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Cell organelles

# Mitochondria quality control: preserving the cells' command center

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**Mitochondria are at the center of growing interest because of their deep connection to health, aging, and longevity. Recent discoveries have granted the mitochondrial genome (mtDNA) further functions than a genetic information keeper, influencing stress responses and cellular adaptation. Hence, maintaining the mtDNA integrity is pivotal to sustaining mitochondrial functions and cellular health. Here, we discussed the novel insights into the quality control mechanisms of the mitochondrial genome, highlighting a new step of control and future strategies to mitigate mitochondrial damage.**

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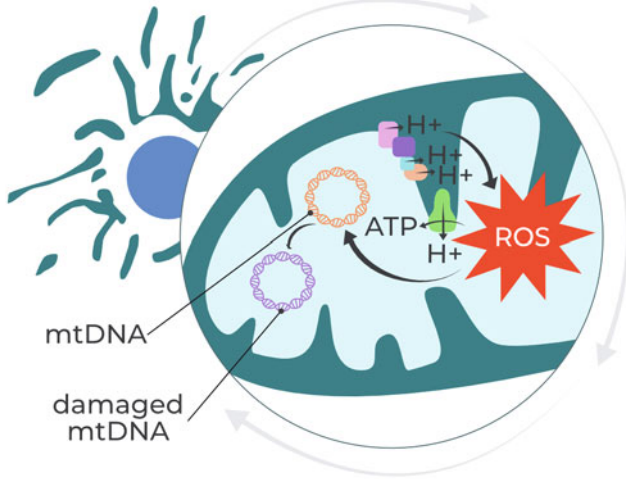
Classically understood as energy-producing organelles, mitochondria are particularly critical for the maintenance of all cells. Mitochondrial dysfunction is associated with a wide range of severe human pathologies, but also with more common conditions such as diabetes, and even with the natural process of aging [1]. As a result, the development of therapies targeting mitochondria has been a central focus in biomedical research, especially since the emergence of the molecular medicine era.

The recent rise in mitochondrial research has revealed that mitochondrial biology is far more complex than originally believed. Contrary to the simplified view presented in basic biology textbooks, cells do not contain just a few bean-shaped mitochondria. Instead, mitochondria form a highly dynamic network that can grow, fragment, change shape, and move throughout the cell, sometimes traveling considerable distances to meet local cellular demands. Moreover, mitochondria are not just energy-producing organelles. Now, mitochondria are recognized as central hubs for cellular signaling, functioning as the "command center" of the cell and coordinating dozens of cellular processes such as metabolic networks, immune signaling, and cell differentiation [2].

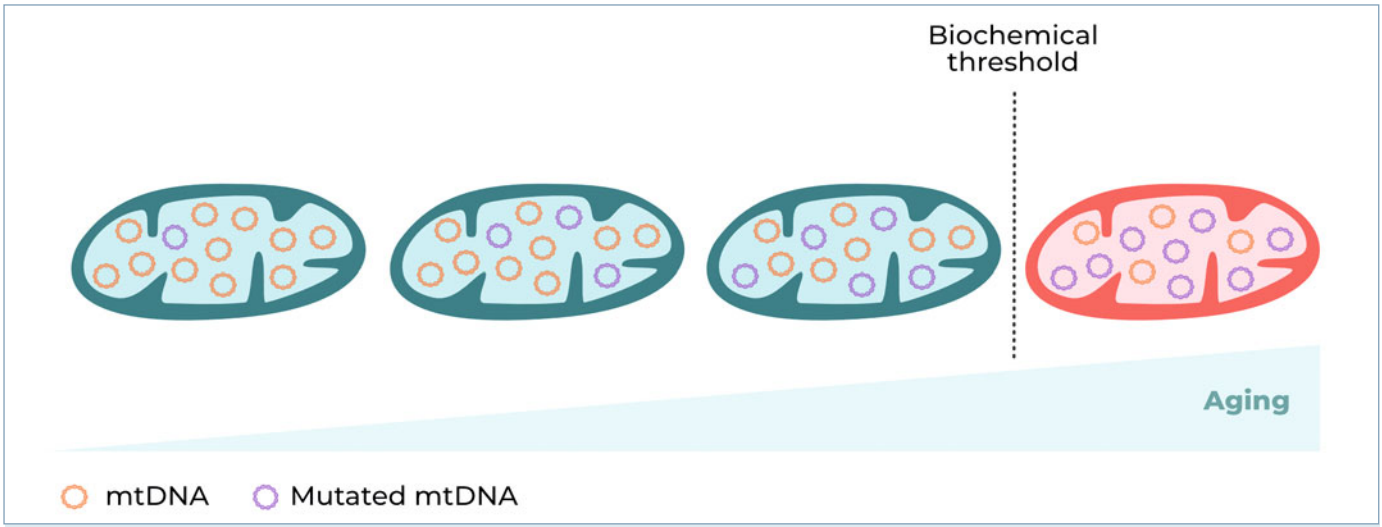



◀ **Fig. 1:** Schematic representation of the vicious cycle of mtDNA damage. The respiratory chain generates highly reactive oxidative species (ROS), which attack the mtDNA, causing biochemical alterations. These changes impair mitochondrial function, leading to increased ROS production that further damages mtDNA, perpetuating the cycle.

