to activate signaling pathways in isolated nuclei (Guilluy et al., 2014), and the nucleus is under constant actomyosin tension in cultured cells (Arsenovic et al., 2016). This raises the fascinating prospect that alterations in actin-nuclear connections may contribute to $cPLA_2$ translocation and eicosanoid signaling. Indeed, shear stress, which is imparted to the nucleus, activates $cPLA_2$ and eicosanoid signaling (Pearce et al., 1996).

As alterations in nuclear morphology are associated with numerous diseases (e.g., cancer) and mutations in proteins of the nuclear membrane and lamina cause a wide variety of diseases, it will be interesting to probe whether alterations in these mechanosensing systems contribute to the disease state.

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# Mitochondria: Masters of Epigenetics


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**Accumulating evidence argues that aging exerts a profound influence on epigenetics, and vice versa. A pair of studies by Merkwirth et al. and Tian et al. now provide insights on how mitochondrial stress experienced by *C. elegans* larvae propagates a specific and persistent epigenetic response that protects adult cells and extends lifespan.**


Transient early life stress impacts adult health in humans and animals alike. Children of women pregnant during the Dutch "hunger winter" of 1944 were not only smaller at birth, but also more susceptible to obesity, diabetes, and cardiovascular disease throughout their lives. Not all early life stresses produce pathology, however. Several animal models of mild early stress actually generate long-lived adults. For example, in mice, increasing normal litter size by 50% extends the subsequent lifespans of the pups (Sun et al., 2009). In *C. elegans*, experimentally induced mitochondrial stress during larval development increases adult lifespan (Dillin et al., 2002). Such stress experiences are thought to anticipate future conditions that require remodeling of the adult phenotype, and the concept of epigenetic regulation has recently been thrown around like a football at a Sunday picnic. In this issue of *Cell*, the groups of Dillin and Auwerx (Merkwirth et al., 2016; Tian et al., 2016) add some beef to these arguments by describing mechanisms that persistently reprogram genome function into a long-lived alternative state (Figure 1).

Mitochondrial stress can be experimentally induced in *C. elegans* by feeding RNAi disrupting the electron transport chain (ETC) (Dillin et al., 2002) or even by expressing a polyglutamine tract-containing protein in neurons alone (Brignull et al., 2006). Once induced during development, adults express a constellation of protective genes, including mitochondrial chaperones, quality control proteases, and xenobiotic response components that comprise the mitochondrial unfolded protein response ($UPR^{mt}$). These adults are also long lived by a factor of almost 2-fold. Previous studies established that the induction of $UPR^{mt}$ requires the transcription factors *atfs-1* and *dve-1*, the cofactor *ubl-5*, and the quality control protease *clpp-1*.

To understand how these responses are regulated Merkwirth et al. (2016) perform an RNAi screen spanning several chromosomes for genes required for lifespan extension in response to a knockdown of cytochrome C1 (*cyc-1*). In this way they identify *jmjd-1.2*, and using a candidate gene approach, the related *jmjd-3.1* gene. The encoded proteins belong to the family of histone lysine demethylases containing the Jumonji C domain, with overlapping specificity

toward histone H3K27me2 and me3 modifications. Eliminating either *jmjd-1.2* or *jmjd-3.1* function abrogates the ETC stress longevity response, but not the insulin/IGF, germline ablation, dietary restriction, and cytoplasmic or endoplasmic reticulum (ER) responses. *jmjd-1.2* and *jmjd-3.1* are shown to act upstream of the core transcriptional machinery involving *clpp-1*, *ubl-5*, *atfs-1*, *dve-1* that regulates UPR$^{mt}$ and to be required both for the initial establishment of this response during development as well as its propagation throughout adulthood. Overexpression of either *jmjd-1.2* or *jmjd-3.1* is sufficient to induce the UPR$^{mt}$ response and extend lifespan, with both effects being dependent on demethylase catalytic activity. Remarkably, overexpression of *jmjd-1.2* in neurons induces UPR$^{mt}$ in the intestine, and overexpression in neurons but not other tissues elicits lifespan extension.

