What is the Whole Mitochondrial Control Circuit?

The **whole mitochondrial control circuit** is the integrated network that builds, repairs, remodels, surveils, and clears mitochondria to keep a healthy mitochondrial population.

It is broader than energy production alone: the circuit links **biogenesis, fusion-fission dynamics, mitophagy, proteostasis, import surveillance, signaling, and backup disposal routes** into one homeostatic system (Ye et al., 2025; Liu et al., 2024; Ng et al., 2021; Choong et al., 2020).

Core Circuit

The core of the circuit is usually defined as **biogenesis, dynamics, and mitophagy** (Liu et al., 2024; Ye et al., 2025; Chang et al., 2023; et al., 2020). Biogenesis replenishes the pool by coordinated nuclear and mitochondrial gene expression (Liu et al., 2024; Ye et al., 2025; Martínez-Reyes & Chandel, 2020). Fusion lets partially damaged mitochondria mix contents and preserve function, whereas fission segregates injured parts for removal (Liu et al., 2024; Ye et al., 2025; Zerihun et al., 2023).

Mitophagy removes mitochondria that cannot be repaired, typically through lysosomal degradation (Liu et al., 2024; Ye et al., 2025; et al., 2020; Eldeeb et al., 2022). The cycle is closed when degraded components are renewed through protein synthesis and fresh mitochondrial biogenesis (Liu et al., 2024; Ye et al., 2025).

Additional Layers

Circuit Layer	What It Does	Example Evidence
Protein QC	Refolds or degrades damaged mitochondrial proteins	Chaperones, proteases, UPS, mitoproteases (Eldeeb et al., 2022; Song et al., 2020)
Import QC	Monitors protein entry and removes mislocalized preproteins	Entry-gate ubiquitylation, deubiquitylation, degradation (Schulte et al., 2023)
Selective Cargo QC	Removes local damage without clearing whole organelles	**MDV pathway** complements mitophagy (Collier et al., 2025)
Backup Disposal	Exports impaired mitochondria when mitophagy is perturbed	**Extracellular release** rises when autophagy fails (Choong et al., 2020)

FIGURE 1 Major layers of the whole mitochondrial control circuit beyond the canonical triad.

The circuit therefore includes **proteostasis** in addition to organelle turnover. Mitochondrial chaperones can refold unstable proteins, while proteases, the ubiquitin-proteasome system, and mitochondria-associated degradation eliminate proteins that cannot be repaired (Eldeeb et al., 2022; Song et al., 2020; Ng et al., 2021). Import quality control is also part of the circuit because proper function depends on synchronized nuclear-mitochondrial gene expression and efficient protein import, with dedicated pathways removing stalled or misdirected precursors at the entry gate (Song et al., 2020; Schulte et al., 2023).

Control Logic

The circuit is **damage-graded** rather than all-or-none. Mild damage can be buffered by fusion and local repair, more persistent damage is partitioned by fission, and severe damage triggers whole-organelle mitophagy (Ng et al., 2021; Collier et al., 2025). Some damage is handled even more selectively through mitochondrial-derived vesicles, showing that MQC is not limited to whole-mitochondrion turnover (Collier et al., 2025).

This circuit is tightly linked to **cell-fate signaling**. Mitochondria regulate ROS, calcium, apoptosis, immunity, and metabolite signaling, and failed quality control can release mtDNA, cytochrome c, and other danger signals that drive inflammation or cell death (Ye et al., 2025; et al., 2020; Martínez-Reyes & Chandel, 2020). TCA-cycle metabolites also act as retrograde signals to the nucleus, so the circuit helps determine not only mitochondrial quantity and shape but broader transcriptional and stress responses (Martínez-Reyes & Chandel, 2020).

Why “Whole”

“Whole” matters because the system works as an **interconnected network**, not as isolated modules (Ye et al., 2025; Ng et al., 2021; Chang et al., 2023). Different lesions recruit different routes, including mitophagy-dependent clearance, receptor-dependent pathways, metabolite-sensitive regulation, and even extracellular mitochondrial expulsion when canonical clearance is insufficient (Zhang et al., 2021; Choong et al., 2020).

