

33. The Mitochondrial-Nuclear Crosstalk in Eukaryotic Evolution and Disease

1 unit, Agnel Sfeir, October 16, 2025

I. Introduction: The Endosymbiotic Legacy and Its Modern Consequences

- A. Evolutionary Context of Genome Coordination
- B. Fundamental Differences Between Mitochondrial and Nuclear Genetic Systems
- C. Why Retain the Mitochondrial Genome?

II. Fundamental Principles of Mitochondrial DNA Maintenance and Expression

- A. mtDNA maintenance: Replication and Repair
- C. Gene Expression Cross-talk for Stochiometric OXPHOS biogenesis

III. Heteroplasmy: The Challenge of Genetic Mosaicism

- A. Origins and Propagation of Heteroplasmy
- B. Genetic Buffering and Threshold Effects
- C. Selfish Mitochondrial Elements

IV. Pathological Consequences of Coordination Breakdown

- A. Classical Mitochondrial Diseases
- B. Aging and Neurodegeneration: When Coordination Fails
- C. Mitochondrial Mutations in Cancer

V. Pathways of Mitochondrial-Nuclear Communication

- A. Integrated stress response
- B. Immune System Cross-talk
- C. Horizontal Mitochondrial Transfer

VII. Conclusions: Lessons Learned and the Path Forward

BOX 1. New Tools for Studying Genome Coordination

- Functional genomics strategies to study mtDNA molecular biology
- Single-cell approaches to mitochondrial-nuclear analysis
- CRISPR-based tools for mitochondrial genome editing

BOX 2. Therapeutic Implications and Interventions

- Mitochondrial replacement therapies
- Targeting nuclear-mitochondrial communication pathways (hypoxia, ISR)
- Precision medicine approaches based on mitochondrial genetics (base editing, morpholino)

Paper for Discussion:

Hoover G, Gilbert S, Curley O, Obellianne C, Lin MT, Hixson W, Pierce TW, Andrews JF, Alexeyev MF, Ding Y, Bu P, Behbod F, Medina D, Chang JT, Ayala G, Grelet S. Nerve-to-cancer transfer of mitochondria during cancer metastasis. *Nature*. 2025 Aug;644(8075):252-262. doi: 10.1038/s41586-025-09176-8. Epub 2025 Jun 25. PMID: 40562940; PMCID: PMC12328229.

Review Papers:

Liu D, Gao Y, Liu J, Huang Y, Yin J, Feng Y, Shi L, Meloni BP, Zhang C, Zheng M, Gao J. Intercellular mitochondrial transfer as a means of tissue revitalization. *Signal Transduct Target Ther*. 2021 Feb 16;6(1):65. doi: 10.1038/s41392-020-00440-z. PMID: 33589598; PMCID: PMC7884415.

Li B, Li B, Qiao X, Meng W, Xie Y, Gong J, Fan Y, Zhao Z, Li L. Targeting mitochondrial transfer as a promising therapeutic strategy. *Trends Mol Med*. 2025 May 6:S1471-4914(25)00089-9. doi: 10.1016/j.molmed.2025.04.002. Epub ahead of print. PMID: 40335384.