# Mitochondria

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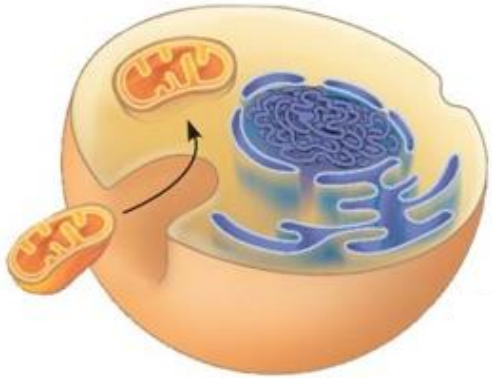
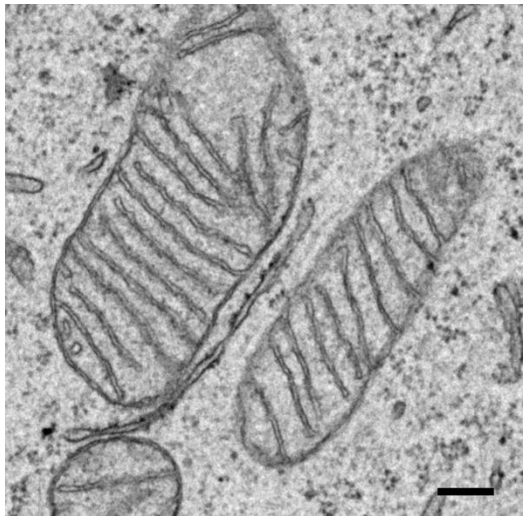
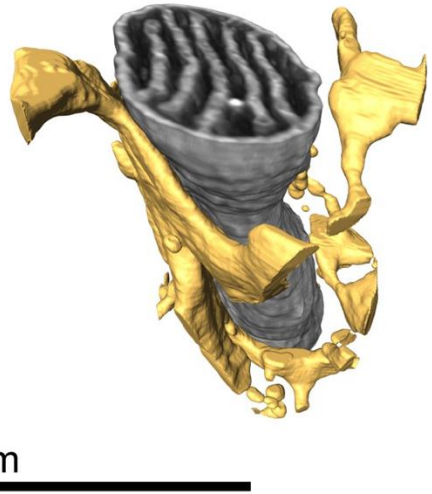
# The Origins of Mitochondria

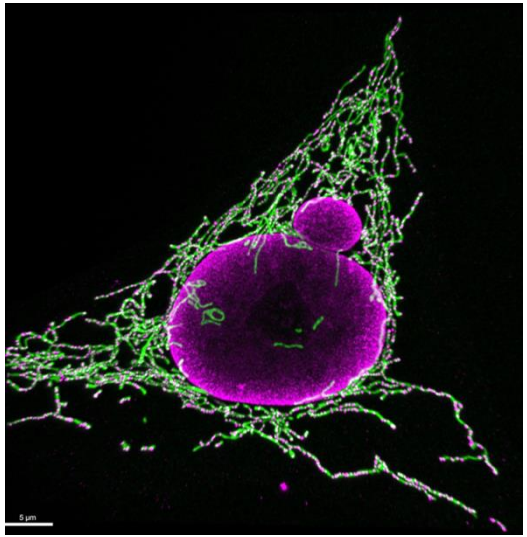


- 1.5 billion years ago an “endosymbiotic” transformation of aerobic proto-bacteria into anaerobic proto-eukaryotic cells occurred, concomitantly with an increase in atmospheric oxygen generated by photosynthetic cyanobacteria
- Endosymbiosis created mitochondria and resulted in a radical change in cellular metabolism, which started to oxidize metabolic substrates for energy transformation

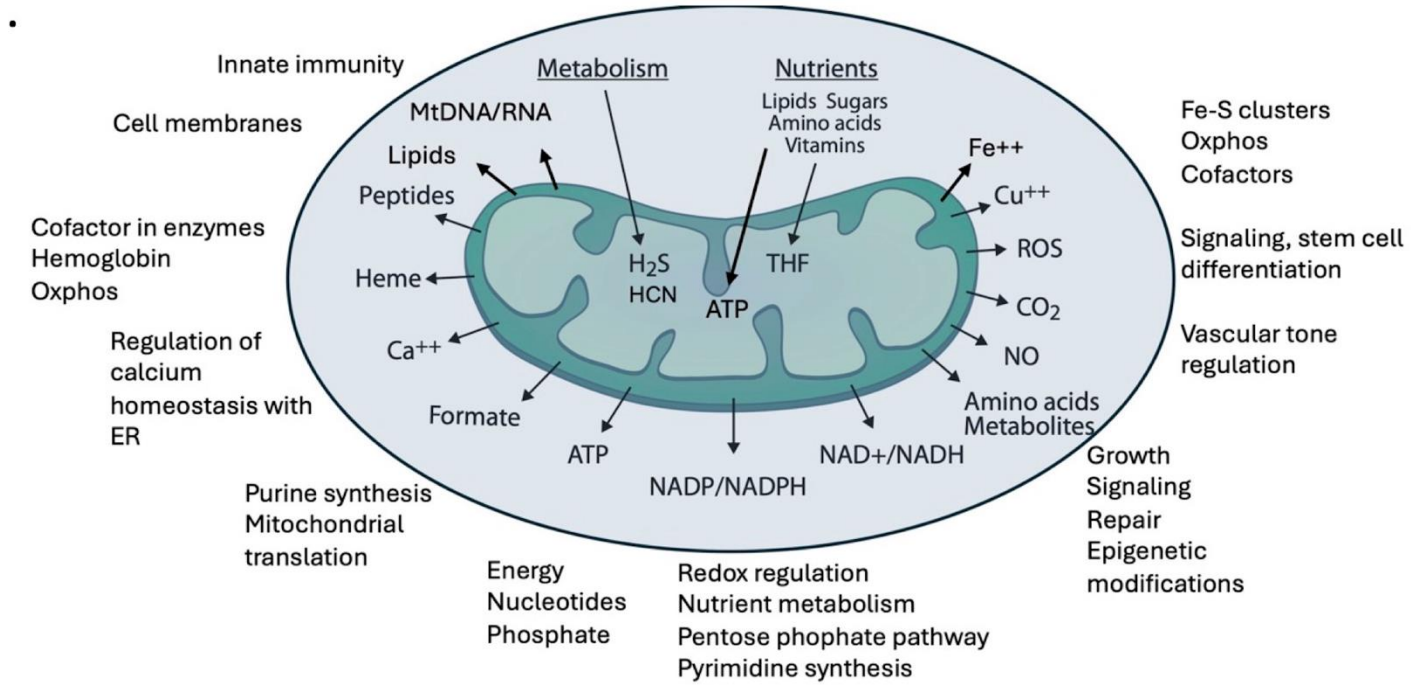
# Mitochondrial structure





# Mitochondria are involved in many cellular functions



## Some organs are highly reliant on mitochondria for energy

- The total body content of ATP is 250 g
- 150 Kg of ATP are consumed by the human body daily
- 550 liters of molecular oxygen are consumed daily
- The brain consumes 20% of the ATP, despite accounting for only 2% of body weight
- ~90% ATP in brain is produced by mitochondria

# Pro and coms of mitochondria

## **On the upside**:

•High production of ATP for each molecule of glucose utilized

•Compartmentalization and concentration of substrates and specialized enzymes (especially of the Krebs cycle)

•Oxidation of NADH in mitochondria allows for faster rate of glycolysis in cytosol

•Fine tuning of intracellular Ca2+ concentration, especially in excitable cells, such as neurons, heart, and muscle

## **Downsides**:

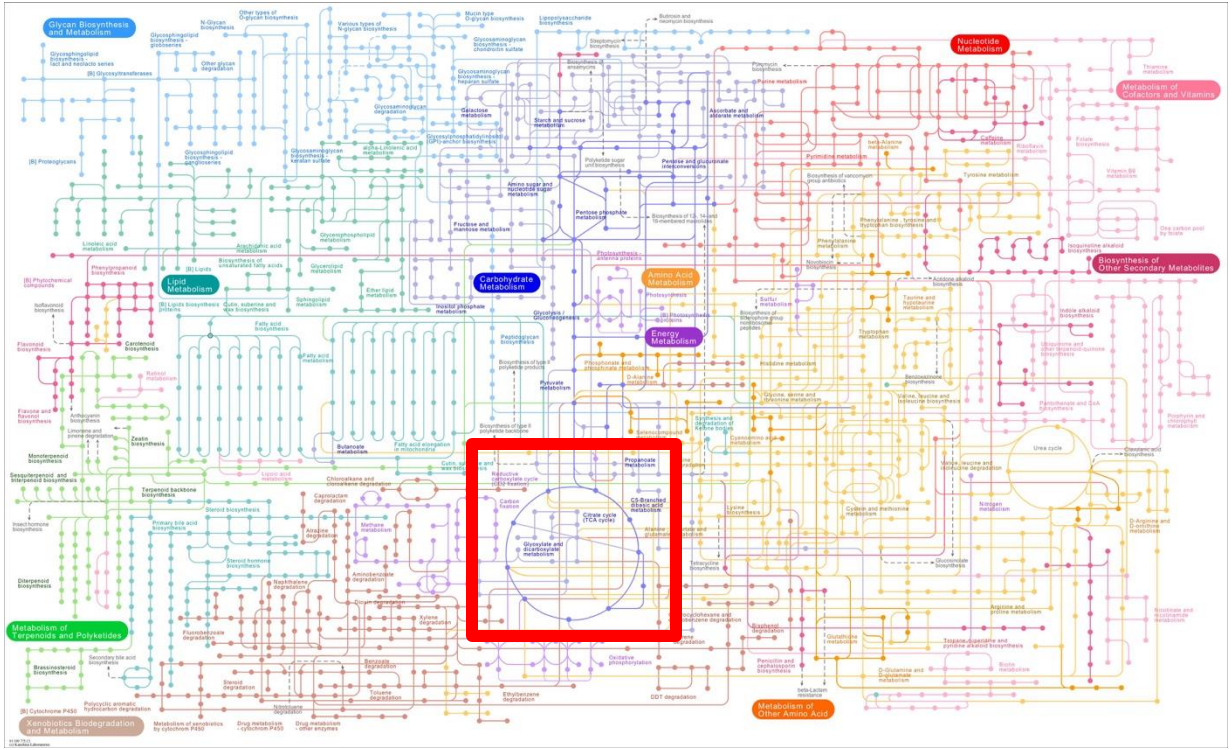
•Complex coordination of iron and lipid homeostasis

• Intracellular production of toxic reactive oxygen species

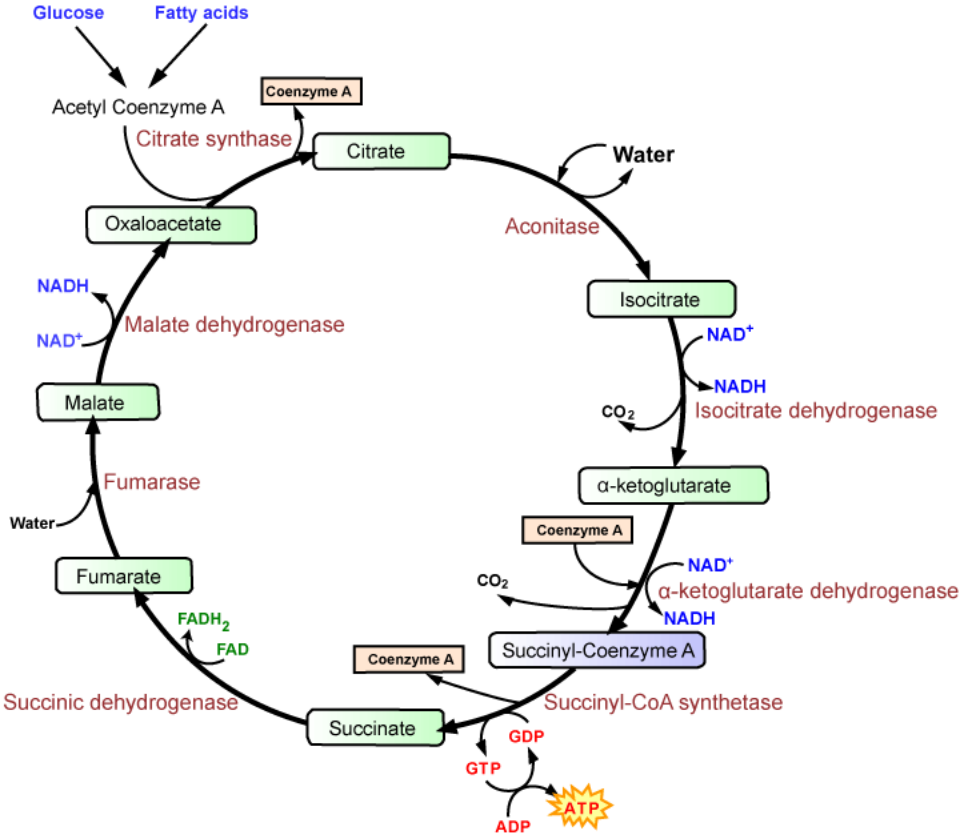
•Undesired apoptosis in pathological conditions

