AGEING

Mitochondria and telomeres come together

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“telomere dysfunction can lead to defects in mitochondrial biology”

There are mixed views as to what makes us age: one hypothesis proposes that ageing is caused by accumulating genotoxic stress provoked by the progressive loss of telomeres, which leads to replicative senescence and apoptosis, whereas another postulates that ageing is the result of progressive mitochondrial malfunction. A study by DePinho and colleagues now brings these two theories together by identifying a direct molecular link between telomere and mitochondrial dysfunction.

In highly proliferative tissues, age-related telomere decline is associated with telomere dysfunction and

activation of p53-mediated growth arrest and apoptosis, leading to organ atrophy. To investigate the mechanism underlying the physiological decline of more quiescent tissues, such as heart and liver, the authors generated mice lacking telomerase reverse transcriptase (TERT). These were intercrossed for four generations, giving rise to offspring (G4 *Tert*^{-/-} mice) with severe telomere dysfunction and signs of premature ageing across different organs.

Next, the authors sought to identify the molecular mechanism underlying the effects of this telomere dysfunction. By comparing the transcriptomes of wild-type and G4 *Tert*^{-/-} mice, they observed that peroxisome proliferator-activated receptor-γ co-activator 1α (PGC1α) and PGC1β (two known regulators of mitochondrial biogenesis and function) were repressed in G4 *Tert*^{-/-} mice, as were their target genes. Consistent with this, the hearts and livers of G4 *Tert*^{-/-} mice had decreased mitochondria numbers and mitochondrial DNA (mtDNA) copy numbers, increased production of mitochondrial reactive oxygen species (ROS), decreased levels of ROS-detoxifying enzymes and reduced rates of respiration and ATP production. These changes depended on the degree of telomere attrition and dysfunction, as G1 *Tert*^{-/-} mice displayed only mild PGC1 repression; this suggests that repression of PGC1α and PGC1β leads to mitochondrial dysfunction.

Similar findings were obtained *in vivo*: G4 *Tert*^{-/-} mice showed decreased mitochondrial biogenesis, impaired glucose production and

cardiomyopathy, phenotypes that are consistent with PGC1α and PGC1β repression. Furthermore, introduction of either TERT or PGC1α in the livers of G4 *Tert*^{-/-} mice *in vitro* and *in vivo* led to rescue of gluconeogenesis and increased respiration 5 days and 1 week after treatment, respectively.

Interestingly, the authors found that the effects of telomere dysfunction on mitochondria are mediated by p53-induced PGC1α and PGC1β repression. Indeed, loss of p53 in G2 mice lacking telomerase RNA component, which have the same telomere-related phenotypes as G4 *Tert*^{-/-} mice, restored PGC1α and PGC1β expression, as well as mtDNA copy numbers. Furthermore, G4 *Tert*^{-/-} mice lacking p53 had higher gluconeogenic capacity in the liver and reduced severity of cardiomyopathy than G4 *Tert*^{-/-} mice with intact p53. These data establish that p53 activation leads to PGC1α and PGC1β repression and, consequently, to the phenotypes associated with PGC1 deficiency.

So, it seems that telomere dysfunction can lead to defects in mitochondrial biology that are mediated by p53-induced PGC1α and PGC1β repression. The authors propose that the multi-system decline caused by telomere dysfunction is contributed both by the compromise in mitochondrial and metabolic activity following PGC1α and PGC1β repression and by the activation of apoptotic and proliferative checkpoints.

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ORIGINAL RESEARCH PAPER Sahin, E. et al. Telomere dysfunction induces metabolic and mitochondrial compromise. *Nature* **470**, 359–365 (2011)