NEURODEGENERATIVE DISEASE

Germline influences protein aggregation in somatic tissues

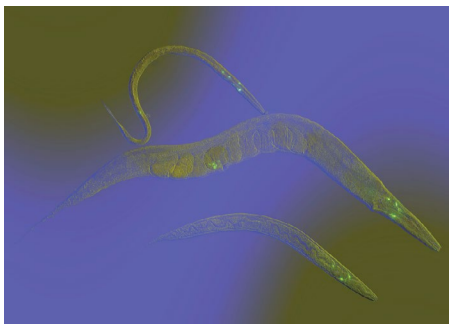
Calculli, G. et al. *Sci. Adv.* **7**, eabg3012 (2021)

Protein homeostasis (proteostasis) is essential for maintaining the integrity and functionality of the proteome. Deficits in proteostasis can lead to the accumulation of cytotoxic protein aggregates, a characteristic feature of many age-dependent neurodegenerative diseases, including Alzheimer's disease, Huntington's disease and amyotrophic lateral sclerosis (ALS).

Using *Caenorhabditis elegans* as a model organism, investigators from the University of Cologne now demonstrate that proteostasis deficits in germline cells can influence protein aggregation in distal tissues, including neurons. The findings, published in *Science Advances*, could increase our understanding of why protein aggregates accumulate in degenerating brains and lead to the development of new therapeutic approaches for neurodegenerative diseases.

While it is generally considered that proteostasis functions cell-autonomously within each cell, increasing evidence indicates that the process is also regulated by cell non-autonomous mechanisms. Studies in *C. elegans* have identified the nervous system as a central modulator of organismal proteostasis and a 2016 study showed that accumulation of an aggregation-prone protein in *C. elegans* neurons is sufficient to induce a mitochondrial stress response in other tissues, suggesting that proteostasis deficits can be communicated between somatic tissues.

Here, Calculli and colleagues asked whether germline cells can also communicate their proteostasis status to somatic tissues. "We identify a cell non-autonomous mechanism that coordinates the proteostasis status of germline cells with systemic mitochondrial function, a capacity previously ascribed only to the nervous system," explain the investigators in their report.



Caenorhabditis elegans. Credit: Heiti Paves/Alamy Stock Vector

To change the proteostasis status of the germline, the team induced the accumulation of Guanyl-specific ribonuclease PGL-1 — an RNA-binding protein involved in the formation of germ granules — by knocking down (KD) the expression of Y-box proteins CEY-2 and CEY-3, two germline-specific proteins that prevent aberrant protein aggregation. After confirming that loss of *cey-2* and *cey-3* resulted in the accumulation of PGL-1 into aberrant foci in the germline cells, Calculli et al. examined somatic proteostasis.

First, the investigators assessed the effects of CEY KD on neuronal proteostasis using a *C. elegans* model of neurodegeneration, in which the worms express expanded toxic protein repeats (polyQ) throughout the nervous system. In this model, loss of CEY proteins triggered neuronal aggregation of polyQ peptides and increased the motility defects induced by polyQ aggregation compared with polyQ control worms. Similarly, in a worm model of ALS, loss of CEY induced aggregation of disease-related proteins FUS (Fused in Sarcoma) and TDP-43 (TAR DNA-binding protein 43) in the nervous system and accelerated the disease-like loss of motility.

Next, Calculli and colleagues demonstrated that loss of CEYs also triggered aggregation in *C. elegans* models that specifically express expanded polyQ peptides in the intestine or muscle, indicating that the effects of PGL-1 aggregation on somatic proteostasis were not limited to the nervous system.

Finally the investigators showed that PGL-1 germline accumulation induced changes in the mitochondrial network of germline cells and somatic tissues and activated the mitochondrial unfolded protein response (UPRmt) in somatic tissues, leading to the aggregation of disease-related proteins. They also determined that Wnt signaling had a critical role in the germline-to-soma communication of proteostasis status.

In the discussion, the investigators explain that their findings could have implications for future research on aging and degeneration. "Environmental and metabolic conditions such as stress or aging that impinge on proteostasis are tightly correlated with a decline of germline integrity in animals. Thus, we speculate that proteostasis deficits in germline cells ensued from stress conditions or aging could contribute to the dysregulation of mitochondrial function and aggregation of disease-related proteins that often appear in postmitotic tissues such as muscle or nervous system with age," they write, adding that future investigations should also determine whether germline-to-soma communication of proteostasis is evolutionary conserved.

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