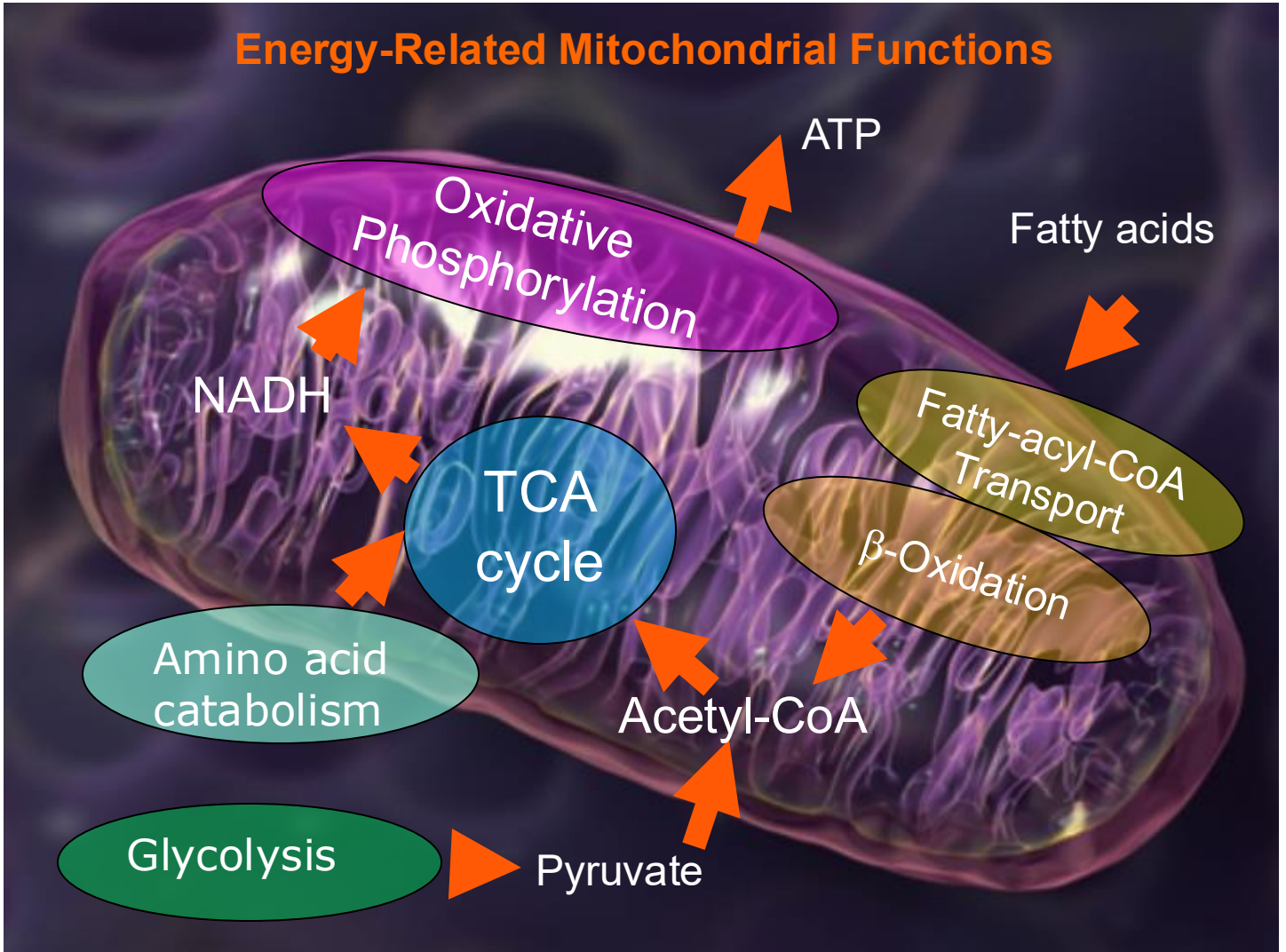
•Complex coordination of mitochondrial biogenesis (under the control of two genomes)

# Oxidative phosphorylation is central to all metabolism

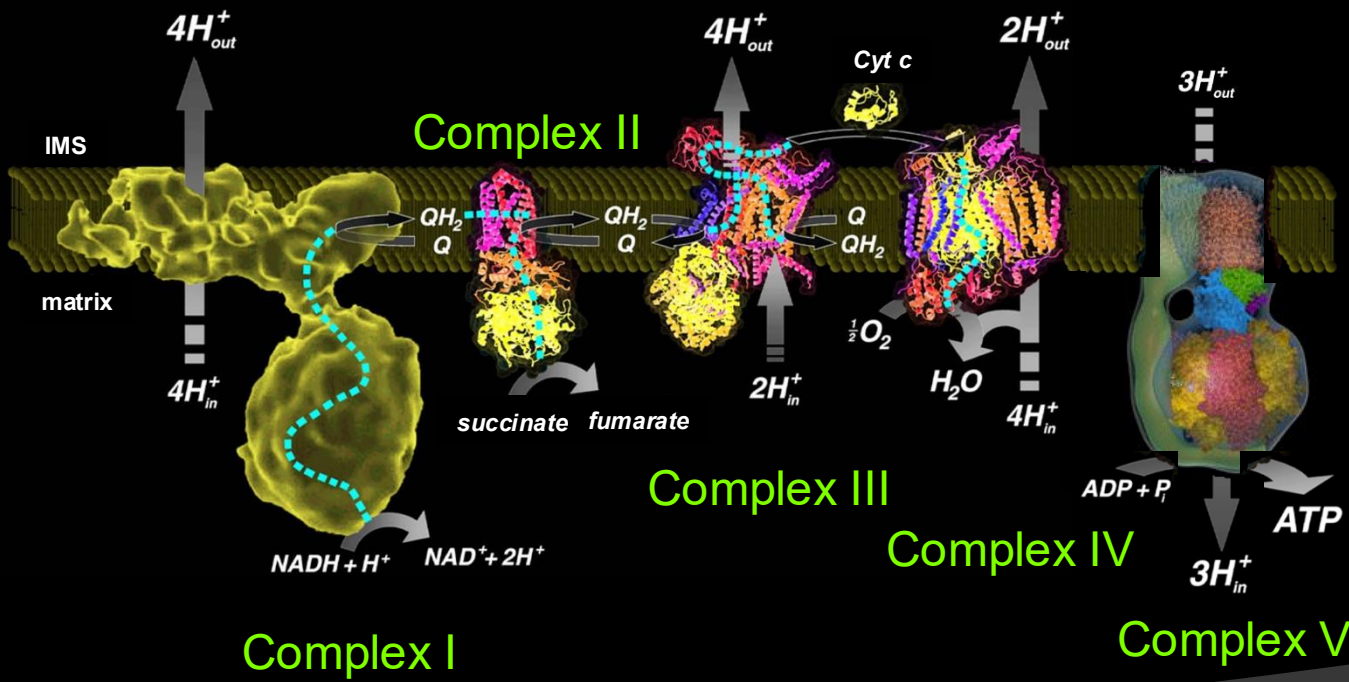


# KREBS CYCLE (CITRIC ACID CYCLE )



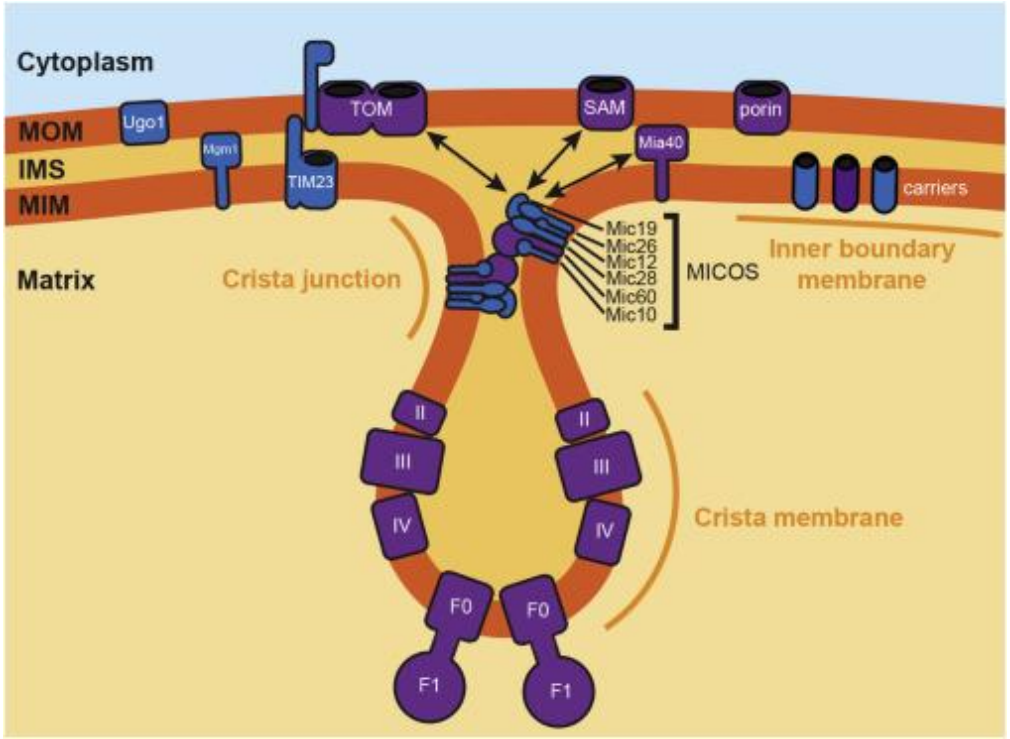

Energy-Related Mitochondrial Functions
ATP
Oxidative Phosphorylation
Fatty acids
NADH
Fatty-acyl-CoA Transport
TCA cycle
β-Oxidation
Amino acid catabolism
Acetyl-CoA
Glycolysis
Pyruvate

# The Oxidative Phosphorylation System



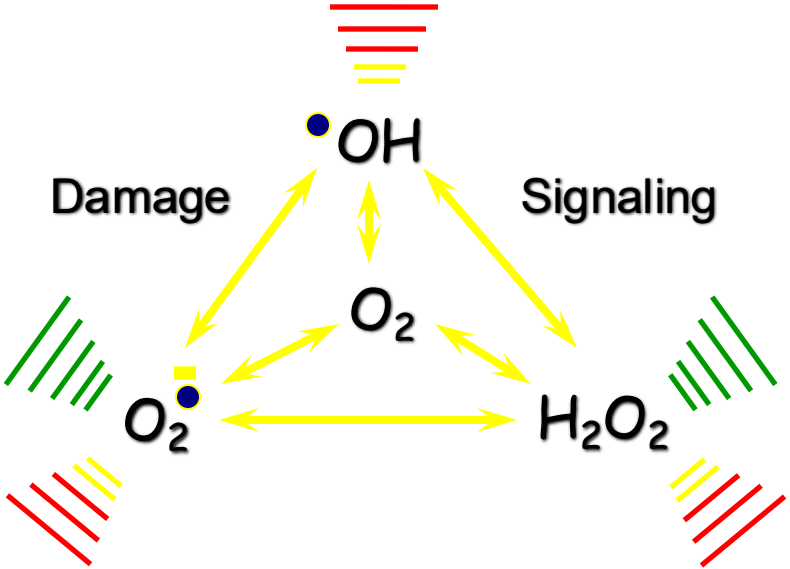

By Jose-Antonio Enriquez

# Mitochondrial cristae host the electron transfer chain




(*S. Cerevisiae*)