Reflecting their evolutionary origin from ancient proteobacteria, mitochondria contain their own DNA (mtDNA). Over millions of years of evolution, however, the number of genes retained in the mammalian mitochondrial genome has been drastically reduced to just 13 protein-coding genes, 22 tRNAs, and 2 rRNAs. These genes encode essential proteins of the core components of the mitochondrial energy production system, the respiratory chain.

Similar to the mitochondrial network, the mitochondrial genome is not static. Each cell contains hundreds to thousands of mtDNA copies, which can fluctuate and functionally support the mitochondrial dynamic system. Compared to other components in cells, mtDNA is especially susceptible to damage. This vulnerability is closely tied to oxidative metabolism. Albeit indispensable, this process comes with a risky byproduct: reactive oxygen species (ROS). These highly reactive molecules can cause significant damage to the mtDNA, modifying its chemical properties and disrupting mtDNA replication and transcription, potentially leading to mutations and transcriptional errors. This initiates a self-amplifying vicious cycle that threatens mitochondrial function, increases mtDNA damage, and ultimately disturbs cellular health (**Fig. 1**).

Interestingly, cells can tolerate the accumulation of some mtDNA mutations, as long as a sufficient number of intact copies remain, a phenomenon known as heteroplasmy of the mtDNA. However, under conditions of acute cellular stress or simply through the passage of time, the proportion of mutated molecules may increase by clonal expansion. When the balance shifts too far, and mutated mtDNA surpasses a functional threshold, mitochondrial dysfunction arises (**Fig. 2**). This phenomenon is especially pronounced




▲ **Fig. 2:** Heteroplasmy of mtDNA and the development of mitochondrial dysfunction. Wild-type (orange) and mutated mtDNA (purple) coexist within mitochondria. When, due to various stimuli or just by the natural aging process, the proportion of mutated mtDNA molecules surpasses a specific cellular threshold, mitochondrial dysfunction occurs.

in tissues such as skeletal muscle, sperm, ovaries, retina, and specific regions of the brain, like the substantia nigra, particularly prone to accumulating mtDNA damage.

One interesting phenomenon observed over the last decade is the ability of mtDNA to engage the immune system. Similar to bacterial DNA, mtDNA is a circular, double-stranded molecule that contains unmethylated CpG motifs, features that make it a potent trigger for innate immune sensors when released into the cytoplasm. Under stress conditions, mtDNA escapes from the organelle and activates pattern recognition receptors, such as cGAS-STING and toll-like receptors (TLR9). This immunogenic potential is of particular interest for understanding the mitochondrial contributions to disease conditions, including a low-level inflammatory stage occurring upon aging [3].

The progressive accumulation of mitochondrial damage is partially mitigated by the cellular recycling system. To maintain homeostasis, cells rely on a sophisticated network of mechanisms that selectively eliminate damaged proteins, macromolecules, and even entire organelles. A central pathway in this process is autophagy. During autophagy, a membrane-derived organelle called the autophagosome expands to sequester portions of cytoplasmic material targeted for removal. Further, the autophagosome fuses with a lysosome, a specialized compartment enriched with degradative enzymes, where the captured material is broken down into its basic molecular building blocks and recycled.

Mitochondria are not exempt from this process. The selective degradation of mitochondria is known as mitophagy. Although first characterized in yeast in the early 2000s, it took a couple of years to confirm its existence in mammalian cells [4]. The first well-characterized mitophagy pathway is now known as the PINK1–PARKIN pathway. Briefly, when mitochondria become dysfunctional, their inner membrane potential collapses, following a cascade of events that ultimately leads to the engulfment of the organelle in an autophagosome and lysosomal delivery for degradation.

Even before it was characterized in mammalian cells, mitophagy was proposed as a key mechanism for limiting the accumulation of somatic mutations of the mtDNA with aging [5]. In fact, mitophagy removal of the mtDNA is a key mechanism during erythropoiesis [6] and early embryogenesis [7]. However, the prevalence of macroautophagy of the mitochondria in the physiological context to maintain the mitochondrial network has long been debated. Is it necessary to remove an entire mitochondrion when there is only a defective part? Given the dynamic nature of the mitochondrial network, even with today's technologies, it remains difficult to define what exactly constitutes a single mitochondrion. If we consider a fully active segment of the network, mitochondria contain two membranes, hundreds of proteins assembled into functional complexes, metabolites, and a nucleoid, the mitochondrial chromosome, harboring from one to two copies of mtDNA. Then, is it really necessary to dismantle all of these components just because a group of proteins or mtDNA carry some errors?

