Revealing the intra-cellular mechanism underlying ALS

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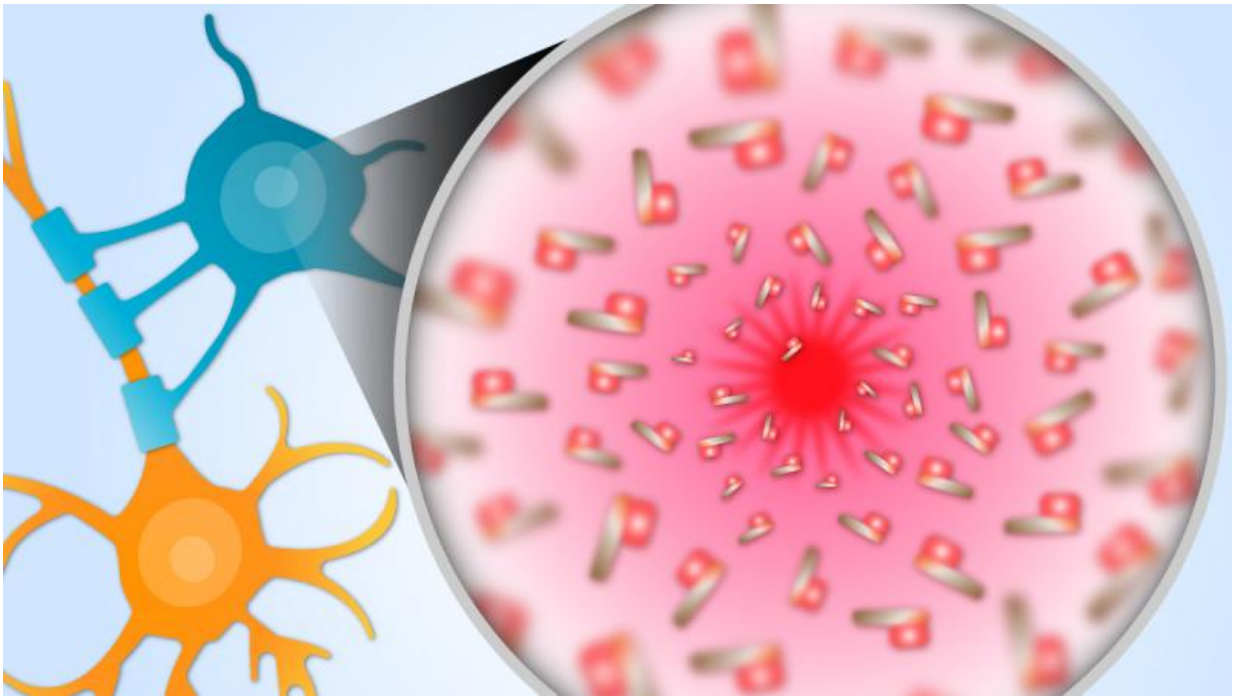

Research by Kyoto University reveals that a cancer suppression protein may cause disease progression in ALS, bringing doctors a step closer to identifying drug targets for the malady. Credit: Eiri Ono/Kyoto University

A new study uncovering the mechanism behind amyotrophic lateral sclerosis (ALS or also Lou Gehrig's disease) has brought doctors a step closer to identifying drug targets for the malady. Tsukasa Uchida and collaborators at Kyoto University have identified proteins associated

with cancer suppression and prevention of hypoxia as key players in the progression of ALS.

One of the main factors triggering the onset of ALS is the malfunctioning of nerve support cells called oligodendrocytes. Recent studies have implied that the misfolding and accumulation of the protein TDP-43 in oligodendrocytes was likely linked to the development of ALS, as with other neurological diseases like Alpha-synuclein in Parkinson's. The current research takes this a step further, explaining how this protein ends up accelerating ALS' characteristic decline in muscle strength.

Uchida's team found that the von Hippel Lindau (VHL) protein—associated with a gene most notable for cancer suppression—strongly binds to malformed versions of TDP-43 in oligodendrocytes.

"TDP-43 appears to be a very fragile protein, and becomes fragmented in the cytoplasm. When this happens it binds to VHL, which is typically only found in blood vessels, but surprisingly enough, we also found them in oligodendrocytes," explains Uchida.

VHL forms a complex with cullin 2 (CUL2), a protein that rescues the cell in hypoxic conditions, then facilitating the breakdown of malformed TDP-43 even under normal conditions.

"CUL2 was known to break down other proteins, but again, our study reports for the first time that it's also involved in the breakdown of TDP-43," says Uchida.

Additionally, the team found that when VHL becomes overly abundant, VHL/TDP-43 complex accumulates in the cytoplasm, forming a protein cluster thought to be detrimental to the functioning of oligodendrocytes.

"VHL overload in the cytoplasm and the imbalance between VHL and CUL2 seems to be the root cause of oligodendrocyte dysfunction," says Makoto Urushitani, a senior author of the study. "Once we have a clearer idea of how the VHL and CUL2 balance is maintained, I believe we'll be able to make a huge contribution to the treatment of ALS."

More information: Tsukasa Uchida et al. CUL2-mediated clearance of misfolded TDP-43 is paradoxically affected by VHL in oligodendrocytes in ALS, *Scientific Reports* (2016). DOI: 10.1038/srep19118

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