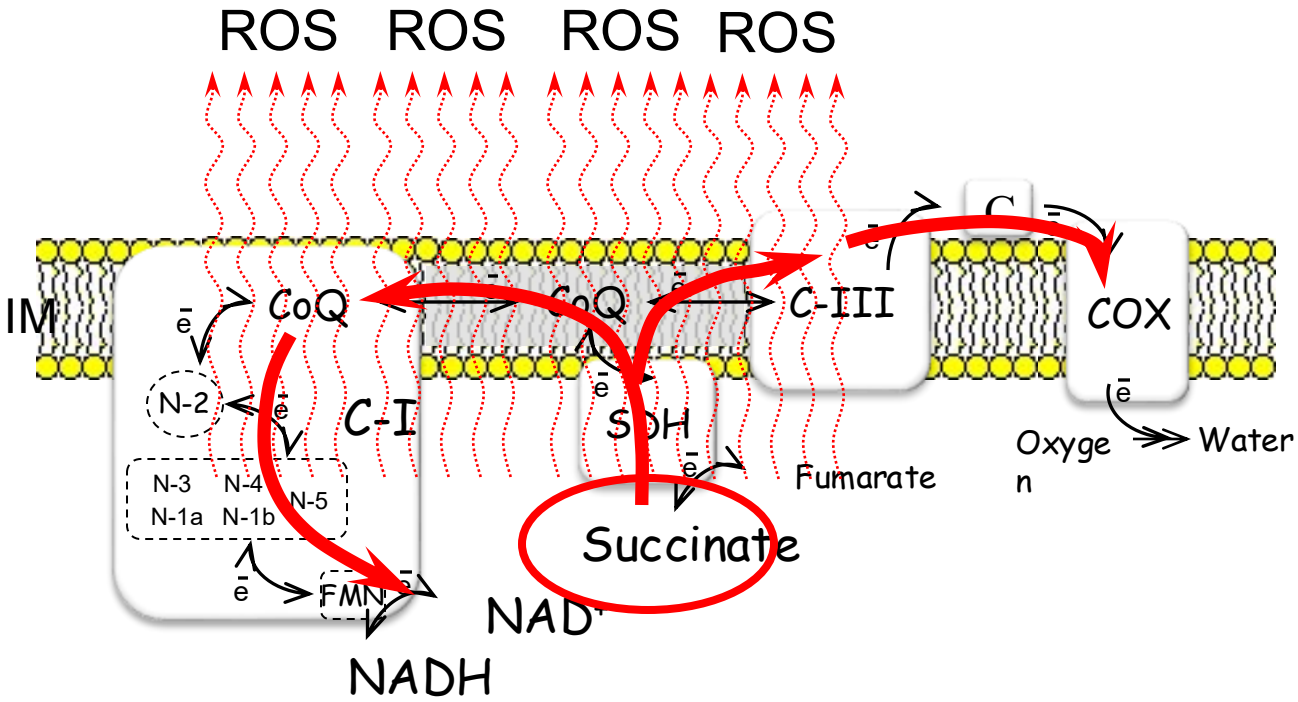
# ROS: Reactive Oxygen Species



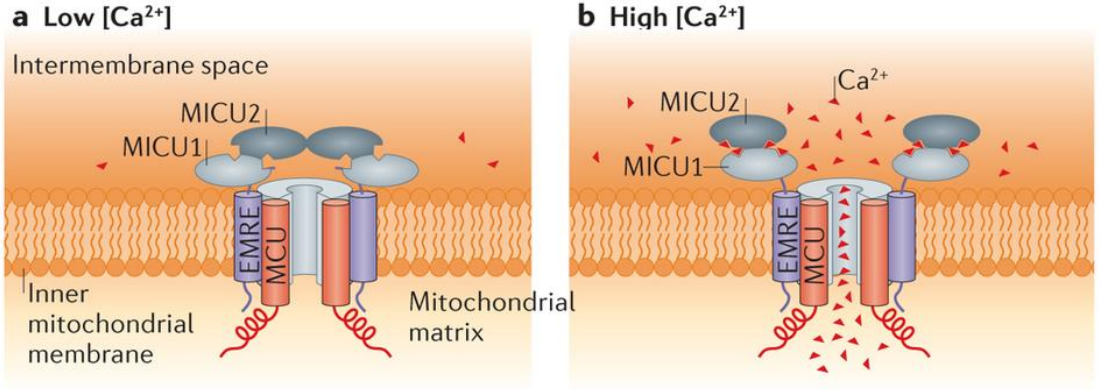
Reverse electron transfer (RET):

(NAD+) C-I ← CoQ

Ischemia/reperfusion

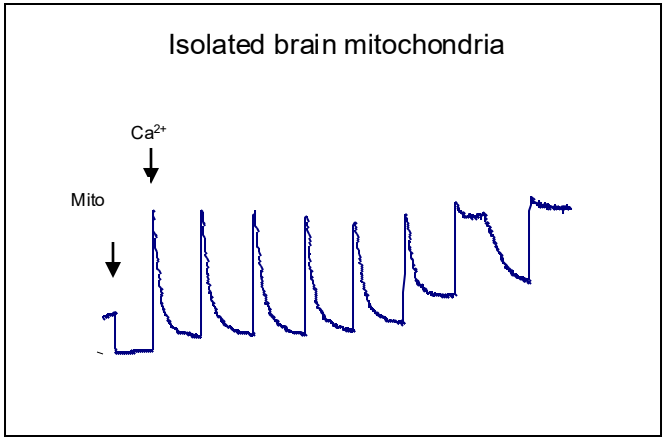


# $Ca^{2+}$ is taken up by mitochondria through the uniporter (MCU)

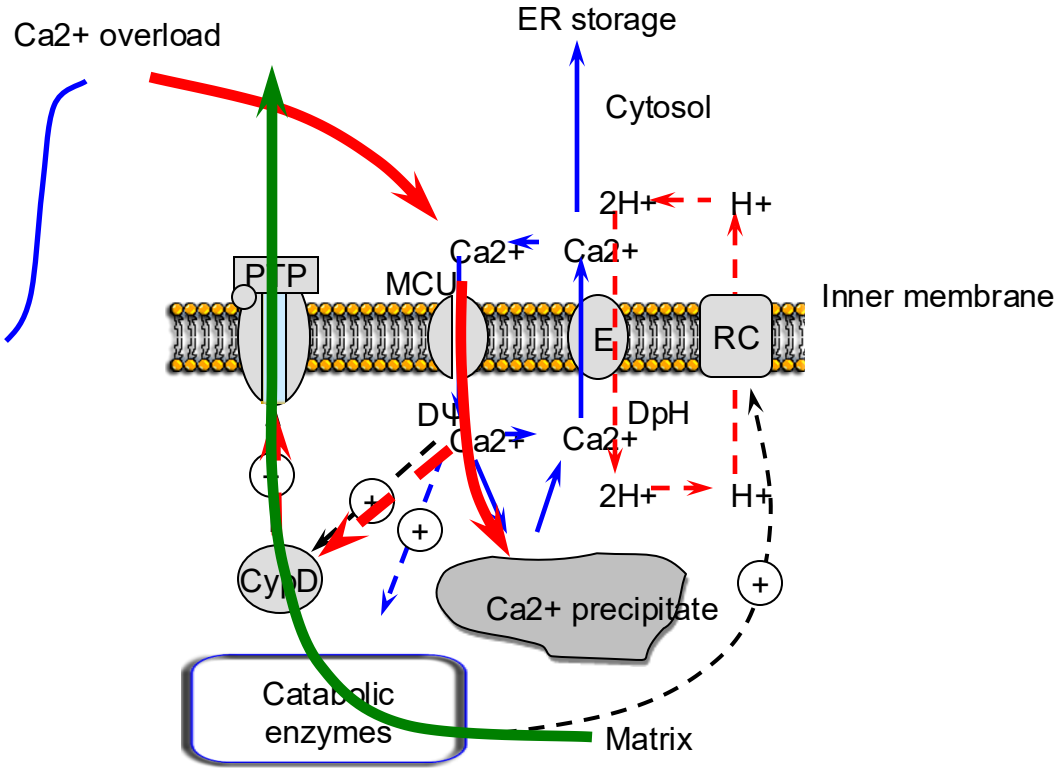



Nature Reviews | Molecular Cell Biology

16, 545–553 (2015)



# Ca2+ overload in mitochondria

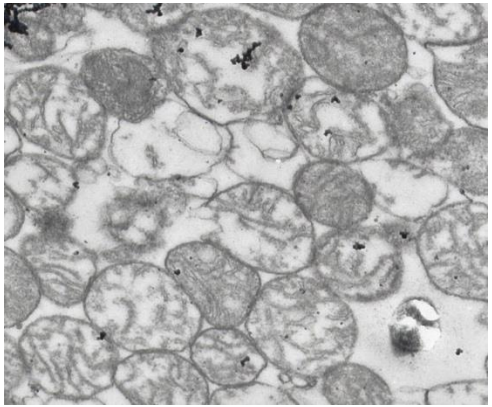


# Mitochondrial permeability transition

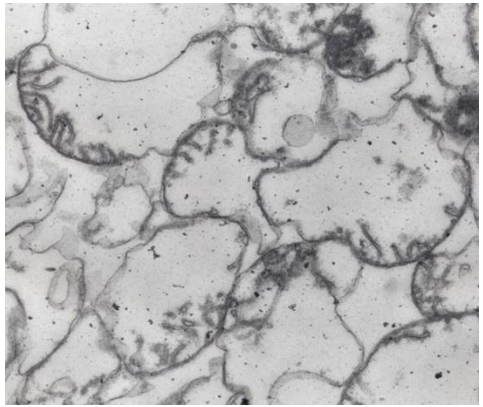
•Mitochondrial permeability transition (MPT) is a sudden increase in the permeability of the mitochondrial inner membrane to molecules <1,500 Da

•MPT results from opening of a mitochondrial permeability transition pore (PTP), a proteinaceous pore in the mitochondrial membranes