This question has puzzled mitochondrial scientists for long, and finally, we may be approaching an answer. The selective degradation of mitochondria can also be selective for its components. The highly dynamic nature of the mitochondrial network enables the recruitment and isolation of damaged components within distinct regions, which are then recycled through various mechanisms of microautophagy, preserving the integrity of the remaining system. Thus, examples of these highly selective pathways include piecemeal mitophagy [8], and the formation of mitochondria-derived vesicles (MDVs, [9]). These processes represent a more refined level of control compared to the macroautophagy of entire organelles. Consequently, mitochondrial turnover is not merely a bulk cleanup process, but rather a sophisticated, multi-layered system (**Fig. 3**).

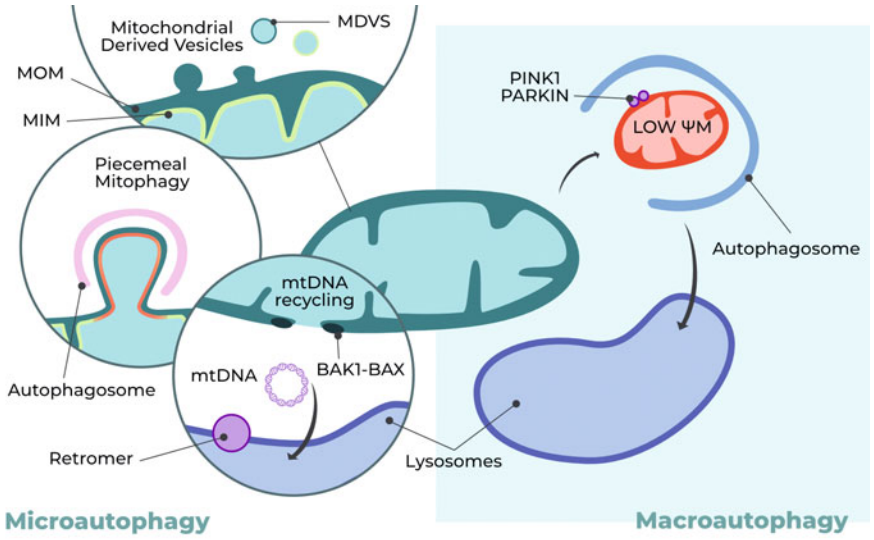
One particularly intriguing idea is that MDVs might help to eliminate defective mtDNA without invoking full mitophagy. Since its discovery as a stress-related mechanism, MDVs were proposed to work as a very selective quality control pathway [9]. MDVs can originate from various parts of the mitochondrion and may contain different material, depending on the nature of the stress. Yet, mtDNA has been found inside MDVs, although current evidence suggests that its presence may serve more of a signaling function rather than being part of a selective degradation process. For instance, cell-free

mtDNA (cf-mtDNA) found circulating in blood in certain cancers and other pathological conditions might escape the cells through MDVs, acting as an indicator of tissue damage [10].

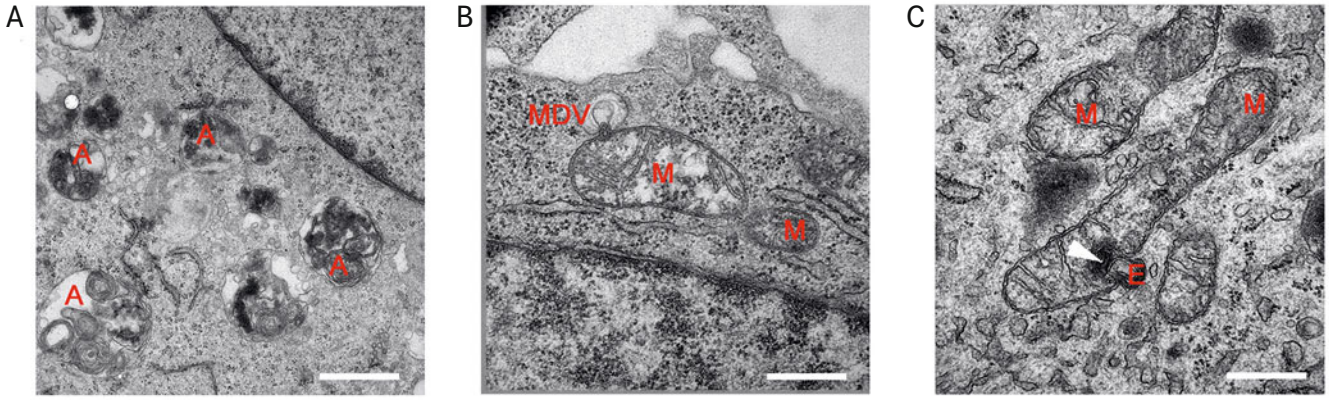
Nevertheless, mitochondria seem to possess alternative mechanisms for genome removal that do not require generating a vesicle. Upon a cell death stimulus, mtDNA can be ejected directly through a transient pore in the mitochondrial membrane, effectively "spitting out" the genetic material. These macropores, generated by the oligomerization of proteins such as VDAC1, BAK1, and BAX, trigger the ejection of the mitochondrial genome, either in small pieces or even the complete mitochondrial chromosome [3]. Release of the mtDNA initiates the engagement of cytoplasmic immune sensors for cytosolic DNA and, eventually, the cell death cascade.

