

ULK1: A guardian of neuronal quality control in the ageing Alzheimer's brain

Jun-Ping Pan (✉)

Department of Clinical Molecular Biology, University of Oslo and Akershus University Hospital, Lørenskog 1478, Norway

Received: 16 June 2026 | Accepted: 23 June 2026

Alzheimer's disease is defined pathologically by amyloid- β accumulation and Tau-related abnormalities, while its clinical course is dominated by progressive cognitive decline, but these changes occur within an ageing brain that gradually loses the ability to maintain proteostasis and mitochondrial quality [1, 2]. Autophagy and mitophagy are therefore critical protective systems, and their impairment may accelerate disease progression. The study "Reduced ULK1 links impaired autophagy and mitophagy to Alzheimer's disease pathology" identifies ULK1 as a central regulator of these processes [3]. As an initiator of macroautophagy and an important contributor to PINK1-, FUNDC1-, and AMBRA1-associated mitophagy, ULK1 may serve as a key node connecting protein aggregate clearance, mitochondrial quality control and neuronal resilience.

Using human biofluids, postmortem brain tissue and disease models, the study shows that ULK1 declines with ageing and is further reduced in Alzheimer's disease. Lower ULK1 was observed in serum, cerebrospinal fluid and vulnerable brain regions, including the hippocampus and entorhinal cortex. Importantly, higher baseline CSF ULK1 was associated with slower clinical progression, suggesting that preserved ULK1-linked quality control may help maintain cognitive resilience. These findings support the view that ULK1 decline is not only a biomarker of impaired cellular maintenance but may also contribute to Alzheimer's disease progression.

Functionally, ULK1 overexpression protected neurons from excitotoxic, metabolic and amyloid- β -induced stress. In 5xFAD mice, ULK1 improved learning and memory, reduced amyloid burden, enhanced microglial amyloid- phagocytosis, reduced astrogliosis and preserved dendritic spine density. These benefits were accompanied by improved mitochondrial homeostasis, increased ATP levels, reduced damaged mitochondria and enhanced mitophagy. In hTau.P301S mice, ULK1 also improved memory and reduced disease-relevant Tau pathology, including pTau-Thr181, pTau-Thr217, and acTau-Lys174.

Mechanistically, ULK1 appears to function as a multi-layered protective hub. Through autophagy, it promotes the clearance of amyloid- β and Tau aggregates; through mitophagy, it removes damaged mitochondria and restores bioenergetic stability; and through the NAD⁺/SIRT1 axis, it reduces pathogenic Tau acetylation. Pharmacological activation of ULK1 by Rac-BL-918 further reduced Tau aggregation, promoted degradation of pre-formed Tau puncta and improved memory-like behaviour in Tau-expressing *C. elegans*, partly through PINK1- and FUNDC1-dependent mitophagy. These findings highlight ULK1 activation as a potential strategy to restore neuronal quality control.

Several questions remain. The mechanisms driving ULK1 decline during ageing and Alzheimer's disease are still unclear, and the relative contributions of macroautophagy and mitophagy require further clarification. Cell-type-specific roles of ULK1 in neurons, microglia and astrocytes also need to be defined. In addition, whether serum or CSF ULK1 reflects protective pathway activation, neuronal injury, or both remain to be determined. Overall, this study positions ULK1 as a key link between ageing, impaired autophagy, defective mitophagy and Alzheimer's disease pathology, suggesting that restoring ULK1-dependent quality control may offer a broader therapeutic approach against neurodegeneration.

References

- [1] Selkoe, D. J. Alzheimer's disease: Genes, proteins, and therapy. *Physiological Reviews*, **2001**, 81(2): 741–766. <https://doi.org/10.1152/physrev.2001.81.2.741>
- [2] Parra Bravo, C., Naguib, S. A., Gan, L. Cellular and pathological functions of tau. *Nature reviews Molecular cell biology*, **2024**, 25(11): 845–864. <https://doi.org/10.1038/s41580-024-00753-9>
- [3] Pan, J. P., Wang, P. J., Zhang, J. Y., Knapkog, A. B., Watne, L. O., Wang, H. L., Lagartos-Donate, M. J., Lautrup, S., Mao, L. P., Wang, Q. et al. Reduced ULK1 links impaired autophagy and mitophagy to Alzheimer's disease pathology. *Nature Aging*, **2026**, 6(5): 1079–1102. <https://doi.org/10.1038/s43587-026-01108-z>