The whole mitochondrial control circuit is therefore the full **homeostatic decision system** that senses mitochondrial damage, repairs what is salvageable, separates what is defective, removes what is irreparable, rebuilds the network, and signals cellular stress state to the rest of the cell. That is why reviews describe it as the machinery that preserves mitochondrial integrity and homeostasis, not just ATP production (Liu et al., 2024; Ye et al., 2025; Zhang et al., 2021).

References

K., Chen, G., Li, W., Kepp, O., Zhu, Y., & Chen, Q. (2020). Mitophagy, Mitochondrial Homeostasis, and Cell Fate. *Frontiers in Cell and Developmental Biology, 8*. https://doi.org/10.3389/fcell.2020.00467

Chang, X., Liu, R., Li, R., Peng, Y., Zhu, P., & Zhou, H. (2023). Molecular Mechanisms of Mitochondrial Quality Control in Ischemic Cardiomyopathy. *International Journal of Biological Sciences, 19*, 426 - 448. https://doi.org/10.7150/ijbs.76223

Choong, C., Okuno, T., Ikenaka, K., Baba, K., Hayakawa, H., Koike, M., Yokota, M., Doi, J., Kakuda, K., Takeuchi, T., Kuma, A., Nakamura, S., Nagai, Y., Nagano, S., Yoshimori, T., & Mochizuki, H. (2020). Alternative mitochondrial quality control mediated by extracellular release. *Autophagy, 17*, 2962 - 2974. https://doi.org/10.1080/15548627.2020.1848130

Collier, C. L., Ruedi, C., Thorne, N. J., & Tumbarello, D. A. (2025). PINK1 Loss of Function Selectively Alters the Mitochondrial-Derived Vesicle Pathway. *FASEB BioAdvances, 7*. https://doi.org/10.1096/fba.2024-00200

Eldeeb, M. A., Thomas, R. A., Ragheb, M. A., Fallahi, A., & Fon, E. (2022). Mitochondrial quality control in health and in Parkinson's disease.. *Physiological reviews*. https://doi.org/10.1152/physrev.00041.2021

Liu, B.-H., Xu, C., Liu, Y., Lu, Z.-L., Fu, T.-L., Li, G.-R., Deng, Y., Luo, G., Ding, S., Li, N., & Geng, Q. (2024). Mitochondrial quality control in human health and disease. *Military Medical Research, 11*. https://doi.org/10.1186/s40779-024-00536-5

Martínez-Reyes, I., & Chandel, N. (2020). Mitochondrial TCA cycle metabolites control physiology and disease. *Nature Communications, 11*. https://doi.org/10.1038/s41467-019-13668-3

Ng, M. Y. W., Wai, T., & Simonsen, A. (2021). Quality control of the mitochondrion.. *Developmental cell*. https://doi.org/10.1016/j.devcel.2021.02.009

Schulte, U., Brave, F. D., Haupt, A., Gupta, A., Song, J., Müller, C. S., Engelke, J., Mishra, S., Mårtensson, C. U., Ellenrieder, L., Priesnitz, C., Straub, S. P., Doan, K. N., Kulawiak, B., Bildl, W., Rampelt, H., Wiedemann, N., Pfanner, N., Fakler, B., & Becker, T. (2023). Mitochondrial complexome reveals quality-control pathways of protein import. *Nature, 614*, 153 - 159. https://doi.org/10.1038/s41586-022-05641-w

Song, J., Herrmann, J., & Becker, T. (2020). Quality control of the mitochondrial proteome. *Nature Reviews Molecular Cell Biology, 22*, 54 - 70. https://doi.org/10.1038/s41580-020-00300-2

Ye, L., Fu, X., & Li, Q. (2025). Mitochondrial Quality Control in Health and Disease. *MedComm, 6*. https://doi.org/10.1002/mco2.70319

Zerihun, M., Sukumaran, S., & Qvit, N. (2023). The Drp1-Mediated Mitochondrial Fission Protein Interactome as an Emerging Core Player in Mitochondrial Dynamics and Cardiovascular Disease Therapy. *International Journal of Molecular Sciences, 24*. https://doi.org/10.3390/ijms24065785

Zhang, T., Liu, Q., Gao, W., Sehgal, S. A., & Wu, H. (2021). The multifaceted regulation of mitophagy by endogenous metabolites. *Autophagy, 18*, 1216 - 1239. https://doi.org/10.1080/15548627.2021.1975914