Pre MPT

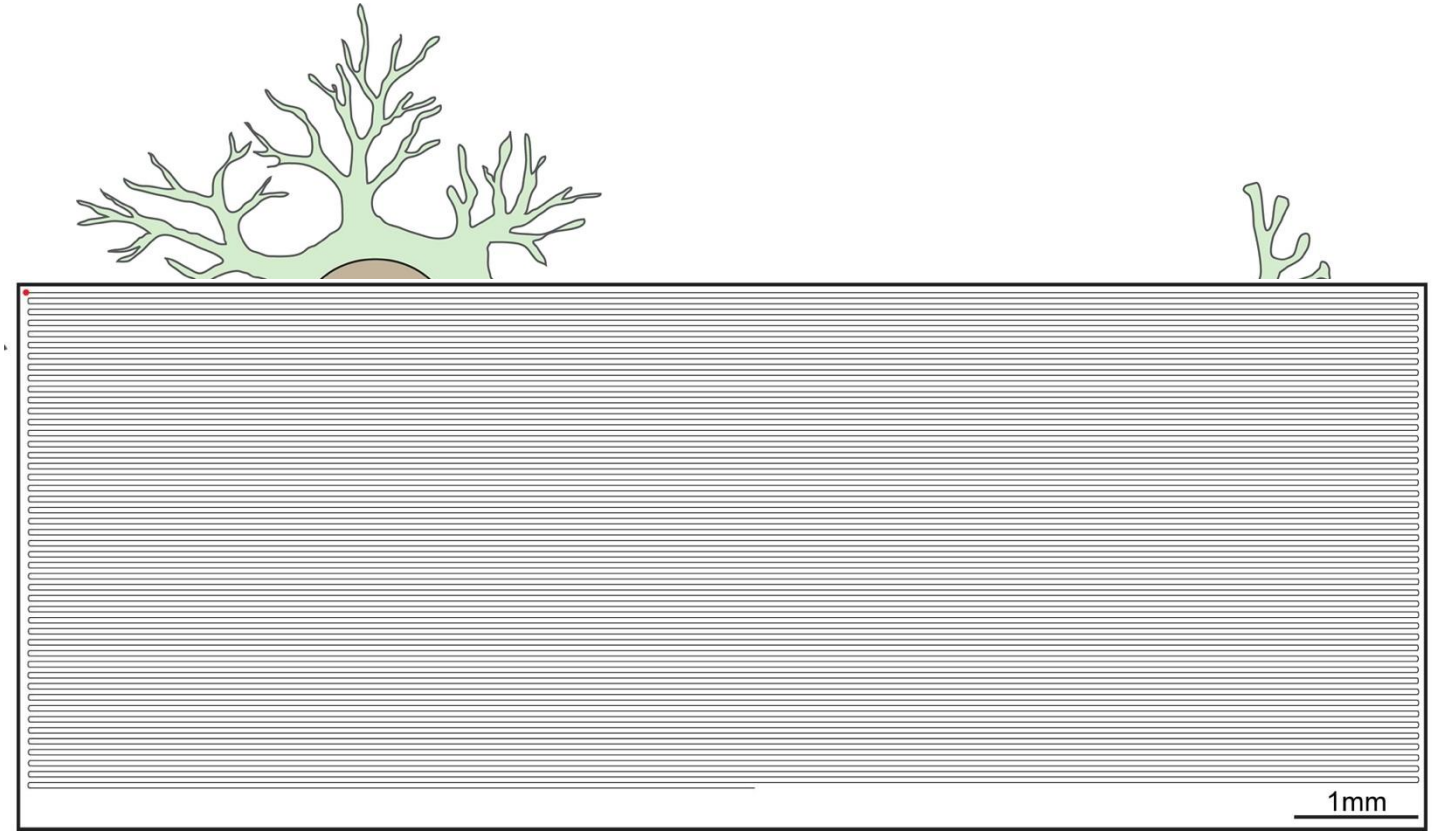


Post MPT



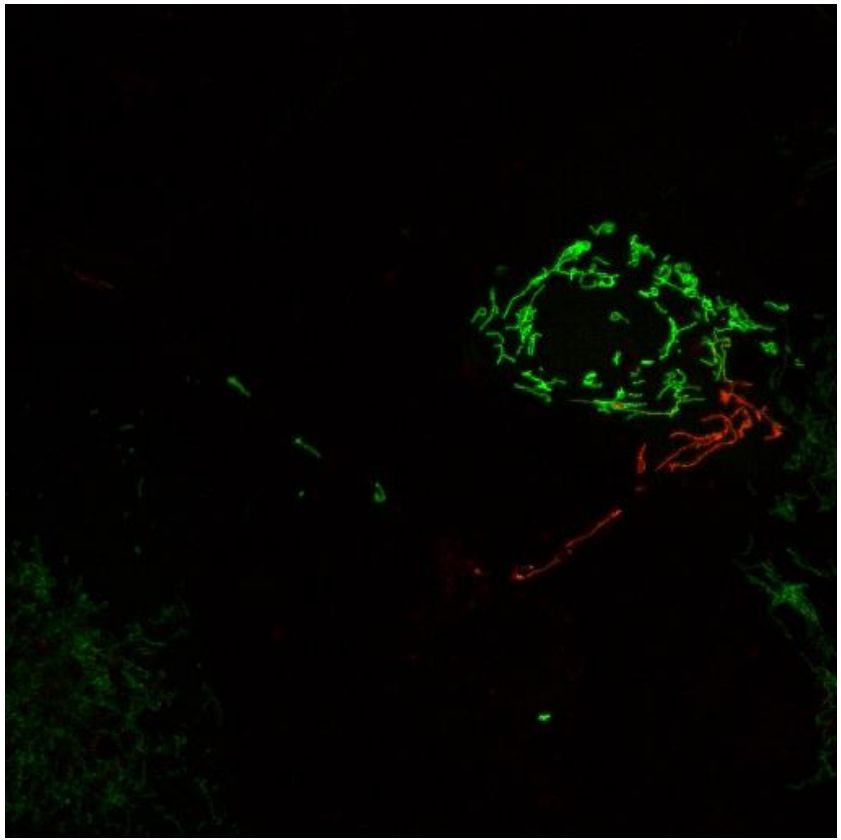
Mouse brain mitochondria

# Mitochondrial transport along microtubules




Motor neuron: axon is 20,000x longer than cell

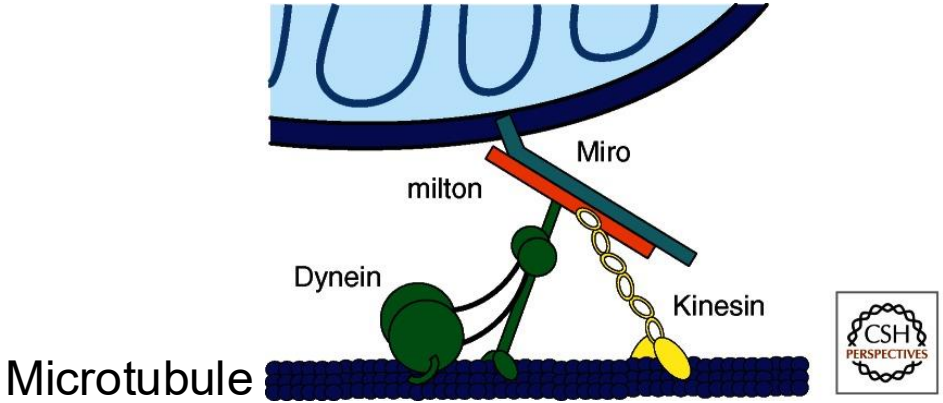
# Mitochondria are dynamic organelles



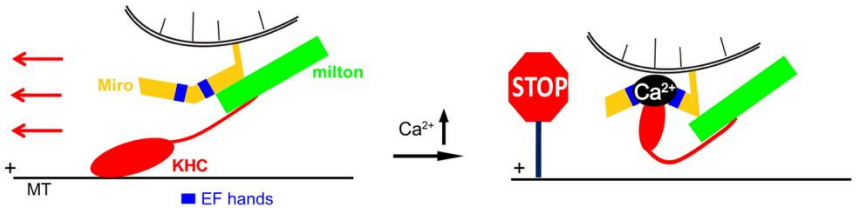
## Why are mitochondrial motility and localization important?

- Fast transport allows for shuttling mitochondria to sites of energy need, for example to active synapses
- Localized production of ATP
- Localized buffering of $Ca^{2+}$
- Mitochondrial turnover by mitophagy

# Regulation of mitochondrial movement

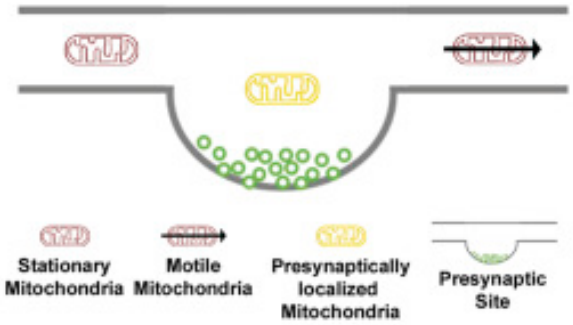


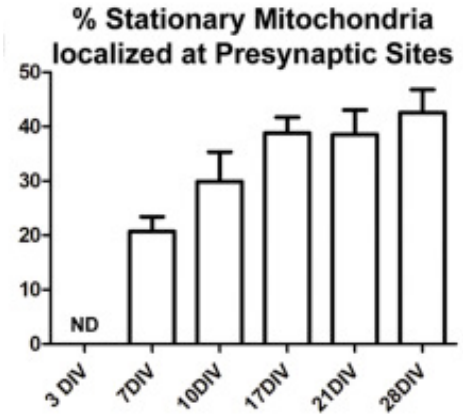

Cold Spring Harb Perspect Biol. 2013 Jun; 5(6): a011304.



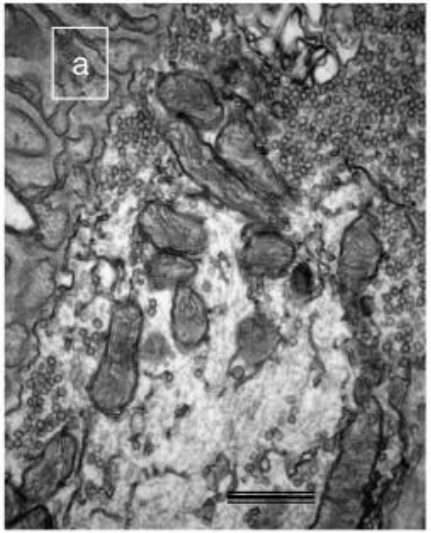

Wang X, Schwarz TL.Cell. 2009 Jan 9;136(1):163-74

# Immobile mitochondria localize at presynaptic sites



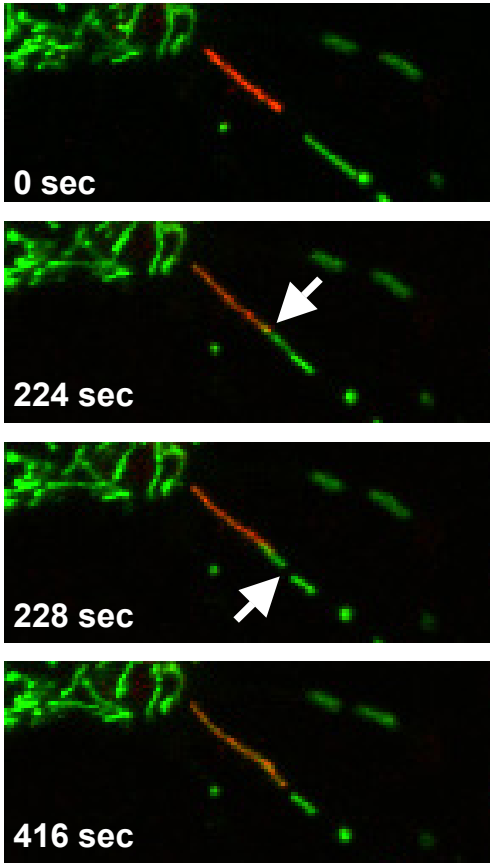

Lewis et al., 2016



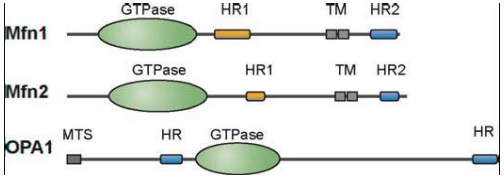

Mitochondria are enriched at synaptic sites

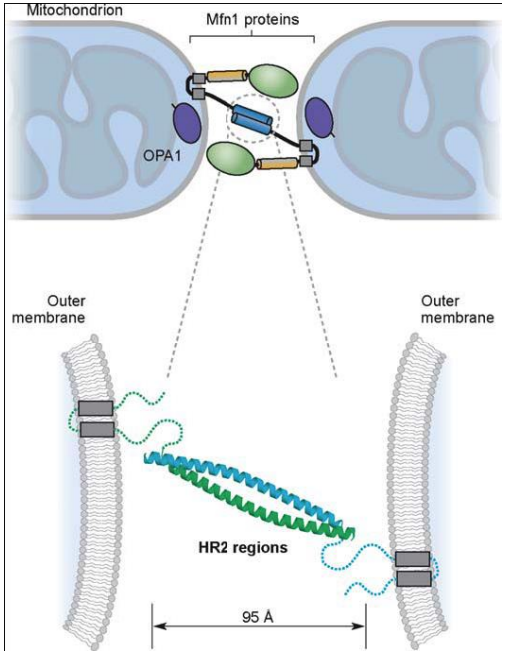
Garcia et al., 2013

# Mitochondria are subject to fusion and fission



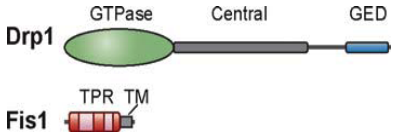
# Factors involved in mitochondrial fusion and fission

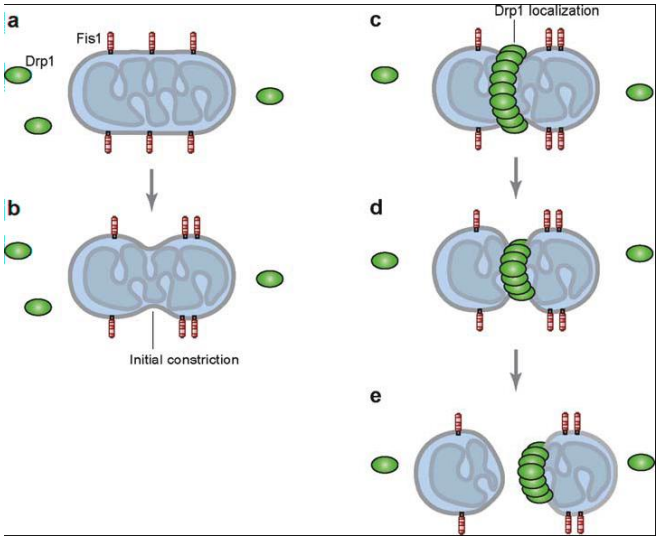



Fusion

Fis1, Mff, MiD49, and MiD51



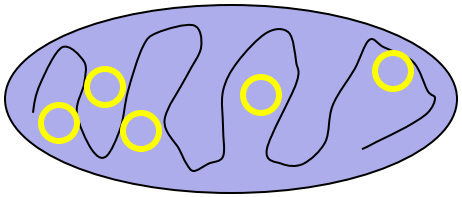

Fission

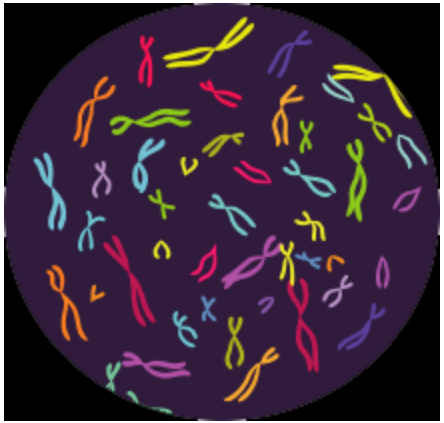
Chan DC, Annu Rev Cell Dev Biol. 2006;22:79-99.

# Mitochondrial Biogenesis: “a tale of two genomes”

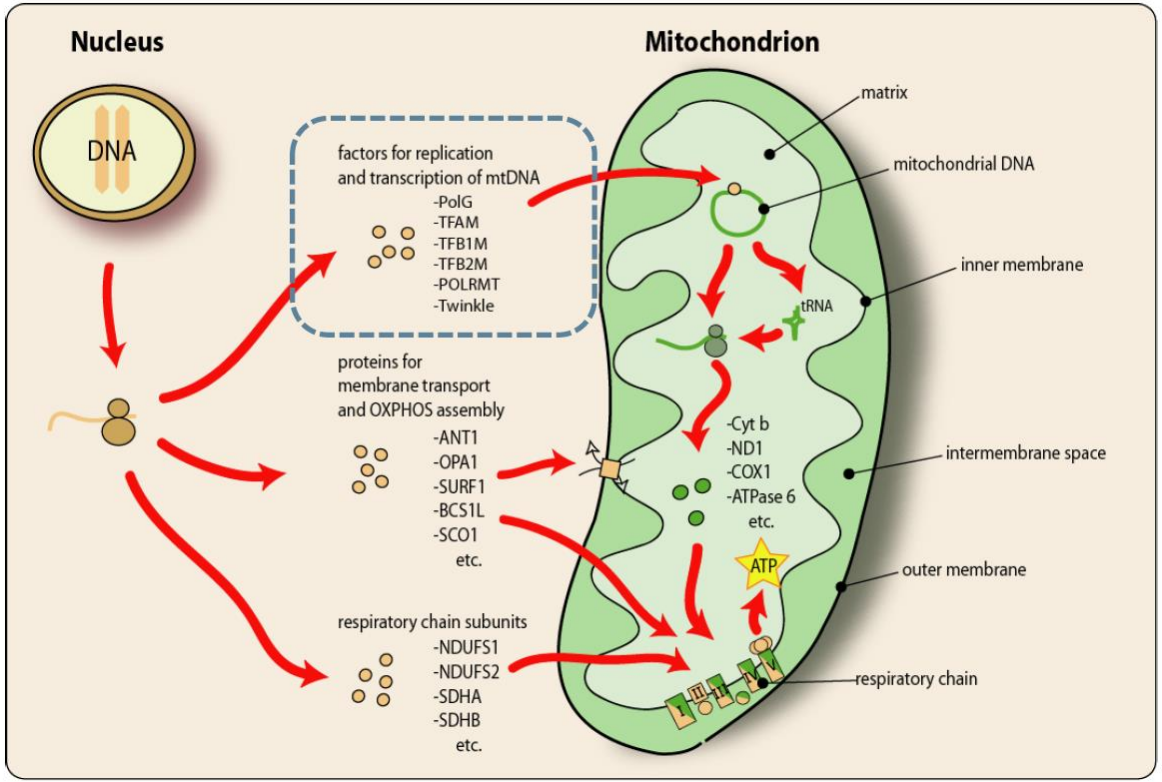
- > 1,300 mitochondrial proteins are coded by nuclear DNA, synthesized in cytosolic ribosomes, and imported into mitochondria

- Only 13 polypeptides are encoded by the mitochondrial DNA (mtDNA) and synthesized in mitochondrial ribosomes.

