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Spotlight

Germline regulation of the somatic mitochondrial stress response

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Mitochondria are pivotal organelles for cellular energy production and the regulation of stress responses. Recent research has elucidated complex mechanisms through which mitochondrial stress in one tissue can impact distant tissues, thereby promoting overall organismal health. Two recent studies by Shen *et al.* and Charmpilas *et al.* have demonstrated that an intact germline serves as a crucial signaling hub for the activation of the somatic mitochondrial unfolded protein response (UPR^{mt}) in *Caenorhabditis elegans*.

Mitochondria are essential organelles, primarily recognized for their critical role in cellular bioenergetics as the producers of ATP, as well as their pivotal functions in regulating apoptotic pathways and immune responses. Additionally, mitochondria are involved in various biological processes, including amino acid and nucleotide synthesis, calcium homeostasis regulation, iron–sulfur cluster biogenesis, and the metabolism of intermediate metabolites and fatty acids [1]. To preserve mitochondrial homeostasis, organisms have evolved multiple stress response pathways that enable adaptation to diverse environmental challenges [2].

In response to diverse types of mitochondrial dysfunction, an adaptive transcriptional response known as the UPR^{mt} is activated via mitochondrial-to-nuclear signaling. UPR^{mt} is crucial for maintaining organismal fitness during normal development, aging, bacterial infections, and disease. Originally identified in mammalian cells, the UPR^{mt} has been extensively characterized in *Caenorhabditis elegans* [3]. In this model organism, UPR^{mt} activation is mediated by stress-activated transcription factor-1 (ATFS-1), which contains both a mitochondrial targeting sequence and a nuclear localization sequence [4]. This dual targeting renders UPR^{mt} activation highly sensitive to mitochondrial protein import efficiency. Additionally, chromatin remodeling induced by mitochondrial stress is also important for UPR^{mt} activation [5]. Beyond its cell-autonomous effects, UPR^{mt} can also be activated in a cell-nonautonomous manner, where mitochondrial dysfunction in neurons induces UPR^{mt} activation in the intestine [6,7]. However, the communication between germline and soma for cell-nonautonomous UPR^{mt} activation remains complex and unclear.

Previous studies have demonstrated that knockdown of the cytochrome c ortholog *cyc-2.1* in the germline extends lifespan by triggering cell-nonautonomous activation of UPR^{mt} and AMPK in the intestine [8]. However, the mitokines produced by the germline and the specific signaling pathways involved in germline-to-intestine UPR^{mt} communication remain unidentified. It has been observed that dysfunction in endocytosis within coelomocytes can perturb this communication [8]. Furthermore, a breakdown in proteostasis within germline stem cells can adversely affect mitochondrial proteostasis and morphology in somatic tissues, thereby inducing UPR^{mt} activation. A long-range Wnt/EGL-20 signaling pathway has been implicated in transmitting mitochondrial network deficits from the germline to somatic tissues [9].

In a recent study, Shen *et al.* identified the germline as a critical hub for neuron-to-intestine UPR^{mt} signaling [10]. Utilizing a genetic model of cell-nonautonomous UPR^{mt} activation, they performed an ethyl methanesulfonate (EMS) mutagenesis screen to uncover regulators of this pathway. Their investigation revealed that the mitochondrial-localized protein UCR-2.3, as opposed to UCR-2.1 or UCR-2.2, is crucial for this signaling process. The loss of *ucr-2.3* suppressed cell-nonautonomous UPR^{mt} activation without affecting cell-autonomous UPR^{mt}. Unlike the ubiquitously expressed UCR-2.1 and UCR-2.2, UCR-2.3 is specifically enriched in germline and neuronal cells. The germline-specific expression of *ucr-2.3* is crucial for cell-nonautonomous UPR^{mt} signaling, affecting mitochondrial respiration, morphology, and content within the germline. Additionally, the depletion of the complex I subunit gene *nduf-2.2* also inhibited cell-nonautonomous UPR^{mt} signaling, suggesting that the quality of germline mitochondria is crucial for neuron-derived, cell-nonautonomous UPR^{mt} signaling. To investigate whether an intact germline is necessary for this signaling, Shen and colleagues used two temperature-sensitive mutants, *glp-4(bn2)* and *glp-1 (e2141ts)*, as well as floxuridine (FUDR) treatment to ablate the germline. They found that animals deficient in germline function exhibited a significant reduction in cell-nonautonomous UPR^{mt} activation. Therefore, an intact germline is essential for this process. It was previously reported that neuronal overexpression of *egl-20* and *jmjd-1.2* robustly induces UPR^{mt} activation in the intestine. However, the loss of *ucr-2.3* suppresses this activation, indicating that *ucr-2.3* functions downstream of these established neuronal factors. To further explore the signaling pathways mediating communication between the germline and neurons, the researchers conducted a targeted RNA interference (RNAi) screen. They identified lipid synthesis and transport pathways as key components of cell-nonautonomous UPR^{mt} signaling. However, it remains speculative which specific lipid molecules, if any,

