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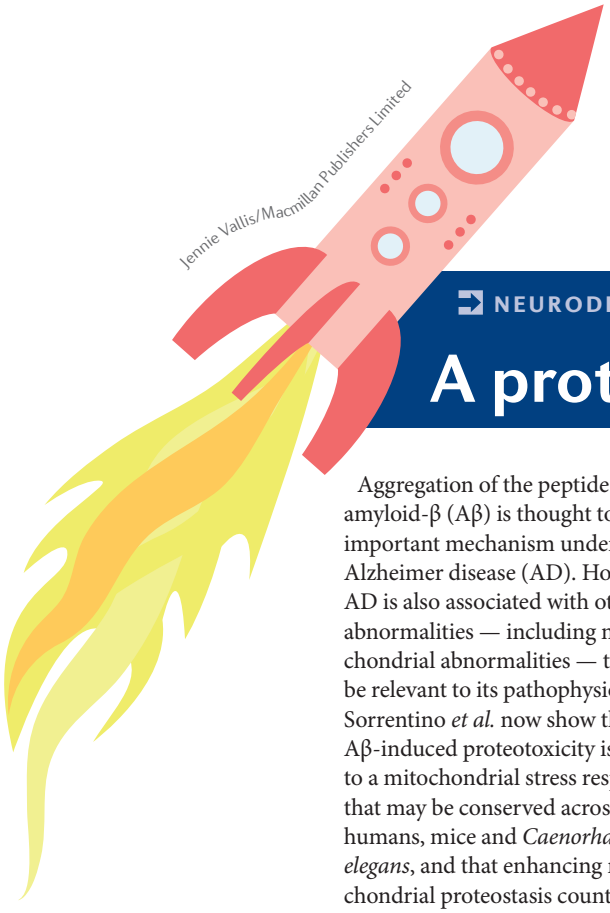


NEURODEGENERATIVE DISEASE

# A proteostatic boost

Aggregation of the peptide amyloid-β (Aβ) is thought to be an important mechanism underlying Alzheimer disease (AD). However, AD is also associated with other abnormalities — including mitochondrial abnormalities — that may be relevant to its pathophysiology. Sorrentino *et al.* now show that Aβ-induced proteotoxicity is linked to a mitochondrial stress response that may be conserved across humans, mice and *Caenorhabditis elegans*, and that enhancing mitochondrial proteostasis counteracts Aβ aggregation in worms and in a mouse model of AD.

Although mitochondrial dysfunction is a feature of AD, it has been unclear whether specific deficits in mitochondrial proteostasis are associated with this disorder. Here, the authors examined the expression of genes implicated in the mitochondrial unfolded protein response (UPR) and mitophagy — two protein quality control pathways utilized by mitochondria — in human cortical tissue. This analysis revealed that several transcripts linked to these pathways were upregulated in tissue from individuals with mild or moderate AD, or mild cognitive impairment (MCI), which may precede the development of AD, compared with that from people without cognitive impairment. Moreover, transcripts linked to oxidative phosphorylation were decreased in the AD and MCI tissue samples. Together, these expression changes suggest that the early stages of AD are associated with the induction of a mitochondrial stress response.

> “These data suggest that Aβ aggregation is associated with a mitochondrial stress response that is conserved across species”

The authors next examined gene expression in cortical tissue from the 3xTg-AD transgenic mouse model of AD, which exhibits Aβ pathology, and showed that genes linked to mitochondrial quality control pathways showed a marked increase in expression with disease development. The authors also found signs of a similar mitochondria-linked stress response in a *C. elegans* model of Aβ-induced proteotoxicity (the GMC101 model), in which the worms express a human isoform of Aβ in muscle cells and show Aβ aggregation and age-dependent paralysis after being exposed to a temperature shift. These data suggest that Aβ aggregation is associated with a mitochondrial stress response that is conserved across species.

The authors further examined the worm model to probe the relationship between Aβ and this stress response. Activating transcription factor associated with stress (ATFS-1) is a major controller of mitochondrial function and the mitochondrial UPR in worms, and an RNAi-induced depletion of this protein exacerbated Aβ aggregation and worm paralysis and decreased the expression of the stress response transcripts. By contrast, GMC101 worm-derived strains that overexpressed ATFS-1 showed induction of the mitochondrial UPR and increased protection against paralysis and premature death. Together, these findings indicate that mitochondria have a key role in counteracting Aβ-induced proteotoxicity in this model.

The authors next explored whether they could promote mitochondrial proteostasis in GMC101 worms by two methods of inducing the mitochondrial UPR in worms to halt disease progression. Silencing the expression of mitochondrial ribosomal protein MRPS-5 or pharmacologically inhibiting mitochondrial translation (through treatment with doxycycline) induced the expression of genes linked to mitochondrial UPR, mitophagy and respiration, reduced Aβ aggregation and promoted survival. Moreover, treating these worms with $NAD^+$-boosting compounds (for example, nicotinamide riboside), which are known to induce the mitochondrial UPR and mitophagy, had similar effects.

Interestingly, treatment of human-derived neuroblastoma cells expressing Aβ with nicotinamide riboside negated intracellular Aβ deposition and promoted the expression of mitochondrial stress response-related transcripts. Furthermore, in a mouse model of AD characterized by accumulation of Aβ, nicotinamide riboside treatment was associated with a reduction in Aβ deposits in the cortex and induction of mitochondrial stress response-linked transcripts. This treatment also appeared to promote memory function in these mice, as assessed in a contextual memory task.

Together, these data indicate that Aβ accumulation induces a mitochondrial stress response that aims to counteract this accumulation. This response seems to be conserved in humans, mice and worms and involves promotion of the mitochondrial UPR and mitophagy.

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**ORIGINAL ARTICLE** Sorrentino, V. *et al.* Enhancing mitochondrial proteostasis reduces amyloid-β proteotoxicity. *Nature* https://doi.org/10.1038/nature25143 (2017)