To extend these findings to mammalian physiology, Merkwirth at al. examine the large database of physiological and molecular phenotypes generated from the BXD reference panel (isogenic recombinant inbreds from a cross of C57BL/6J and DBA/2J strains) (Andreux et al., 2012). *jmjd-1.2* and *jmjd-3.1* are highly conserved in evolution, the mouse homologs being *Phf8* and *Jmjd3*, respectively. In the BXD panel, *Phf8* and *Jmjd3* expression are positively correlated with each other, and with UPR$^{mt}$ related genes. Modulating *Phf8* and *Jmjd3* expression in cell lines impacts the regulation of several UPR$^{mt}$ genes, and PHF8 and JMJD3 can be localized to the relevant promoter regions. These data suggest that PHF8 and JMJD3 may regulate UPR$^{mt}$ in mammals.

In an accompanying paper Tian et al. (2016) perform a suppressor screen to find mutants unable to induce a UPR$^{mt}$ reporter in the intestine in response to the expression of a polyQ protein in neurons. Sixteen mutant strains are obtained, from which the *lin-65* gene is analyzed in detail. LIN-65 is a synmuvB protein of unknown biochemical function that is loosely grouped with chromatin modifiers. lin-65 is shown to be required specifically for UPR$^{mt}$ but not other forms of UPR. After ETC stress LIN-65 protein became abundant and nuclear in intestinal cells, and this accumulation requires the H3K9me1/2 methyltransferase *met-2*, a homolog of mammalian SETDB1. H3K9me2 levels are indeed reduced in stressed *lin-65* animals, and the chromatin compaction normally seen during ETC stress is also reduced.

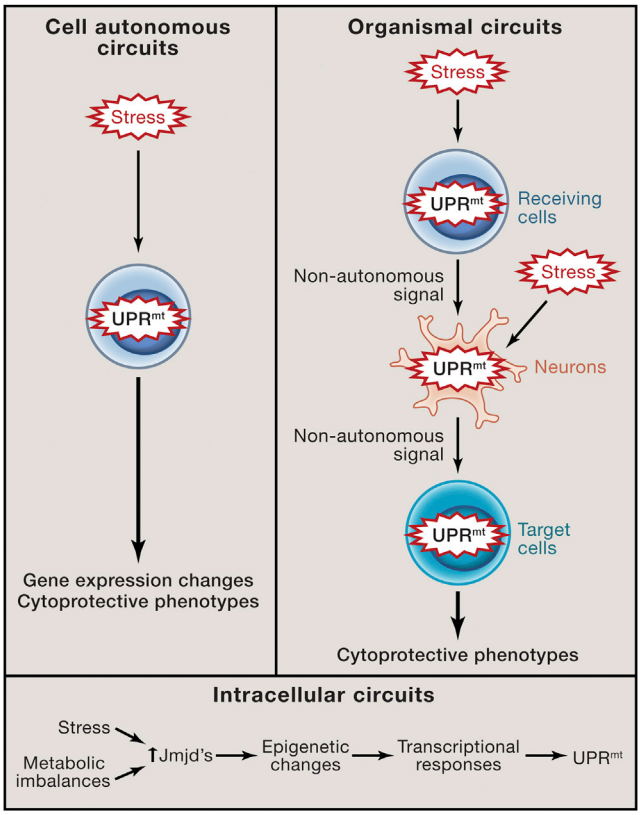


**Figure 1. Non-autonomous Communication of UPR$^{mt}$ Mediates Systemic Epigenetic Changes**

The mitochondrial unfolded protein response (UPR$^{mt}$) is mediated in part by epigenetic changes that enable a protective transcriptional program in response to environmental stresses. These circuits can operate in a cell autonomous manner, but under some conditions, such as when the inputs are received during specific times in development, UPR$^{mt}$ can also be propagated throughout the organism. The central nervous system plays a key role in this cell non-autonomous signaling to distal tissues. At the cellular level, specific histone lysine methylases and demethylases, as well as other chromatin-associated proteins, orchestrate the epigenetic changes. Many aspects of these complex networks, such as the nature of the cell non-autonomous signals, remain to be elucidated.

