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AGEING

The yin and yang of mitochondrial dysfunction

Mitochondrial dysfunction is a hallmark of organismal ageing, but mild mitochondrial stress during development is also known to have beneficial effects, delaying the ageing process. This positive effect on lifespan has been linked to the activation of the mitochondrial unfolded protein response (UPR^{mt}), which is a stress response that leads to the transcriptional activation of nuclear genes, the products of which promote the recovery and regeneration of defective mitochondria. Three studies now provide important insights into mitochondrial function during ageing — they reveal a connection between mitochondrial dysfunction and age-related stem cell senescence and shed light on the epigenetic mechanisms underlying selective gene expression during UPR^{mt} activation and stress-induced longevity.

Reporting in *Science*, Auwerx and colleagues studied muscle stem cells in mice, which are quiescent cell populations that are activated to repair muscles following injury. Their regenerative capacity is reduced during ageing, and the authors assessed whether this may be due to defective mitochondria. Indeed, they found that the tricarboxylic acid and oxidative phosphorylation (OXPHOS) pathways were the most downregulated in stem cells from aged mice compared to young ones, indicating a decline in mitochondrial respiratory function during ageing. As mitochondrial dysfunction has been previously associated with a depletion of nicotinamide adenine dinucleotide (NAD^+), the authors treated old mice with nicotinamide riboside (NR), a precursor of NAD^+. Muscle stem cell numbers and regenerative capacity were substantially increased following NR treatment, which, as shown by reduced expression of senescence and apoptosis markers, protected cells against intrinsic cell senescence. This inhibition of senescence was associated with improved mitochondrial biogenesis and function (with increased OXPHOS). Moreover, expression of UPR^{mt} proteins, which was decreased in muscle stem cells from aged mice, increased following NR treatment. The authors found that this rejuvenating effect of NR treatment was dependent on prohibitins — stress-response proteins that sense mitochondrial stress and modulate senescence in other cell types. This work thus shows that mitochondrial oxidative respiration and the UPR^{mt} are important for the maintenance of functional adult stem cells.

Two other studies, published in *Cell*, report advances in understanding the molecular mechanisms by which the effects of mild mitochondrial dysfunction and the activation of the UPR^{mt} during early development can persist throughout the lifespan of an organism and promote longevity. In one study, Dillin and colleagues report that the activation of the UPR^{mt} in developing *Caenorhabditis elegans* following mitochondrial stress involved a global silencing of chromatin, through the activity of the histone methyltransferase MET-2 and a nuclear co-factor, LIN-65, which together lead to histone H3 Lys9 dimethylation. Moreover, MET-2 and LIN-65 were required for the transcription factor DVE-1 to localize to the nucleus and activate specific stress-response genes. Thus, MET-2 and LIN-65 induce epigenetic modifications that activate a stress-induced gene expression programme that can be transmitted to the whole organism and perpetuated in adult animals. Another joint study by the Dillin and Auwerx laboratories reports that two conserved histone demethylases, JMJD-1.2 and JMJD-3.1, activate the UPR^{mt} during *C. elegans* development, and that they coordinate a specific transcriptional response to enhance mitochondrial function that can be maintained throughout life and promotes longevity. This effect of these two histone demethylases on longevity was not only observed in the worm, but was reproduced in the BXD mouse genetic reference population.

Together, these findings provide insight into three aspects of mitochondrial biology with implications for ageing: they identify a mechanism by which stem cells could be rejuvenated by improving mitochondrial function and UPR^{mt} signalling and shed light on the molecular mechanisms that enable the beneficial propagation of UPR^{mt} signalling, which could be thus exploited for therapeutic purposes.

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ORIGINAL ARTICLES Zhang, H. *et al.* NAD^+ repletion improves mitochondrial and stem cell function and enhances life span in mice. *Science* http://dx.doi.org/10.1126/science.aaf2693 (2016) | Tian, Y. *et al.* Mitochondrial stress induces chromatin reorganization to promote longevity and UPR^{mt}. *Cell* http://dx.doi.org/10.1016/j.cell.2016.04.011 (2016) | Merkwirth, C. *et al.* Two conserved histone demethylases regulate mitochondrial stress-induced longevity. *Cell* http://dx.doi.org/10.1016/j.cell.2016.04.012 (2016)