QUALITY CONTROL

Mitochondrial UPR through generations

Neuronal mitochondria perturbation elicits a mitochondrial unfolded protein response (UPR^{mt}) in peripheral tissues cell non-autonomously, dependent on the Wnt signalling pathway. A study now reveals that a Wnt-mediated increase in maternally inherited mitochondria DNA is responsible for transgenerational UPR^{mt} induced by neuronal mitochondria perturbation.

Mooncheol Park and Meng C. Wang

All organisms have to adapt to environmental variations, especially harsh ones. In response to environmental stress, animals change their physiological and behavioural strategies for a better chance at survival[1]. Recent studies showed that these adaptive responses can be passed on to multiple generations using maternal provisioning, and this transgenerational inheritance can aid descendants to survive better in similar stressful conditions[2]. Then, what cellular materials can be used for transmitting transgenerational information? In *Caenorhabditis elegans* (*C. elegans*), the memorised avoidance behaviour to pathogenic bacteria *Pseudomonas aeruginosa* (PA14) is transmitted across about four generations, which is mediated by the Piwi/PRG-1 argonaute-dependent piRNA (Piwi-interacting RNA) pathway and the TGF-β ligand DAF-17 generated in ASI sensory neurons[3]. A temperature-induced expression change in a *C. elegans* heterochromatic gene array can be transmitted across at least 14 generations, which is associated with trimethylation of histone H3 lysine 9 (H3K9me3)[4]. In this issue of *Nature Cell Biology*, Zhang et al.[5] discovered that mitochondrial unfolded protein response (UPR^{mt}) in the periphery, initially caused by the perturbation of neuronal mitochondria, is transmitted across multiple generations through the maternal inheritance of increased mitochondria DNA (mtDNA) levels. This transgenerational effect requires the Wnt signalling pathway, and descendants that inherit those higher levels of mtDNA and UPR^{mt} exhibit benefits of lifespan extension and enhanced stress resistance.

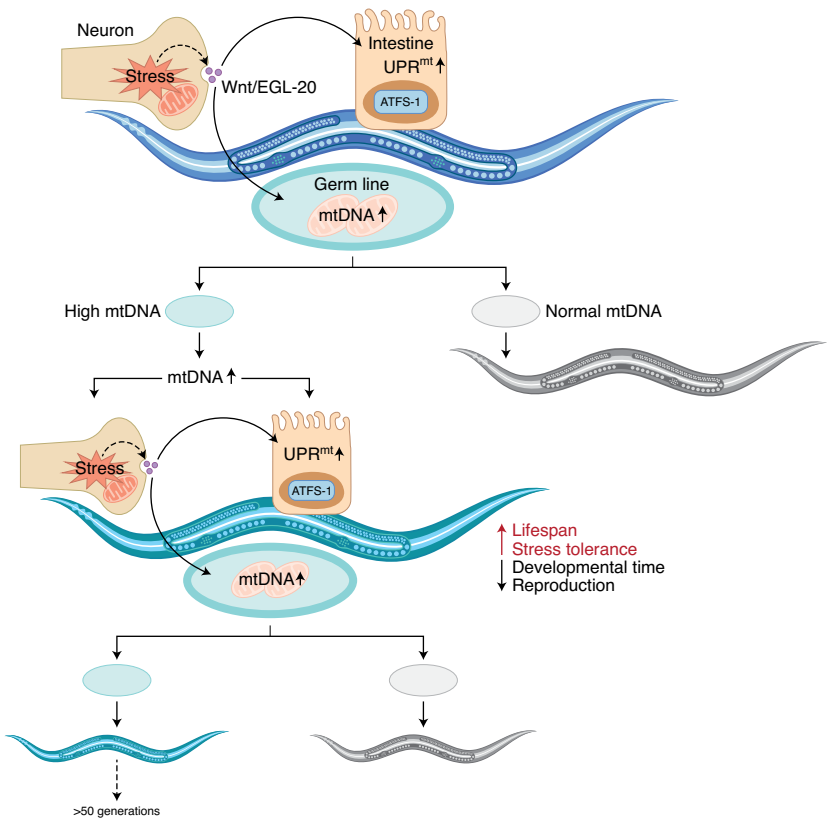

Fig. 1 | Transgenerational induction of UPR^{mt} mediated by increased mtDNA levels. In response to neuronal mitochondrial stress, the activation of Wnt signalling mediates the induction of UPR^{mt} in the peripheral tissue, like the intestine, and also leads to increased mtDNA levels in the germline. Through maternal inheritance, the increased mtDNA level is transmitted into some progeny, where it triggers the mitochondrial dysfunction and UPR^{mt} in all tissues including neurons. The mitochondrial dysfunction in neurons will again act through the Wnt signalling to increase mtDNA levels in the germline and continue the transgenerational inheritance. In each generation, increased mtDNA levels elicit UPR^{mt} via the ATFS-1 transcription factor in the periphery.

Mitochondria dysfunction elicits UPR^{mt}, which facilitates the recovery of mitochondrial integrity and the maintenance of mitochondrial proteostasis[6]. Previous studies showed that in *C. elegans*, expression of polyglutamine repeats (Q40) in neurons disrupts mitochondrial functions and induces UPR^{mt} in the peripheral intestine. This cell non-autonomous induction is mediated by neuronal Wnt and serotonin signalling[7,8], and neuronal expression of EGL-20, *C. elegans* Wnt, sufficiently triggers peripheral UPR^{mt} (ref. [8]). In those studies, a *hsp-6p::gfp* fluorescent reporter was used to visualise UPR^{mt} induction in the periphery. When the authors tracked animals with neuronal expression of Q40 or EGL-20, they discovered that the induction of the *hsp-6p::gfp* reporter was transmitted to their progeny carrying no Q40 or EGL-20 expression for more than

50 generations[5]. They found that neuronal knockdown of *cco-1*, a nucleus-encoded oxidative phosphorylation (OXPHOS) gene, also induced the transgenerational UPR^{mt}, but at low penetration[5]. On the other hand, knocking down *cco-1* in non-neuronal cells did not lead to UPR^{mt} induction over generations[5]. Consistent with maternal inheritance, this transgenerational induction of UPR^{mt} shows incomplete penetrance and heterogeneity among progeny and different generations[5]. It has been previously shown that maternally inherited mtDNA mutations also induce UPR^{mt} (refs. [9,10]). However, no pre-existing deleterious mtDNA mutations have been identified using mtDNA sequencing in the current study, excluding their contribution to the UPR^{mt} induction over generations.