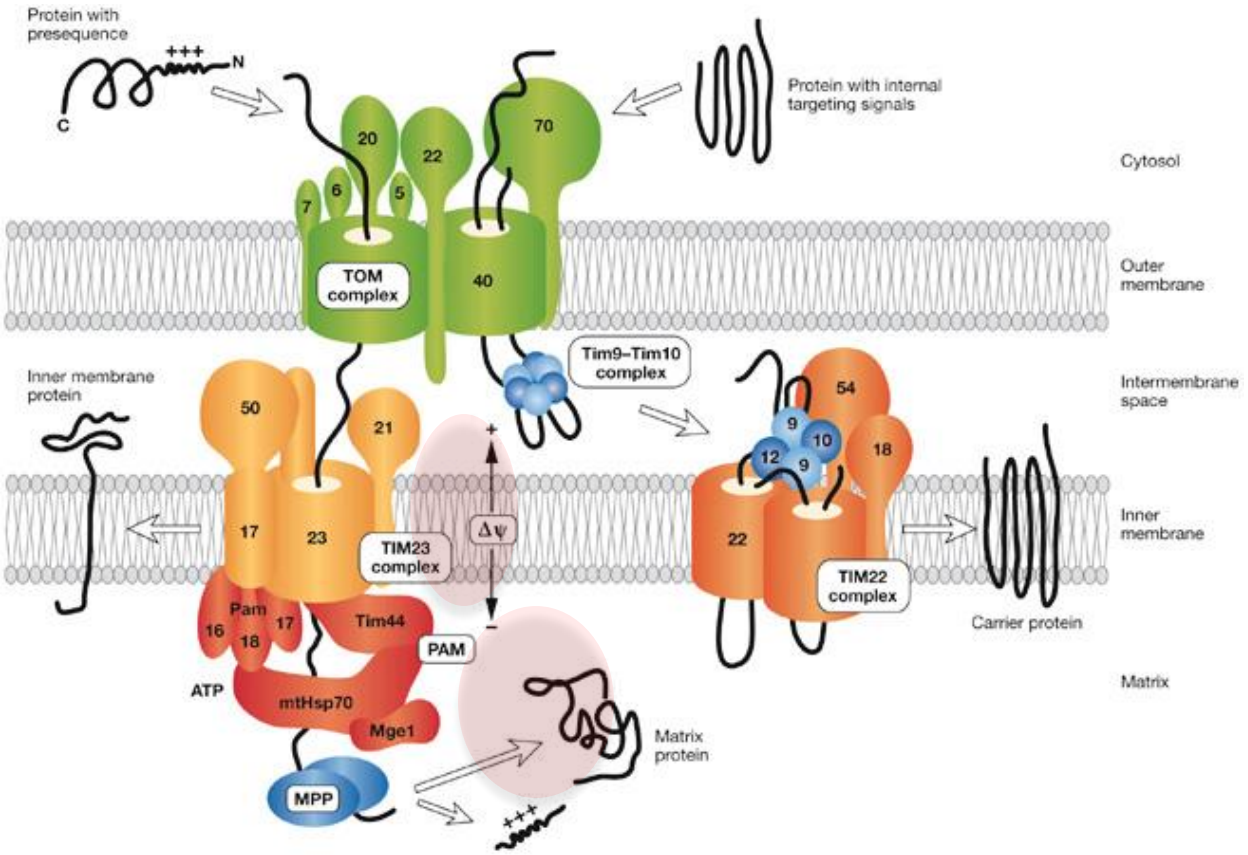




# Nuclear genome contribution in the assembly of mitochondrial respiratory complexes



# Import and sorting of proteins with presequences




Bolender et al. EMBO reports (2008) **9**, 42 - 49

# Mammalian mitochondrial DNA

**mtDNA encodes for:**

7 subuntis of Complex I

0 subuntis of Complex II

1 subunit of Complex III

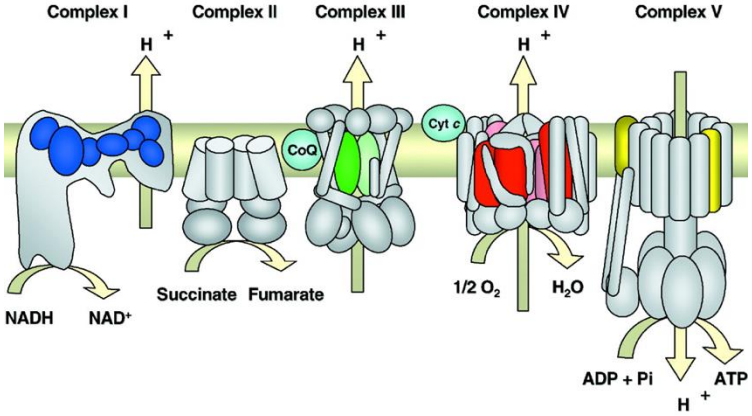
3 subuntis of complex IV

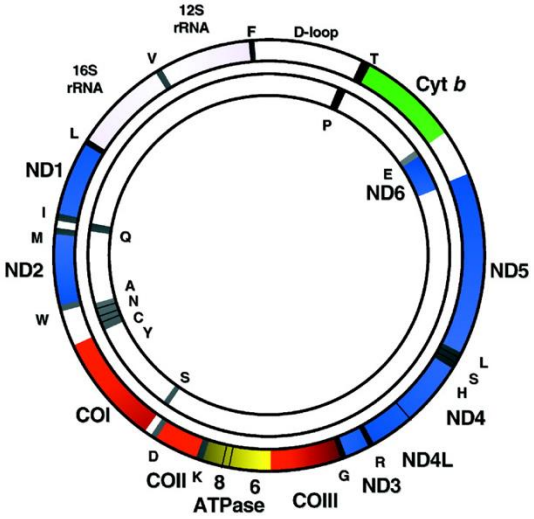
2 subuntis of Complex V

PLUS

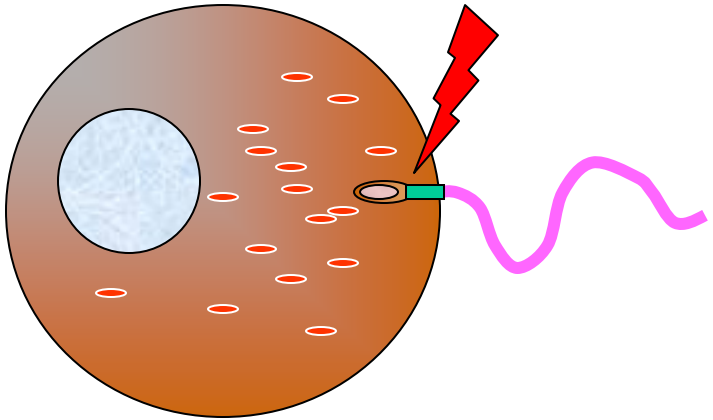
2 rRNAs

22 tRNAs

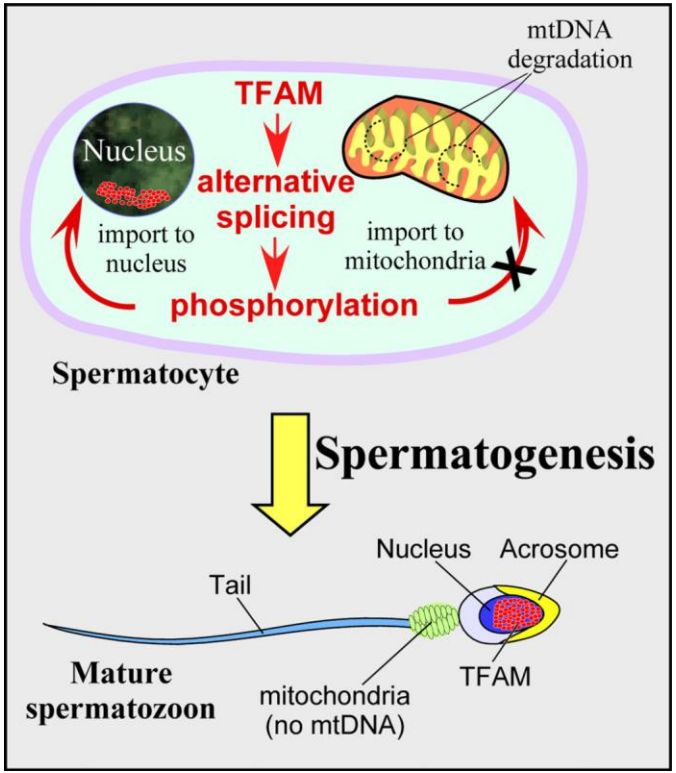


# mtDNA is only maternally inherited

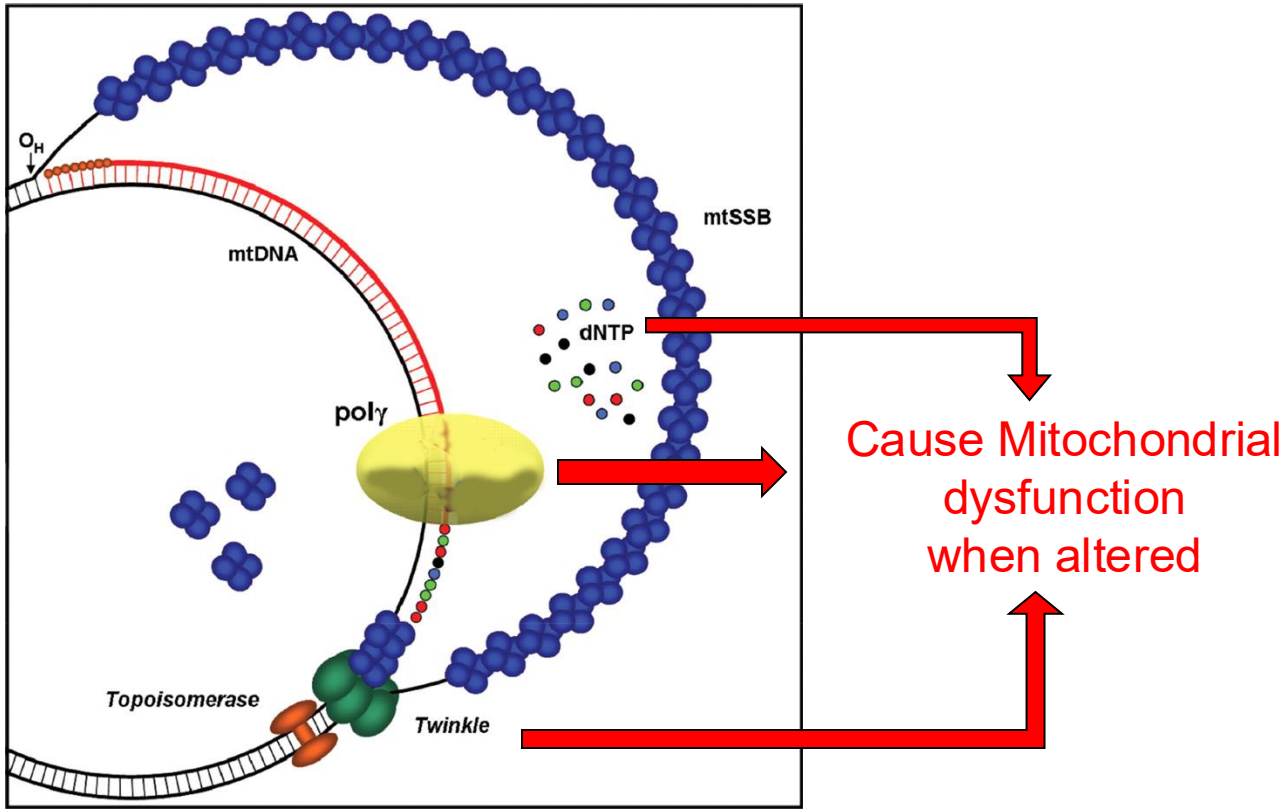


During spermatogenesis, TFAM is phosphorylated and prevented from being imported to mitochondria, resulting in mtDNA degradation. Instead, TFAM is accumulated in the nucleus of mature spermatozoa.