Today we know that this process is not exclusive to cell death. Our group described that mtDNA can be selectively eliminated through an endo-lysosomal pathway, independent of autophagosome formation [11]. Thus, oxidative damage in the mtDNA triggers the activation of mtDNA quality control, characterized by the accumulation of autolysosomes, formation of MDVs, and transfer of the mitochondrial genome to endosomes (**Fig. 4**). More recently, we demonstrated that mitochondrial nucleoids eject through membrane pores and are rapidly encapsulated within lysosomes [12]. In other words, the coordinated interaction between the cell's vesicular system and mitochondrial pores enables the controlled ejection of the mitochondrial genome. This might allow the removal of specific mtDNA damage without compromising the overall mitochondrial pool, thereby providing a selective quality control mechanism that prevents the accumulation of defective genomes.

Since the rise of the molecular biology era, quality control mechanisms of the cell have emerged as key therapeutic targets. Compounds such as rapamycin and metformin are known to stimulate autophagy and are currently under investigation for their therapeutic potential [13, 14]. However, both the broad, non-selective activation of autophagy and the interference with the cellular metabolism might potentially lead to profound alterations in nutrient sensing and systemic energy balance, which may ultimately limit their therapeutic applicability. This brings




▲ **Fig. 3:** Comparison of two major branches of mitochondrial quality control. In macroautophagy, mitochondrial depolarization triggers the recruitment of specific proteins, such as PINK1 and PARKIN, to the mitochondrial membrane. This initiates the formation and engulfment of the entire mitochondrion into an autophagosome, which subsequently fuses with the lysosome for degradation and recycling. In contrast, microautophagy selectively targets specific mitochondrial compartments or proteins for removal. This category includes pathways such as mitochondria-derived vesicles (MDVs), piecemeal mitophagy, and the recently described selective removal of mitochondrial DNA (mtDNA).




▲ **Fig. 4:** mtDNA quality control. Transmission electron microscope (TEM) pictures of C2C12 myoblasts expressing the mitochondrial protein Twinkle fused with APEX2 and treated with ethidium bromide. APEX2 technology can be used in TEM to detect specific proteins or cellular sub-compartments by inducing DAB deposition and enhancing contrast. Activation of quality control upon mtDNA replication stress can be observed by (**A**) presence of auto-lysosomes containing cellular components, (**B**) formation of MDVs and, (**C**) transfer of nucleoids to endosomes. A: autolysosomes containing different cellular components; M: mitochondria; MDV: mitochondrial-derived vesicle; E: endosome. White arrow: mitochondrial nucleoid contrasted with APEX2. Scale bars: 500 nm.

forth a critical question: Is it possible to specifically enhance the removal of damaged mitochondrial components while preserving the overall mitochondrial network pool and cellular integrity?

Among recent discoveries in the mitochondrial quality field, the retromer protein complex has emerged as a promising candidate. Traditionally associated with vesicle trafficking and lysosome maturation, the retromer is starting to be recognized as a contributor to cellular health. Increased retromer expression accelerates the recycling mechanisms, improving cellular performance in several systems, from Parkinson´s disease to Alzheimer´s and ALS [15]. Notably, increased retromer expression also restores mtDNA damage and improves mitochondrial health, at least in proof-of-concept studies [12]. Using the model organism *Drosophila*, we manipulated the genome to generate high levels of mtDNA deletions in the larval epidermis. Remarkably, retromer overexpression selectively eliminated these mtDNA deletions and restored homeostasis [12].

In conclusion, targeting specific components of the mitochondrial network, including defective mtDNA, offers promising therapeutic strategies. Specific elimination of faulty components rather than the complete organelle might help to prevent mitochondrial dysfunction and also the downstream consequences of this damage. Yet, the challenge ahead lies in ensuring selectivity and long-term safety. Translating these findings from model organisms into humans will require the development of precise tools to manipulate mitochondrial quality without disrupting the delicate equilibrium of cellular homeostasis. Addressing these limitations will be critical for advancing this emerging field toward safe and effective therapeutic applications.

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