Next, the authors addressed the molecular mechanisms underlying this transgenerational effect. Through whole-worm RNA sequencing analyses, they discovered that mtDNA-encoded OXHPOS genes, the Wnt signalling pathway, endogenous mitochondria chaperones, and mitochondria DNA polymerase were transcriptionally upregulated in the descendants with induced UPR^{mt} (ref. [5]). Furthermore, these animals exhibited increased mtDNA levels in the germline, but the induction level varied among individuals. Interestingly, the individual with a stronger UPR^{mt} induction showed a relatively higher level of mtDNA, and the one with a weaker UPR^{mt} induction gradually returned to the baseline level in about three generations. Notably, although these animals had increased mtDNA levels, mtDNA-encoded proteins were reduced compared to nucleus-encoded mitochondrial proteins, which is accompanied with decreased oxygen consumption rate and ATP production, as well as fragmented mitochondria in various tissues[5]. It is likely that this mitochondrial–nuclear protein imbalance leads to mitochondrial stress and triggers the UPR^{mt} activation in each generation; however, how increased mtDNA levels cause the mitochondrial–nuclear protein imbalance is currently unclear. Therefore, the authors asked whether a high mtDNA level is sufficient to induce UPR^{mt}. They cleverly took the advantage of wild *C. elegans* strains with higher mtDNA contents, ED3011 and KR314, and revealed the induction of UPR^{mt} in these strains and in their maternally derived intercrossed progeny[5].

A well-characterised regulator of UPR^{mt} is the ATFS-1 transcription factor that governs the transcriptional response upon mitochondrial dysfunction, including the induction of the *hsp-6p::gfp* reporter[11]. The authors found that the loss of ATFS-1 completely suppressed the induction of the *hsp-6p::gfp* reporter in the descendants, but did not affect the increased mtDNA levels or the mitochondrial–nuclear protein imbalance[5]. Once ATFS-1 was restored in the descendants with increased mtDNA levels, the induction of the *hsp-6p::gfp* reporter was fully recovered[5]. These results support the importance of increased mtDNA levels, but not induced UPR^{mt}, for the transmission of mitochondrial stress across generations. In each generation, increased mtDNA levels elicit UPR^{mt} via ATFS-1. On the other hand, the Wnt signalling pathway is known to mediate the cell non-autonomous induction of peripheral UPR^{mt} by neuronal mitochondrial dysfunction in *C. elegans*[8]. The authors found that the loss of Wnt signalling components, including the Wnt ligand/EGL-20, the Wnt secretion receptor/MIG-14, the retromer component/VPS-35, and β-catenin/BAR-1, completely suppressed the transgenerational induction of mtDNA levels and UPR^{mt}, as well as the mitochondrial-nuclear protein imbalance[5]. However, the other Wnt ligands—CWN-1, CWN-1 and LIN-44 and Wnt receptors, LIN-17 and MIG-1—are not involved in the regulation of these transgenerational effects[5]. Importantly, the regulatory effects of EGL-20 and BAR-1 are specifically related to their activities in neurons and the germline, respectively[5].

Based on these findings, a possible model (Fig. 1) is that neuronal mitochondrial dysfunction acts through the Wnt/EGL-20–β-catenin/BAR-1 signalling pathway to induce mtDNA levels in the germline cell non-autonomously, and through maternal inheritance, the increased mtDNA level is transmitted into the next generation and triggers the mitochondrial-nuclear protein imbalance and mitochondrial dysfunction in all tissues including neurons. The neuronal mitochondrial dysfunction in descendants will again increase mtDNA levels in the germline via the Wnt signalling and continue this transgenerational cycle until the mtDNA level returns to normal. Thus, the ability of the Wnt signalling to couple neuronal mitochondrial stress and germline mtDNA induction is key for this transgenerational inheritance. Strikingly, the authors revealed that the role of Wnt signalling in regulating mtDNA levels is well conserved in mammals. In the human HEK293T cell line, pharmaceutical activation of Wnt signalling increases mtDNA levels, which is dependent on two downstream effectors, β-catenin and Myc[5].

Mild mitochondrial stress is known to promote longevity in *C. elegans*[12]. Consistent with the induction of UPR^{mt}, the transgenerational descendants with elevated mtDNA levels exhibited extended lifespan and enhanced resistance to PA14 pathogenic infection, heat shock and oxidative stress[5]. At the same time, these descendants suffered from delayed development and reduced fecundity compared to those with normal mtDNA and UPR^{mt} levels[5]. Given that the penetrance of this mtDNA-mediated transgenerational inheritance is not 100%, the simultaneous presence of descendants with high and normal UPR^{mt} will offer adaptation diversification in the population to survive in upcoming environments.

In summary, Zhang et al. revealed the previously unappreciated role of the mtDNA level in mediating transgenerational stress inheritance and the evolutionally conserved activity of Wnt signalling in regulating mtDNA levels. ❐

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Competing interests

The authors declare no competing interests.