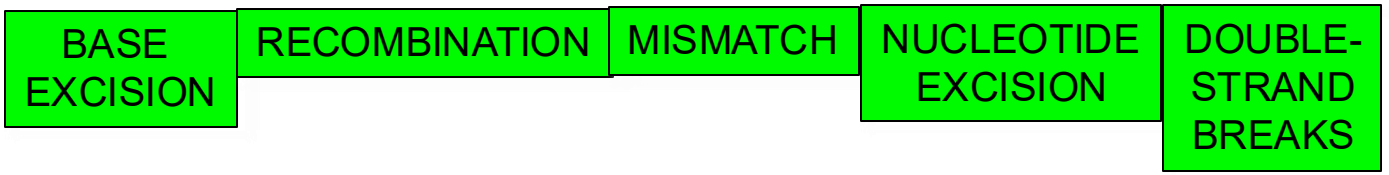

(Nat Genet. 2023 ; 55(10): 1632–1639. doi:10.1038/s41588-023-01505-9 )

# Components of mtDNA nucleoids for DNA replication

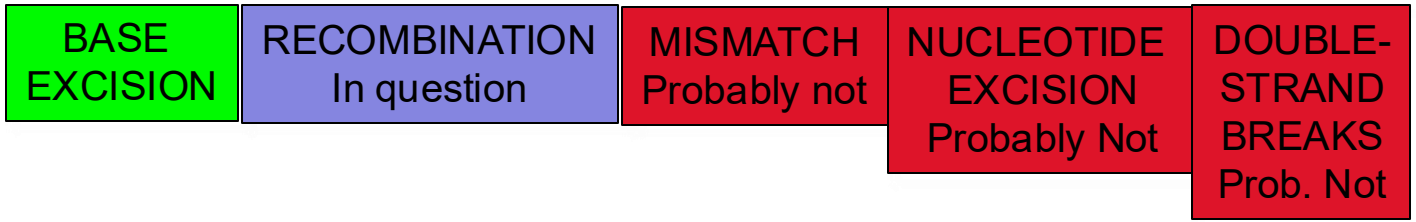


# Mammalian DNA repair mechanisms

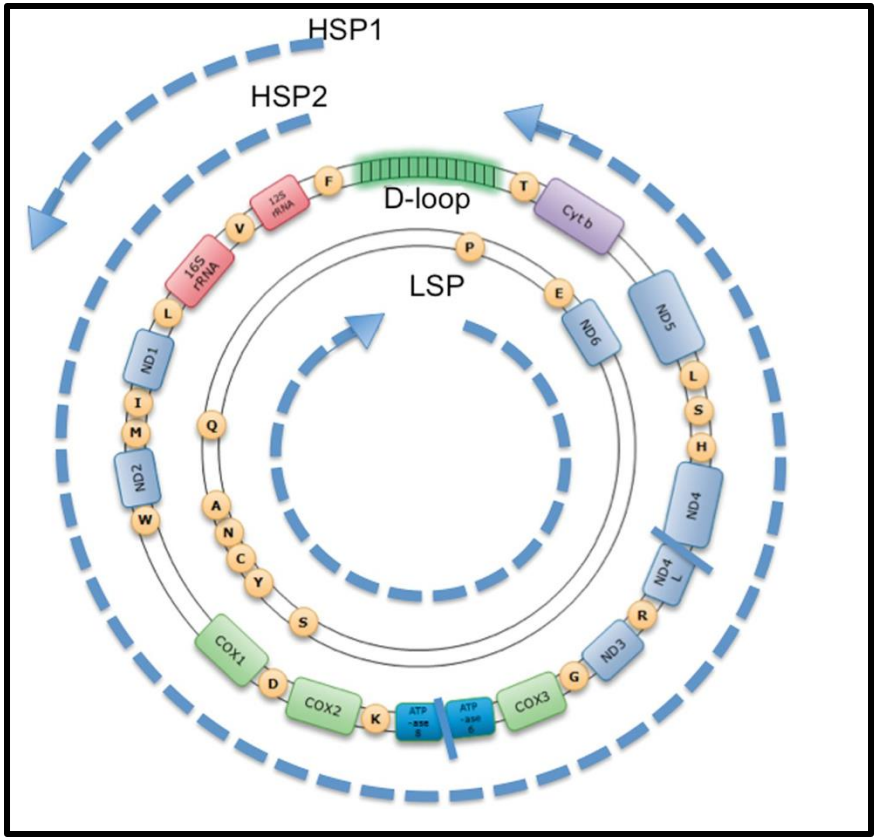
**Nuclear DNA**



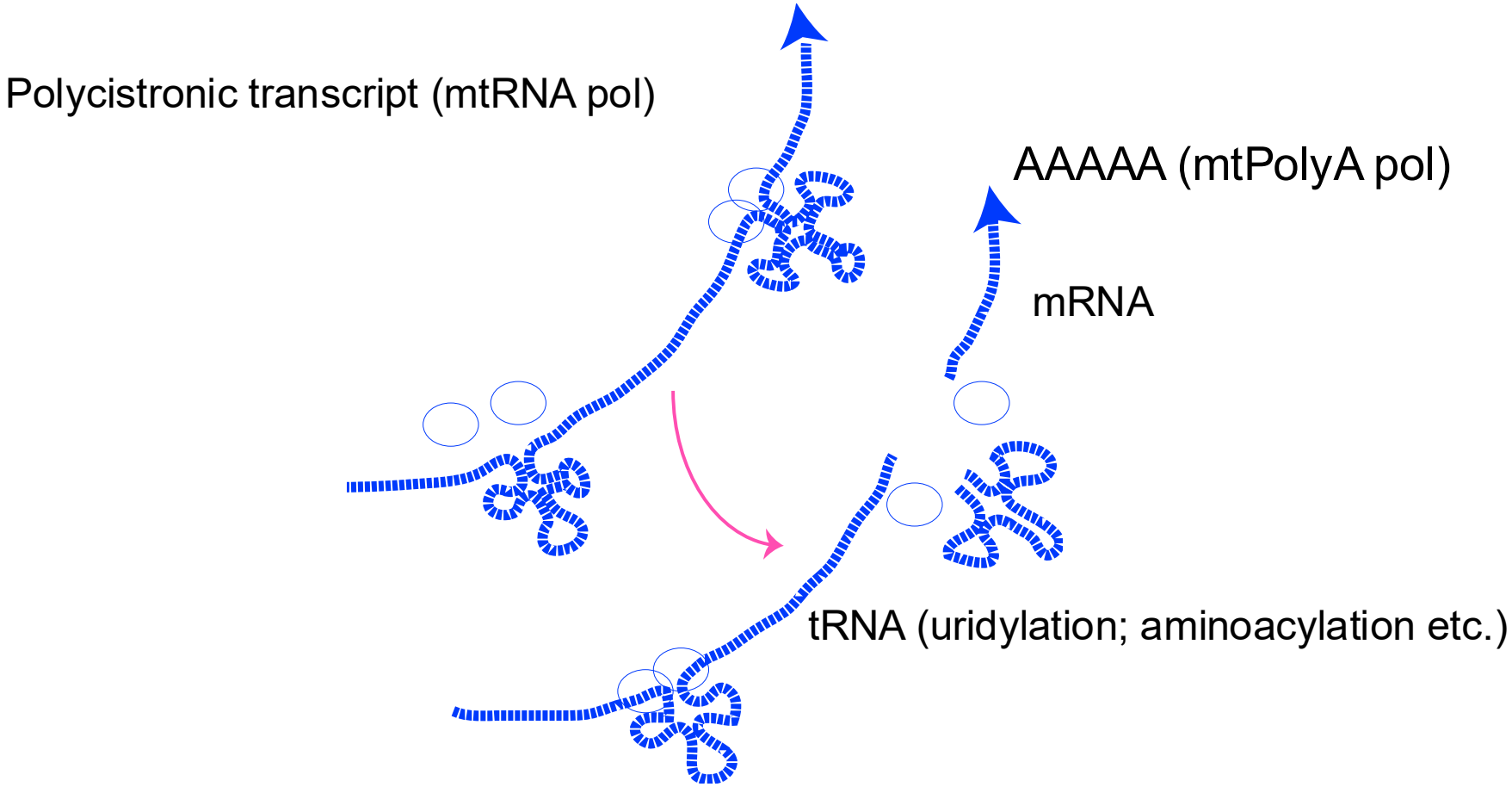

**mtDNA**



# mtDNA transcription by POLRMT creates poly-cistronic transcripts

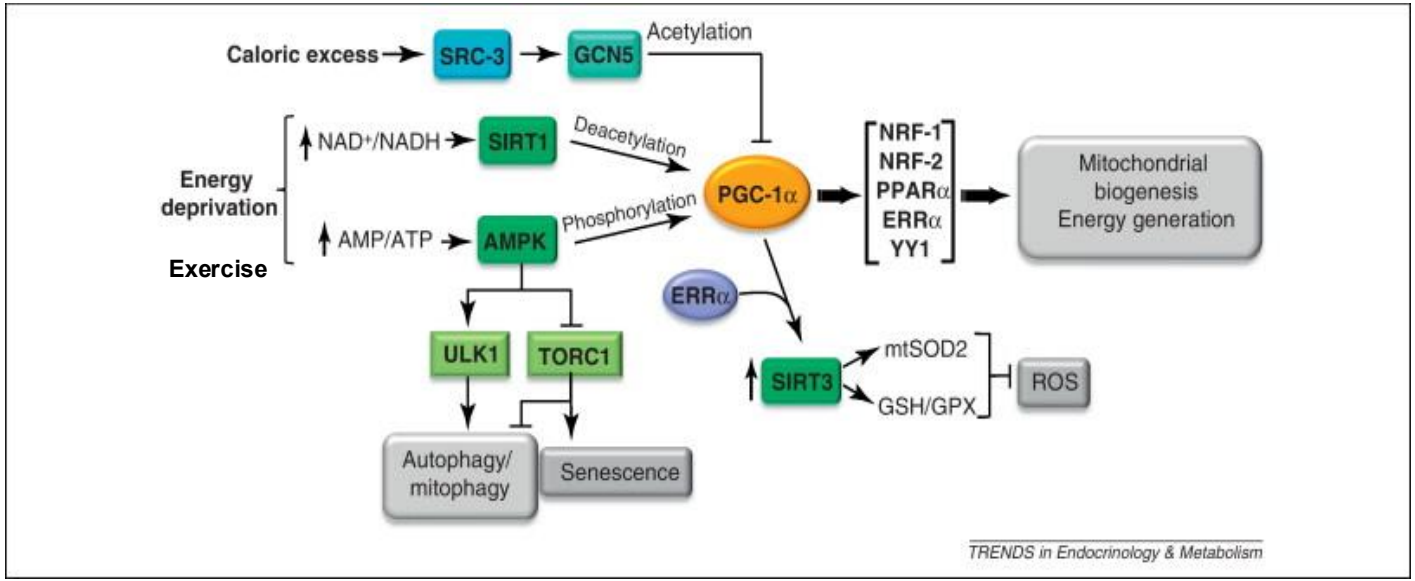


# Maturation of mitochondrial transcripts I



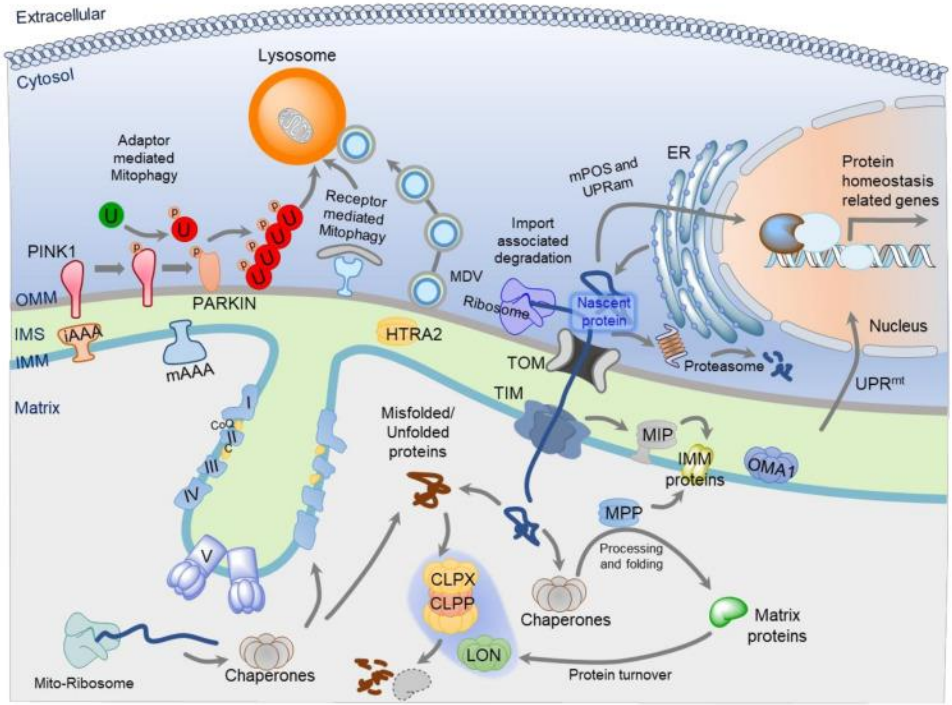
# Regulation of mitochondrial biogenesis

