Reproductive regulation of the mitochondrial stress response in *Caenorhabditis elegans*

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ABSTRACT

Proteome integrity is pivotal for life, as manifested by the elaborate proteostasis network operating in eukaryotic cells. The mitochondrial unfolded protein response (UPR^{mt}), a key component of the proteostasis network, can be activated in a non-cell-autonomous manner in response to mitochondrial stress in distal tissues. However, the importance of inter-tissue communication for UPR^{mt} inducibility under physiological conditions remains largely unknown. Here, we report that an intact germline is essential for optimal UPR^{mt} activation in the somatic tissues of *Caenorhabditis elegans*. A series of nematode mutants with germline defects fail to robustly respond to potent genetic or chemical UPR^{mt} inducers. Our genetic analysis suggests that reproductive signals, rather than germline stem cells, are responsible for somatic UPR^{mt} induction. Consistent with this observation, we show that UPR^{mt} is sexually dimorphic, as male nematodes are inherently unresponsive to mitochondrial stress. Finally, we show that mitochondrial stress in the immortal germline tissue can activate UPR^{mt} in the soma. Our findings establish a novel germline-to-soma communication paradigm, which links the organismal response to mitochondrial stress with the reproductive status of the organism, and highlight the decline in reproductive capacity as a primary cause of proteostasis collapse during ageing.

REFERENCES

Charmpilas N, Sotiriou A, Axarlis K, Tavernarakis N* and Hoppe T*. 2024. *Cell Reports,* **43:**114336