Abstract

Mitochondria are important cellular organelles of α-proteobacterial origin and pivotal in the evolution of eukaryotes. Although most mitochondrial proteins are encoded by the nucleus and imported into mitochondria, this organelle still retains a multicopy genome (mtDNA) which encodes essential proteins of the oxidative phosphorylation system (OXPHOS) in addition to the transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs). On one side, the mitochondrial genome requires considerable resources for mtDNA replication and maintenance to provide templates for mitochondrial gene expression and to ensure the transmission of the genome. On other side a balance between synthesis and degradation exists to ensure regulation of the multiple copies. However, it is still poorly understood what the molecular factors are that control mtDNA replication and copy number.

Here, I found that mitochondrial DNA polymerase gamma (POLG) regulates mtDNA copy number by operating in two opposing modes, synthesis and degradation of the yeast mitochondrial genome during nutrient starvation. The balance between synthesis and degradation depends on the homeostatic functions of autophagy. In autophagy-deficient cells, a combination of oxidative stress and nucleotide insufficiency impairs mtDNA synthesis and shifts POLG to mtDNA degradation in a manner dependent on the 3'-5'-exonuclease activity of POLG, resulting in mtDNA depletion and irreversible respiratory deficiency. Moreover, autophagy is not only required for mtDNA synthesis and stability but also for nuclear genome integrity. Autophagy deficient cells accumulate DNA damage, likely causing senescence. Strikingly, the absence of mtDNA in autophagy deficient cells leads to increase levels of DNA damage and, supports a model where mtDNA and autophagy are required for nuclear genome stability.