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NEURODEGENERATIVE DISEASE

Turning up mitophagy in Alzheimer disease

Accumulation of damaged mitochondria in neurons is a hallmark of neurodegenerative disorders including Alzheimer disease (AD). A new study in *Nature Neuroscience* reports impaired mitophagy — the process that removes damaged mitochondria — in patients and mouse models of AD, and identifies small-molecule mitophagy-inducing agents that improve AD signs and symptoms in preclinical models.

Mitochondrial dysfunction in neurons and AD pathology are thought to amplify one another in a positive feedback loop, but the underlying mechanisms are not fully understood. Mitochondrial homeostasis is regulated through the processes of mitochondrial biogenesis and mitophagy, wherein damaged mitochondria are targeted to lysosomes for degradation and recycling.

In the current study, Fang et al. began by examining mitochondrial morphology in post-mortem hippocampal tissues from a small cohort of patients with AD. Neuronal mitochondria were smaller and showed excessive damage compared with their counterparts in age-matched healthy hippocampal tissues. Interestingly, basal levels of mitophagy (inferred from colocalization of a mitochondrial protein with a lysosomal marker) were 30–50% lower than normal in the AD hippocampus.

Extending their work to human induced pluripotent stem cell (iPSC)-derived neuronal cultures, the authors showed significantly reduced phosphorylation of two key mitophagy proteins, TBK1 and ULK1, relative to wild-type (WT) neurons. Moreover, levels of other important mitophagy proteins were reduced in AD iPSC neurons compared with controls.

The investigators wondered whether drug-induced restoration of mitophagy in AD neurons could provide therapeutic benefit. They created an in vivo drug screening platform in *Caenorhabditis elegans* that were engineered to express a neuronal mitochondria-targeted biosensor, together with an acid-sensing green fluorescent protein variant to indicate lysosomal targeting during mitophagy.

The screen confirmed the known ability of an NAD^+ precursor, nicotinamide mononucleotide (NMN), to stimulate mitophagy and identified urolithin A and actinonin as mitophagy inducers from the researchers' in-house small-compound library. In a human neuronal cell line, urolithin A and actinonin increased the levels of several mitophagy-related proteins such as PINK1 and parkin.

To test the in vivo effects of mitophagy stimulation in AD, Fang et al. used an established *C. elegans* transgenic AD model that expresses pan-neuronal human amyloid-β_{1-42} ($A\beta_{1-42}$). These worms show abnormal energy metabolism and reduced mitophagy compared with WT controls. Mitophagy induction with NMN, urolithin A or actinonin improved memory performance of Aβ mutants in an aversive olfactory chemotaxis learning assay. Moreover, urolithin A reduced whole-body Aβ levels in these worms.

Next, the researchers tested the mitophagy-inducing compounds in a transgenic mouse model of AD. Daily oral treatment with urolithin A or actinonin for 2 months stimulated mitophagy and enhanced the clearance of defective mitochondria in the hippocampi of AD mice, as detected by electron microscopy. In addition, drug treatment restored learning and memory retention in the Morris water maze test to WT levels. These improvements were accompanied by a reduction in several features of AD pathology, such as Aβ plaques.

To probe how mitophagy induction improves memory-related neuronal functions, the authors performed genome-wide transcriptome analysis of hippocampal tissue from WT and AD mice with or without urolithin A treatment. The results revealed that urolithin A treatment restored transcriptomic profiles of AD transgenic mice towards that of WT mice, as well as upregulating signalling pathways related to memory function and suppressing pathways that promote inflammatory responses.

In AD mice, restoration of neuronal mitophagy through treatment with urolithin A or actinonin reduced Aβ burden via increased engulfment of plaques by microglia. As such, stimulation of mitophagy seems to be beneficial in AD through dual effects on neurons and microglia.

Increased activation of microglia could have detrimental effects through a potential contribution to local neuroinflammation. However, the mitophagy-inducing compounds were found to reduce brain levels of key pro-inflammatory cytokines including interleukin-6 and tumour necrosis factor.

Last, mitophagy induction was found to inhibit phosphorylation of tau protein, a key process in AD pathophysiology, which resulted in improved memory in *C. elegans* and mouse models of tauopathy.

Given the many late-stage failures of Aβ-directed candidate therapies for AD, alternative approaches that target broader aspects of AD pathogenesis, such as defective mitophagy, warrant increasing attention.

Katie Kingwell

ORIGINAL ARTICLE Fang, E. F. et al. Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. *Nat. Neurosci.* **22**, 401–412 (2019)
FURTHER READING Murphy, M. P. & Hartley, R. C. Mitochondria as a therapeutic target for common pathologies. *Nat. Rev. Drug Discov.* **17**, 865–886 (2018)