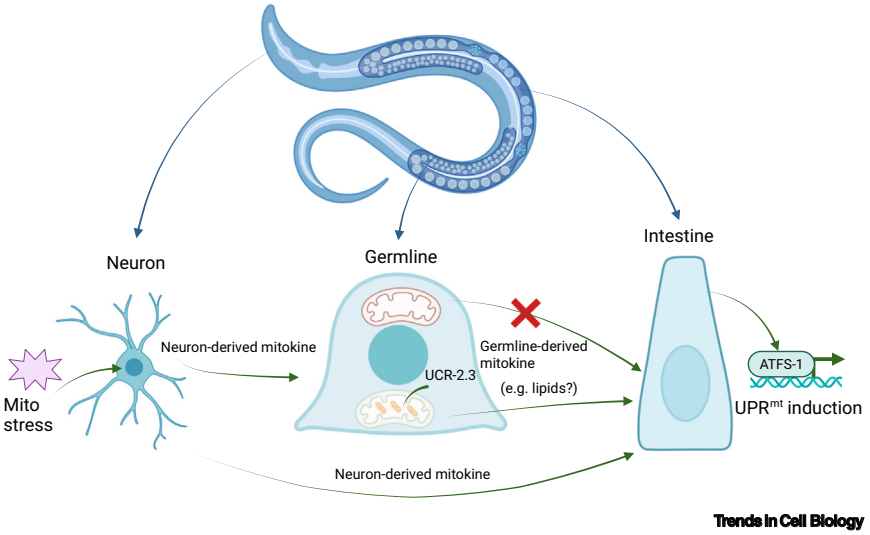

Figure 1. Model of neuron-to-intestine mitochondrial unfolded protein response (UPR^{mt}) regulation mediated by the germline. The germline, including germline mitochondria and germline-expressed UCR-2.3, functions as a pivotal regulator for neuron-to-intestine cell-nonautonomous activation of the UPR^{mt}. In *Caenorhabditis elegans*, the nervous system, upon experiencing mitochondrial stress, initiates a mitokine signal to induce UPR^{mt} in the intestine. There are two potential pathways for neuron-to-intestine UPR^{mt} signal transduction: (i) the nervous system transmits a neuron-derived mitokine to the germline, which processes the signal possibly via the germline, germline mitochondria, or germline-expressed UCR-2.3, and subsequently transmits a germline-derived mitokine to the intestine to regulate UPR^{mt} activation; (ii) the nervous system directly communicates with both the germline and the intestine through neuron-derived mitokines. Additionally, mitokines transmitted from the germline to the intestine are crucial for the comprehensive induction of intestinal UPR^{mt}. The specific mitokine relayed from the germline to the intestine remains unidentified. This figure was created using BioRender (https://biorender.com/).

might be involved in the signal transfer from the germline to the intestine.

In a similar study, Charmpilas *et al.* studied the critical role of the germline in UPR^{mt} activation [11]. They investigated two temperature-sensitive mutants lacking functional germlines, which were subjected to RNAi-mediated depletion of *isp-1*, *cco-1*, and *spg-7*, or treated with the mitochondrial inhibitor antimycin to monitor UPR^{mt} activation. Compared with worms with functional germlines, those lacking germlines exhibited reduced UPR^{mt} activation. Additionally, they utilized *mes-1(bn7ts)* mutant worms, in which approximately half of the progeny are fertile, to validate the role of germline function in somatic UPR^{mt} activation. In the same genetic background, fertile *mes-1(bn7ts)* mutants exhibited robust UPR^{mt} induction, whereas sterile mutants did not. Additionally, treatments that ablate the intact germline, such as FUDR, ionizing radiation, and UV B radiation, led to a reduction in brood size and attenuated UPR^{mt} induction in somatic tissues. These findings demonstrate that an intact germline is crucial for the activation of somatic UPR^{mt}. Utilizing the same genetic model for cell-nonautonomous UPR^{mt} activation, the authors confirmed that the germline is crucial for the full-scale induction of cell-nonautonomous UPR^{mt}. To assess the effects of deficiencies in the somatic gonad, sperm, or oocytes on somatic UPR^{mt}, the researchers subjected gonad-, sperm-, and oocyte-deficient mutants to mitochondrial stress. All these mutants exhibited reduced UPR^{mt} inducibility. Notably, mating sperm-deficient mutants with wild-type males restored somatic UPR^{mt} activation, suggesting that reproductive capability is critical for somatic UPR^{mt} induction. Given that oocytes are essential for full-scale UPR^{mt} induction, the authors hypothesized that males might exhibit weaker inducibility of UPR^{mt} activation. This hypothesis was confirmed by subjecting males to mitochondrial inhibitors. Similar to previous studies, they demonstrated that germline-specific depletion of mitochondrial electron transport chain (ETC) components could induce somatic UPR^{mt} activation. However, unlike previous findings, this cell-nonautonomous UPR^{mt} induction did not correlate with lifespan extension. Investigating the regulatory mechanisms underlying lifespan changes influenced by germline-to-intestine cell-nonautonomous UPR^{mt} activation will be intriguing.

These two studies extend the role of the germline beyond reproduction, positioning it as a crucial regulator of mitochondrial health across the organism. The germline integrates mitokine signals from neurons and modulates lipid metabolism to activate UPR^{mt} in peripheral tissues (Figure 1), ensuring coordinated stress responses that optimize organismal health. These studies open avenues for potential therapeutic strategies aimed at preserving germline mitochondrial function to improve organismal health and extend lifespan.

Declaration of interests

No interests are declared.

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