

MITOCHONDRIAL FUSION PROTECTS MTDNA STABILITY AND PROVIDES TOLERANCE TO MUTATIONS

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Mutations in mitochondrial DNA (mtDNA) cause a spectrum of maternally inherited diseases and are thought to be central to the aging process. It is therefore important to identify factors that safeguard mtDNA stability. We show here that mice lacking both *Mfn1* and *Mfn2* in muscle have a 14-fold reduction in mtDNA levels and, remarkably, have accumulation of mtDNA point mutations and deletions. These mice have severe muscle atrophy with loss of respiratory activity, and die by 8 weeks of age.

With normal levels of mitochondrial fusion, mice carrying an error prone mtDNA polymerase (PolgD257A) can tolerate a heavy mtDNA mutational load into adulthood. However, when mitochondrial fusion is reduced, synthetic neonatal lethality results. Cells from such mice have severely reduced respiratory capacity.

These results indicate that mitochondrial fusion is important for maintaining the levels and fidelity of mtDNA. Furthermore, when levels of mtDNA mutations are elevated, robust mitochondrial fusion is necessary to preserve respiratory function. Therefore, mitochondrial fusion is likely a protective factor in the aging process and mtDNA diseases.