## “PGC-1α is a master regulator”



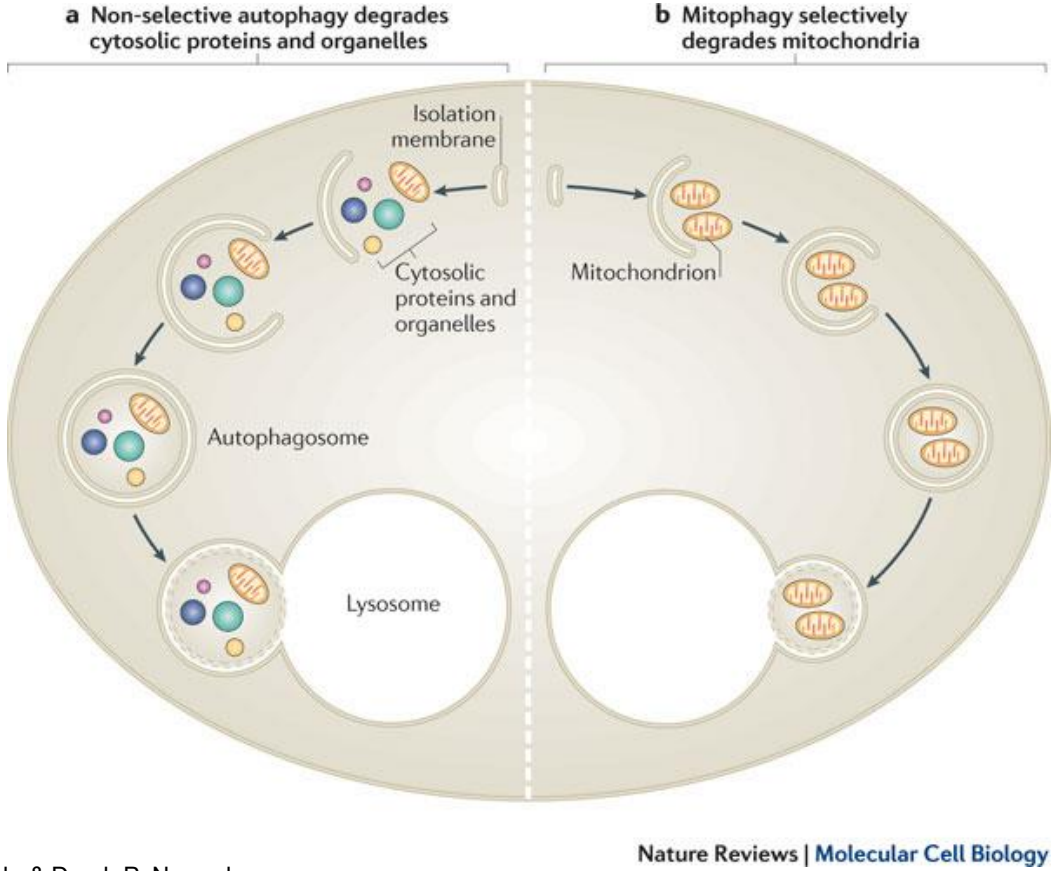

Source: Trends in Endocrinology and Metabolism , Volume 23, Issue 9, Pages 459-466 (DOI:10.1016/j.tem.2012.06.006)

# Mitochondrial quality control mechanisms



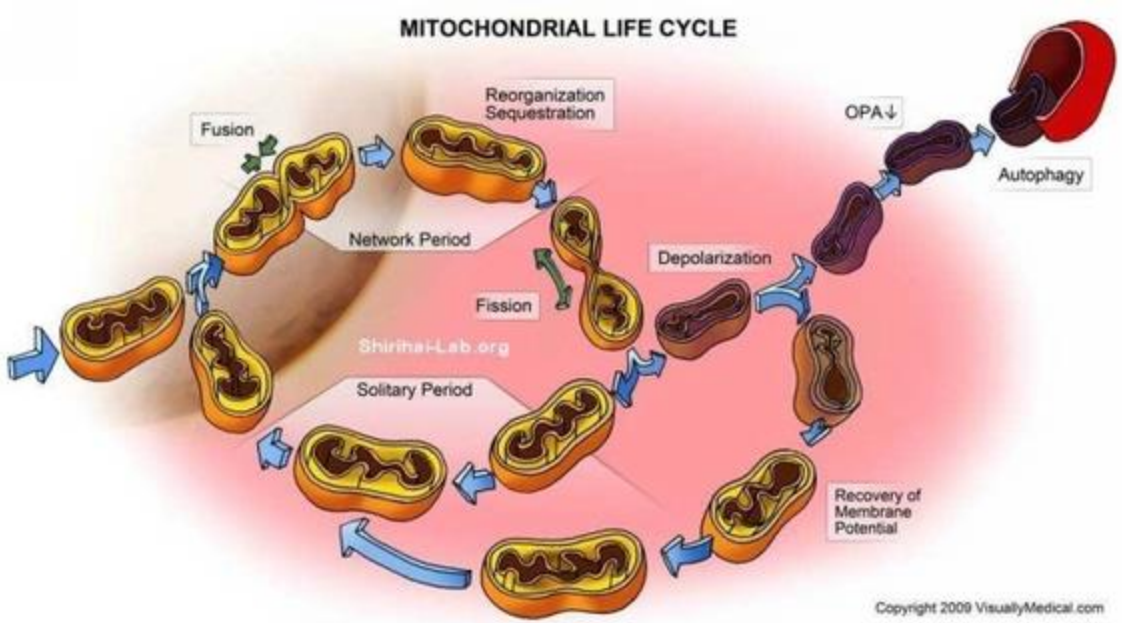

Published online 2020 May 18. doi: 10.3390/genes11050563

# Mitochondria turnover: non-selective autophagy and mitophagy have different roles



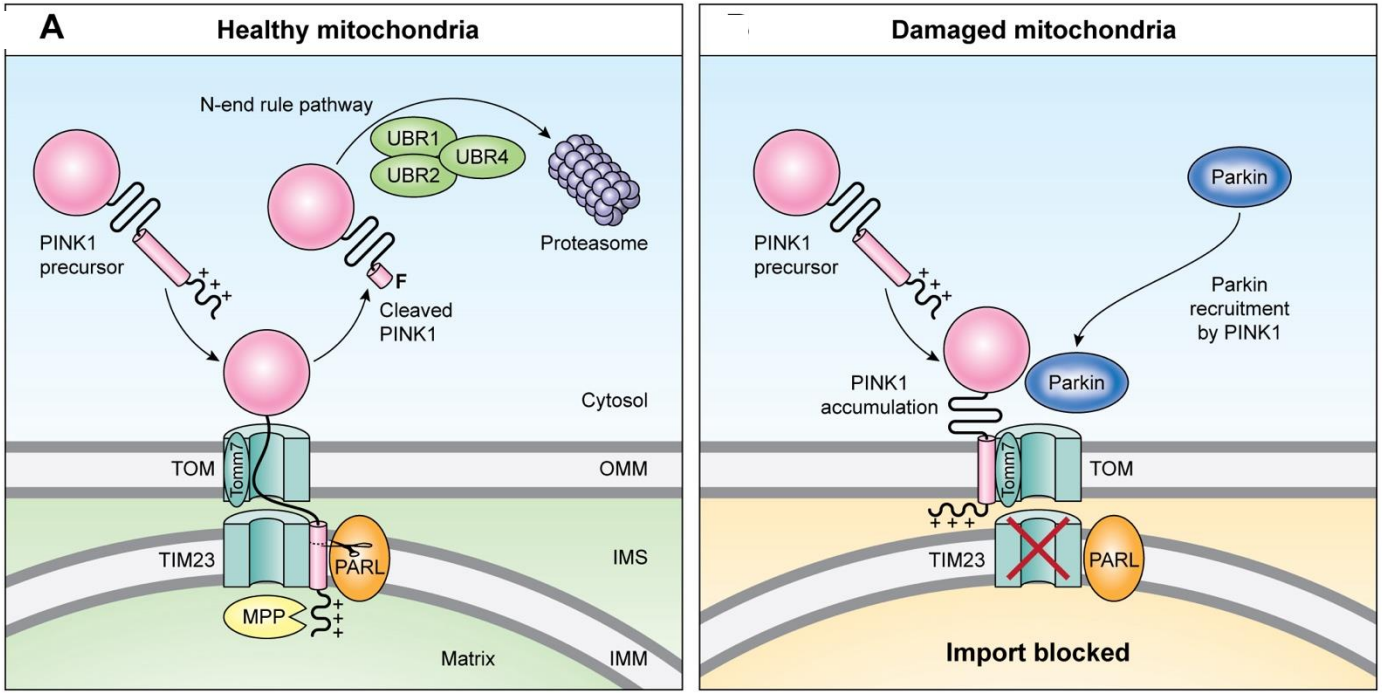

Richard J. Youle & Derek P. Narendra
Nature Reviews Molecular Cell Biology **12**, 9-14

# Mitochondrial recycling vs. autophagy



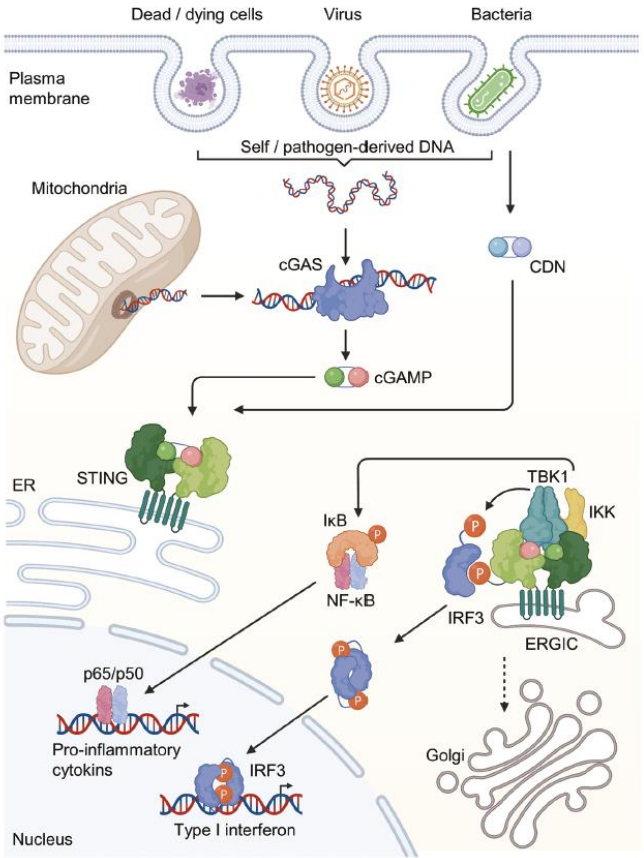

Twig et al. EMBO J. 2008 January 23; 27(2): 433-444

# PINK1/Parkin in mitochondrial quality control



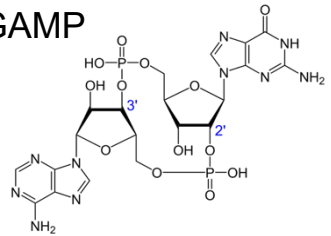

Deas et al., HMG 2011
Lazarou et al., Dev Cell 2012
Hasson et al., Nature 2013
Yamano et al., Autophagy 2013

# Mitochondrial DNA in inflammation and innate immunity damage-associated molecular patterns (DAMPs)




**cGAS (cyclic GMP-AMP synthetase)**

ATP + GTP → cGAMP



REVIEW ARTICLE OPEN

Molecular mechanisms of mitochondrial DNA release and activation of the cGAS-STING pathway

Jeonghan Kim[1✉], Ho-Shik Kim[1] and Jay H. Chung[2✉]

