The Role of Genome Instability in Frailty: Mitochondria versus Nucleus

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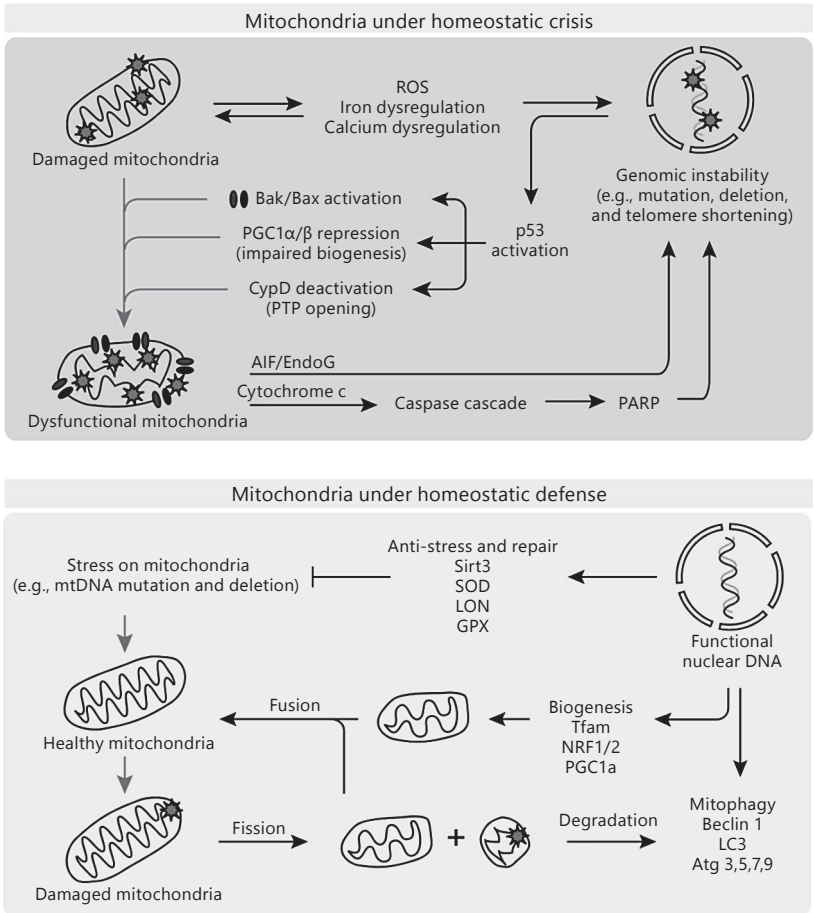
Late-life aging in humans is often associated with severe frailty. This suggests catastrophic events reaching an undeniable biological threshold in cellular stability and a rapidly diminished homeostasis. The driving force of the frailty syndrome is likely 'genetic instability' or 'genomic instability', a high frequency of mutations and deletions within the genome (both nuclear and mitochondrial DNA) of bodily somatic cells caused by DNA damage, and inefficient repair. Reactive oxygen species, calcium deregulation and iron dyshomeostasis are potential chemical triggers of nucleic acid sequence alterations and chromosomal rearrangements (fig. 1). These include mutations, deletions, translocations, chromosomal inversions, and single- and double-strand DNA breaks. Nuclear damage, such as telomere shortening, also appears to cause an abnormal

Fig. 1. Homeostatic interplay between mitochondria and nucleus for the maintenance of genomic integrity in aging cells. Age-associated mitochondrial damages (e.g. mitrochondrial DNA, mtDNA, mutations, and deletions) gradually increase mtDNA instability, which eventually augment nuclear DNA damage and genomic instability along with telomere shortening in aging cells. Without successful DNA damage repair, accumulating abnormalities in the genome (both mitochondria and nucleus) activate p53. Then, activated p53 increases cellular susceptibility towards cell death by inducing apoptosis-regulatory genes (e.g. Bax/Bak) and triggering mitochondrial permeability transition through opening of a channel, the permeability transition pore (PTP), on mitochondria. As a transcriptional repressor, p53 decreases mitochondrial biogenesis by inhibiting peroxisome proliferator-activated receptor-γ coactivator (PGC) 1α and PGC1β activity, leading to a global loss of mitochondrial structural/functional fidelity. Dysfunctional mitochondria also directly affect nuclear genome integrity by perturbing iron-sulfur cluster (ISC) biogenesis or activating regulators in subcellular endonuclease pathways [e.g. apoptosis-inducing factor (AIF), endonuclease G (EndoG), and poly(ADP-ribose) polymerase (PARP)]. In contrast, keeping healthy/functioning mitochondria allows aging cells to increase genome stability by homeostatic defense pathways. A coordinated interplay between mitochondrial dynamics, mitochondrial biogenesis, and degradation (i.e. mitophagy) would play a pivotal role in maintaining mitochondrial quality and genomic stability. CyD = Cyclophilin D.

(*For figure see next page.*)



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expression of several proteins, including p53, which leads to impaired mitochondrial biogenesis, mitochondrial permeability transition pore opening, apoptosis, and other biological events. Moreover, mitochondrial DNA damage could produce inaccurate translation and synthesis of proteins important for energy production in the inner mitochondrial membrane. Another cause of genomic instability may be a reduced expression and function of DNA repair genes, especially when stressful events trigger slow responses. With late-life frailty, overall endogenous damage occurs much more frequently and repair is much less efficient, which further accelerates genomic instability.