Deceleration of fusion-fission cycles improves mitochondrial quality control during aging.

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Details

Abstract

Mitochondrial dynamics and mitophagy play a key role in ensuring mitochondrial quality control. Impairment thereof was proposed to be causative to neurodegenerative diseases, diabetes, and cancer. Accumulation of mitochondrial dysfunction was further linked to aging. Here we applied a probabilistic modeling approach integrating our current knowledge on mitochondrial biology allowing us to simulate mitochondrial function and quality control during aging in silico. We demonstrate that cycles of fusion and fission and mitophagy indeed are essential for ensuring a high average quality of mitochondria, even under conditions in which random molecular damage is present. Prompted by earlier observations that mitochondrial fission itself can cause a partial drop in mitochondrial membrane potential, we tested the consequences of mitochondrial dynamics being harmful on its own. Next to directly impairing mitochondrial function, pre-existing molecular damage may be propagated and enhanced across the mitochondrial population by content mixing. In this situation, such an infection-like phenomenon impairs mitochondrial quality control progressively. However, when imposing an age-dependent deceleration of cycles of fusion and

fission, we observe a delay in the loss of average quality of mitochondria. This provides a rational why fusion and fission rates are reduced during aging and why loss of a mitochondrial fission factor can extend life span in fungi. We propose the 'mitochondrial infectious damage adaptation' (MIDA) model according to which a deceleration of fusion-fission cycles reflects a systemic adaptation increasing life span.

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