Experimental & Molecular Medicine (2023) 55:510–519

# The mitochondrial integrated stress response (mtISR)

*Review*

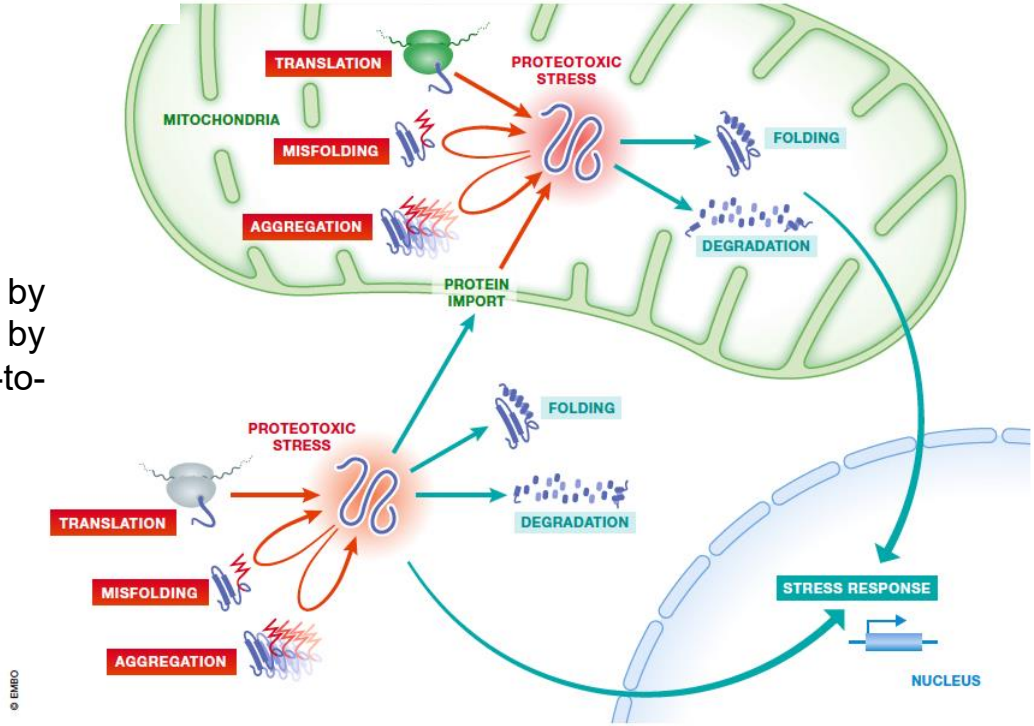
EMBO reports

*EMBO reports* e47865 | 2019

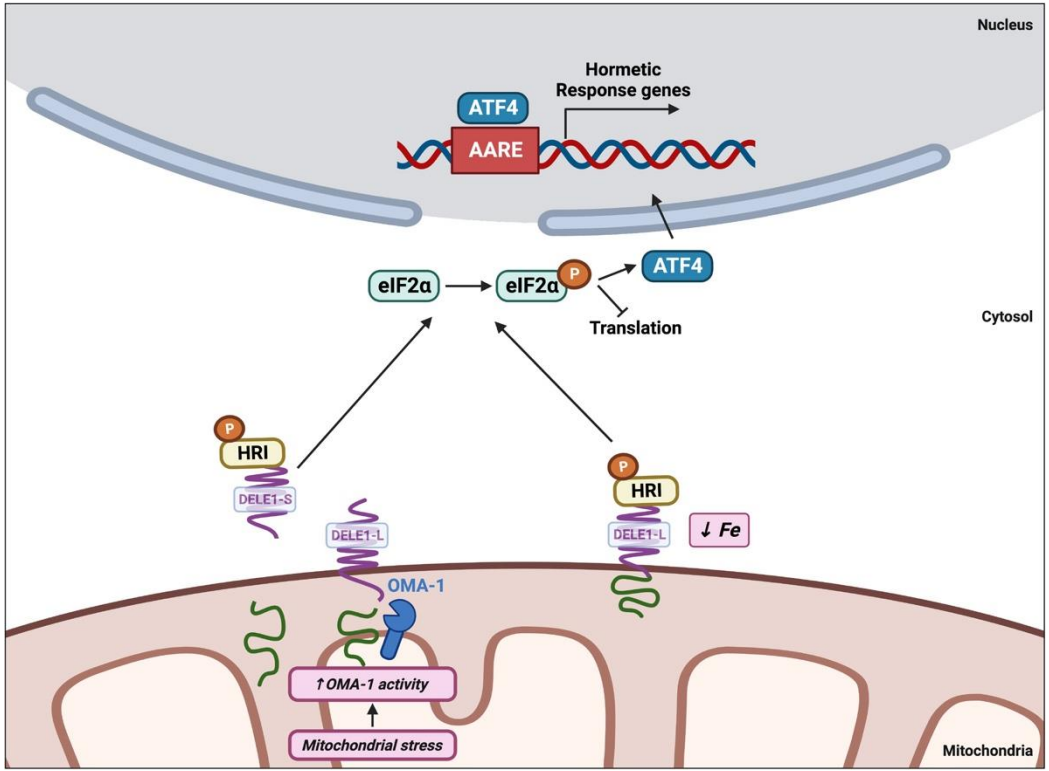
## Mitochondria orchestrate proteostatic and metabolic stress responses

Claes Andréasson[1,*], Martin Ott[2,**] & Sabrina Büttner[1,3,***]

The **mtISR** is a transcriptional program activated by mitochondrial damage/dysfunction caused by proteotoxicity and regulated by mitochondria-to-nucleus communication



# mtISR involves OMA1 and DELE1 cleavage

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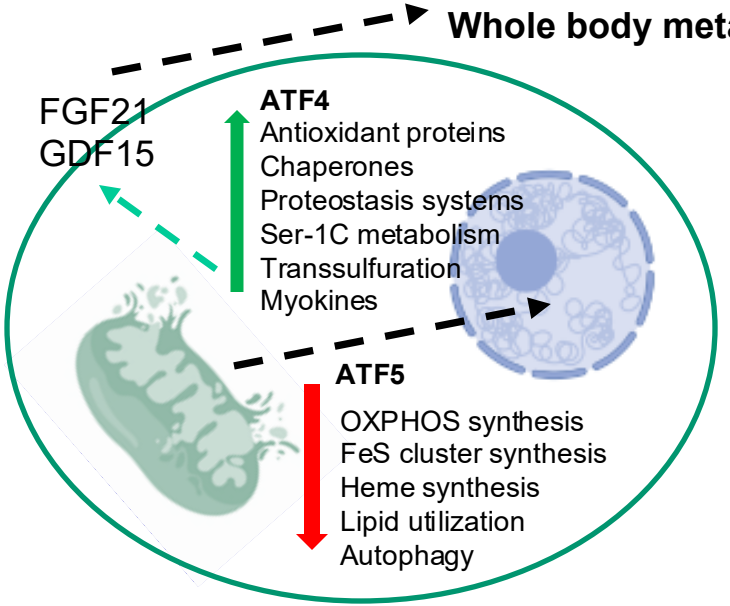
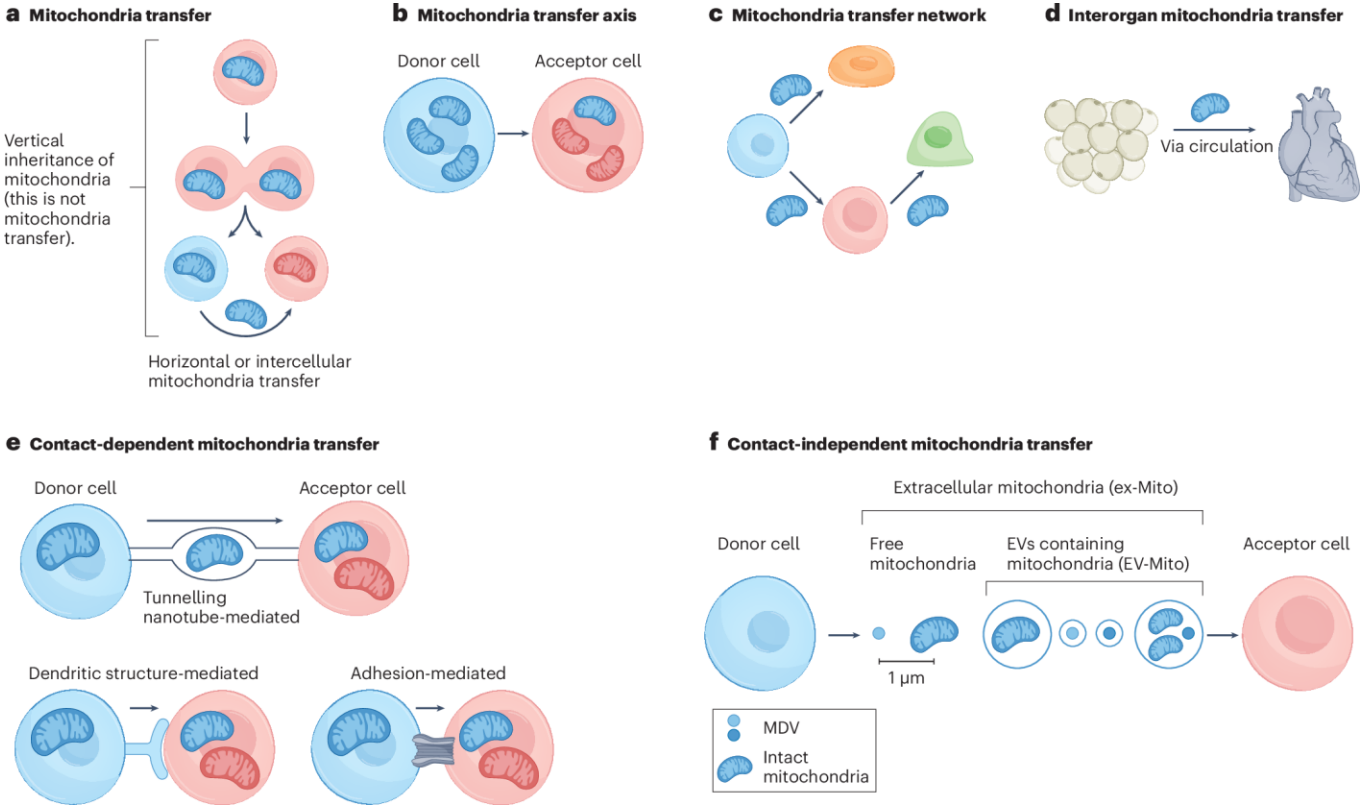
# The role of the mtISR transcriptional program




- **Acute** mtISR can promote cell survival and mitochondrial recovery
- **Chronic** mtISR can participate in mitochondrial dysfunction and contribute to disease pathogenesis

# Recommendations for mitochondria transfer and transplantation nomenclature

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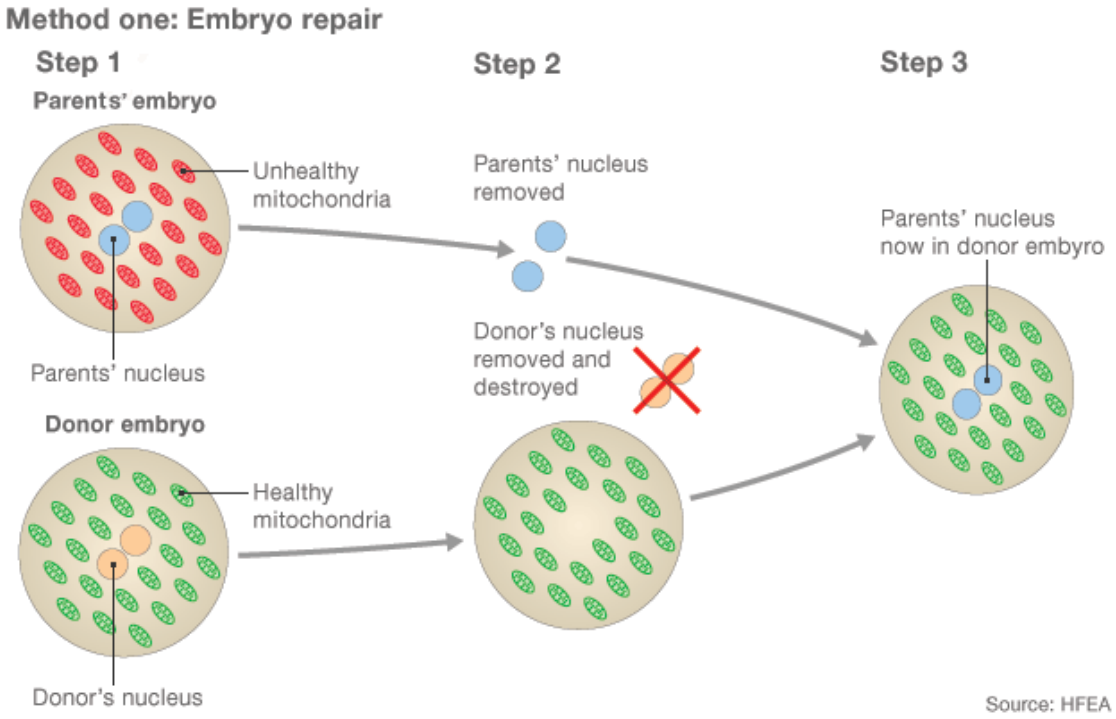
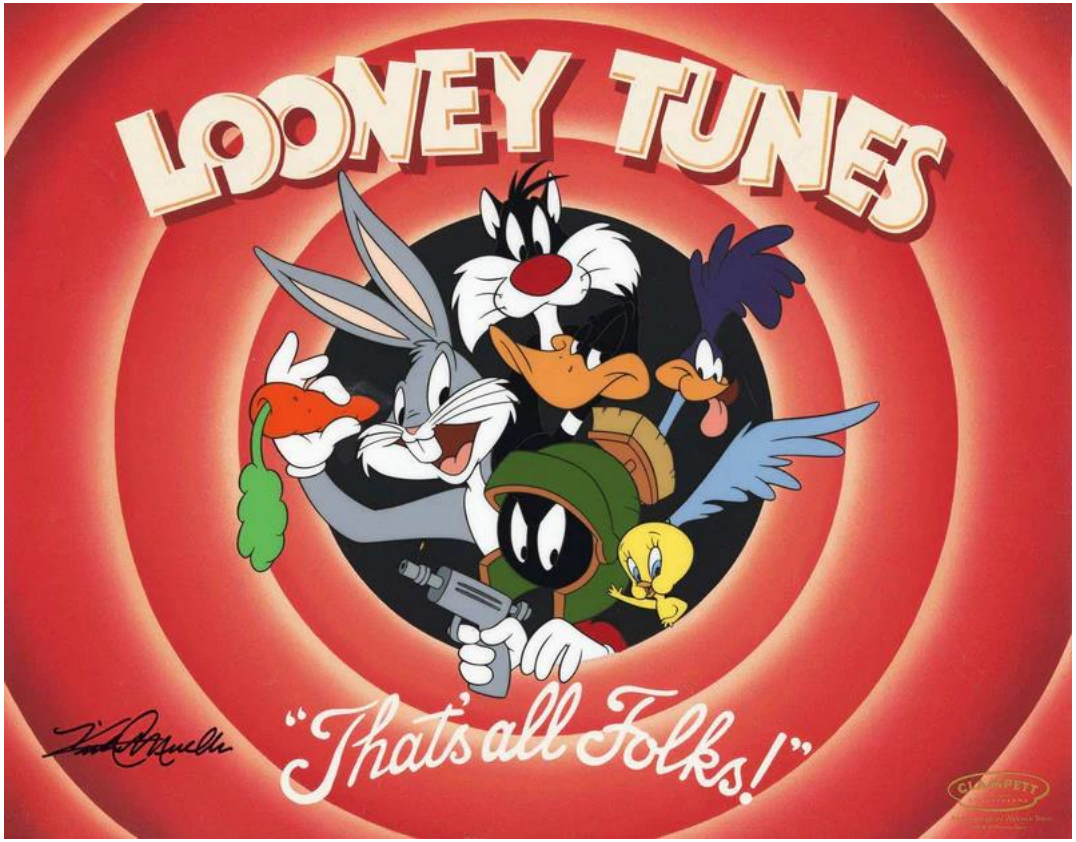
# Mitochondrial replacement in the oocyte to avoid transmission of pathogenic mtDNA




LOONEY TUNES
"That's all Folks!"