the lab of prof. Peter Tompa (VIB-VUB) and the Switch Laboratory (VIB-KU Leuven) collaborating closely with prof. Van Den Bosch's lab. These research groups' expertise in protein aggregation and structural biology was essential to the work. VIB's mass spectrometry core facility also played a pivotal role in identifying which proteins were responsive to the conditions created by the toxic peptides.

Dr. Steven Boeynaems (VIB-KU Leuven): "Based on our collaborative work, future studies could center around developing a molecular 'antifreeze' that prevents these liquid proteins from solidifying, thereby stopping protein aggregation and the death of neurons."

More information: Steven Boeynaems et al. Phase Separation ofC9orf72Dipeptide Repeats Perturbs Stress Granule Dynamics, *Molecular Cell* (2017). DOI: 10.1016/j.molcel.2017.02.013

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