These changes enabled the UPR$^{mt}$ response by displacing the stress responsive transcription factor DVE-1 away from H3K9me2-enriched heterochromatin toward more open regions, where it is found to condense into puncta, presumably to regulate its target genes. Indeed, the UPR$^{mt}$ response, involving over 1,000 genes, is largely abrogated in *lin-65* or *met-2* animals. Critical for the model of epigenetic reprograming, *lin-65* is required only in larval stages for early stress to induce persistent activation of DVE-1 and UPR$^{mt}$-related transcription in adults. And central to the concepts for aging, *lin-65* is required for ETC-disrupting RNAi treatments to fully extend lifespan, although *lin-65* mutants are somewhat short lived on their own.

As is typically the case, profound new insights raise many new questions. What exactly are the "stresses" that elicit these responses in free-living animals under natural conditions? The triggers are likely to be both environmental as well as endogenous. It makes sense to endow neurons with the task of communicating stresses to the rest of the body, but to perceive the initial stress, especially from the environment, cells at the periphery (epidermis, intestine) would seem more appropriate in many organisms. In terms of molecular mechanisms, we are also likely to be just seeing the tip of the iceberg. More players in epigenetic pathways are likely to be involved, and additional triggers, such as other UPR systems, DNA damage, etc., have their own surveillance and protective responses. Interference with several basic macromolecular processes, such as transcription or translation, has been linked to the induction of cytoprotective pathways, broadly linked with longevity (Shore and Ruvkun, 2013). It should also be noted that in some cases (such as

the *C. elegans* UPR$^{mt}$), while the animals are long-lived, they are delayed developmentally and reproductively, and appear to display some physiological compromises in late life (Dillin et al., 2002; Durieux et al., 2011).

Mitochondria have been implicated in the process of aging across generations of research. A long march of ideas has been explored, including the rate of living hypothesis, the free radical theory, mitochondrial DNA mutation, etc., but how mitochondria affect lifespan is still far from settled. The new studies from the Dillin and Auwerx groups discussed here, along with previous work, now provide one possible solution filled with unexpected mechanisms and interesting implications: mitochondria in a few cells, neurons in particular, perceive "stress" and propagate largely unknown systemic signals to induce epigenetic change in peripheral tissues that induce UPR$^{mt}$ and extend lifespan.

The inputs required to set this process into motion have unique qualities. To extend lifespan the timing of the challenge must be of a specific magnitude, and occur during the L3 to L4 transition when germline compartment mitochondria are rapidly proliferating. Mitochondrial stress is well known to produce retrograde signaling that elicits nuclear-based responses, and imbalances on the mitochondrial side are known to induce a UPR$^{mt}$ response (Houtkooper et al., 2013). A new twist to these ideas is that mitochondria may also assess the readiness of cells to generate essential proteins for their proliferation when demand is great. Given that most mitochondrial proteins are nuclear-encoded and translated on cytoplasmic ribosomes, a deficit in their supply might be perceived much like the RNAi interventions used by Merkwirth et al. and Tian et al.

When this roll call is weak, the mitochondria would provoke the sensing cell to generate systemic signals that induce epigenetic changes for a UPR$^{mt}$ response in distant tissues. In contrast to retrograde signaling, where stressed mitochondria call upon the supporting nuclear genome, Dillin and Auwerx describe a cell non-autonomous epigenetic process where mitochondria react to stress in sentinel cells and modify nuclear chromatin across the animal to provide protection for their distant brethren. Adults with these modifications are long lived, but one is left to wonder whom this process has evolved to benefit.

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