Power & Balance: Mitochondrial Homeostasis in Aging

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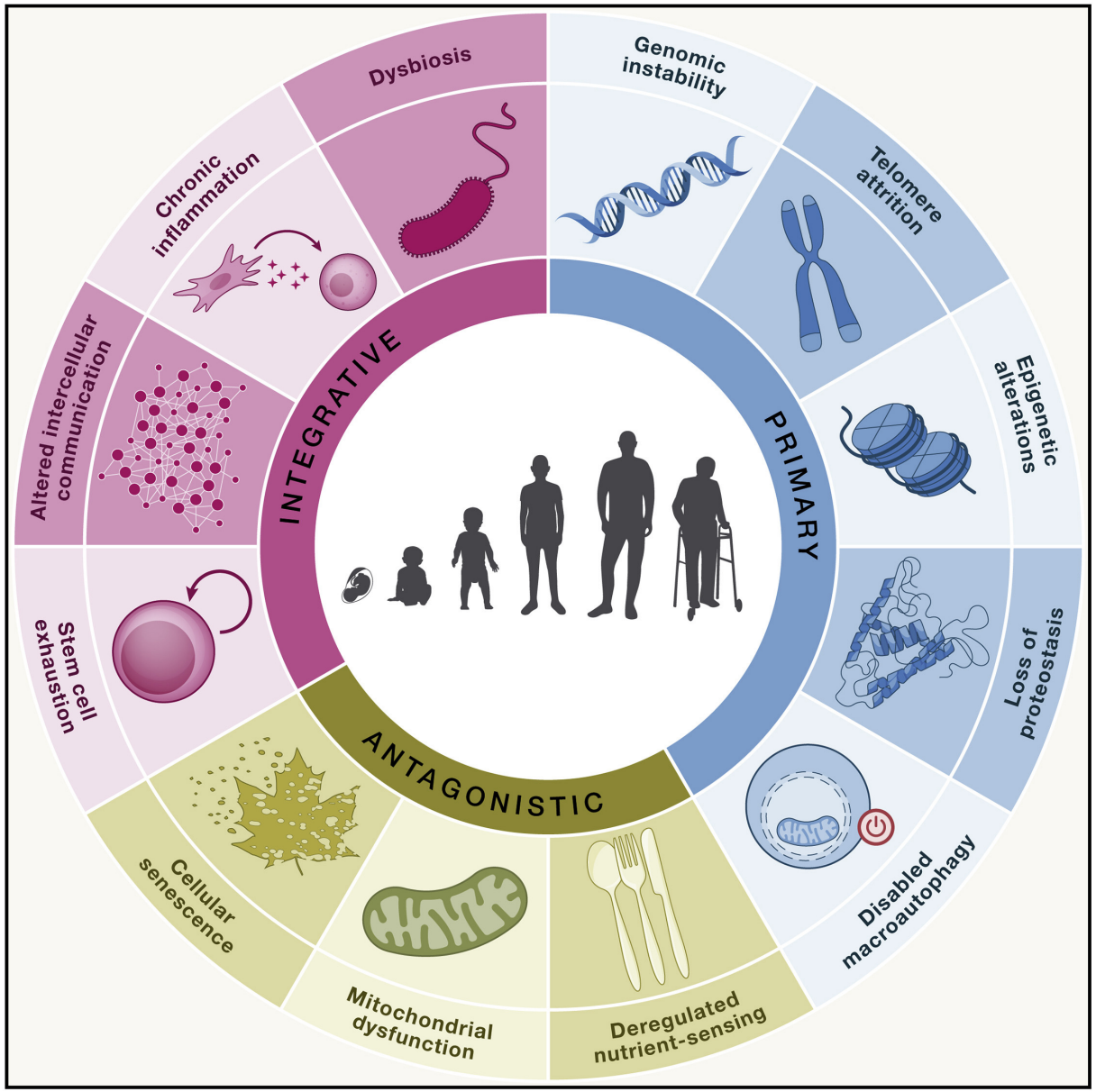
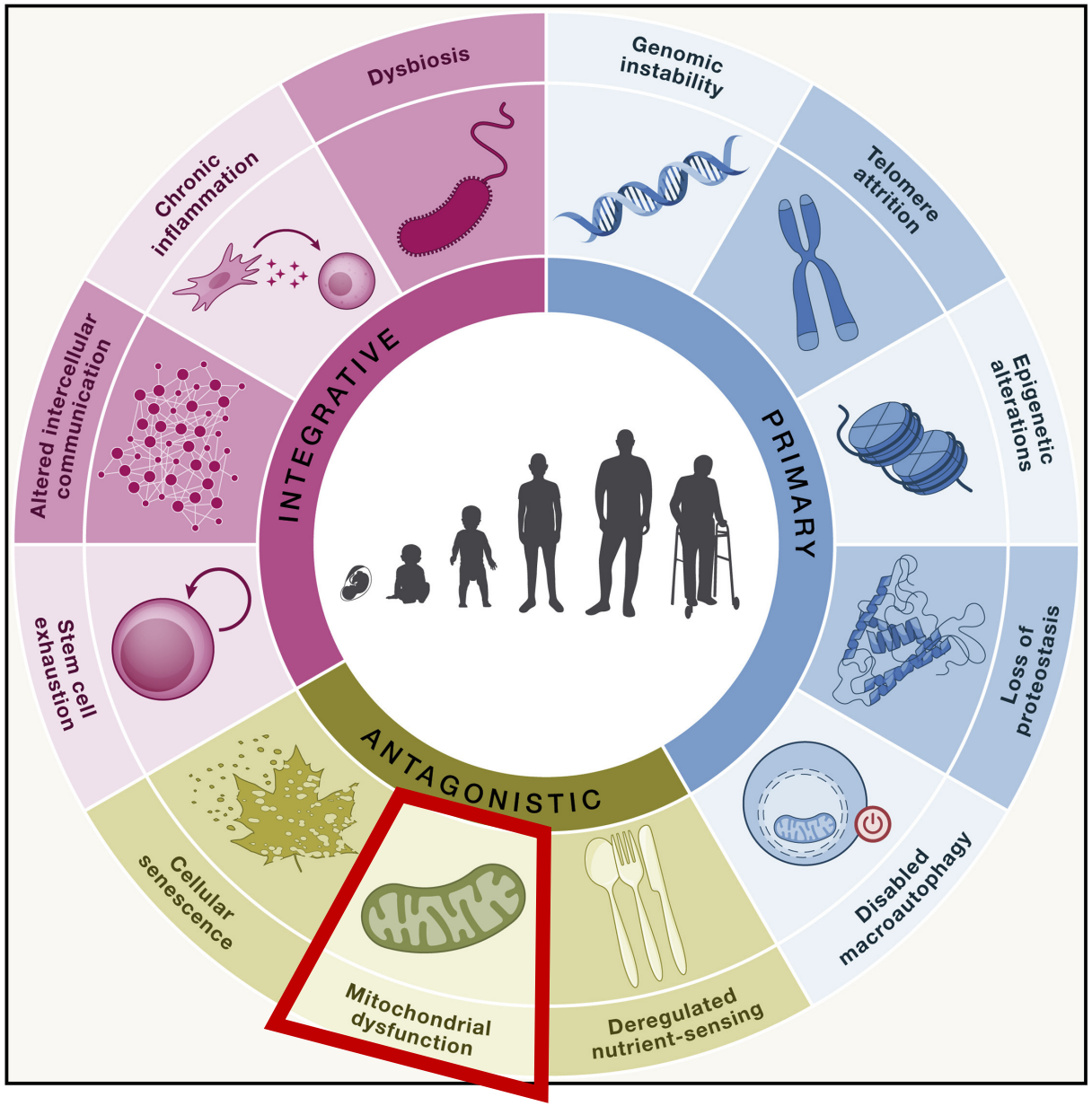
PhD Course:
Why do we age?
Molecular and Cellular Mechanisms of Aging

Hallmarks of Aging



López-Otín et al. 2023 Cell

Hallmarks of Aging



López-Otín et al. 2023 Cell

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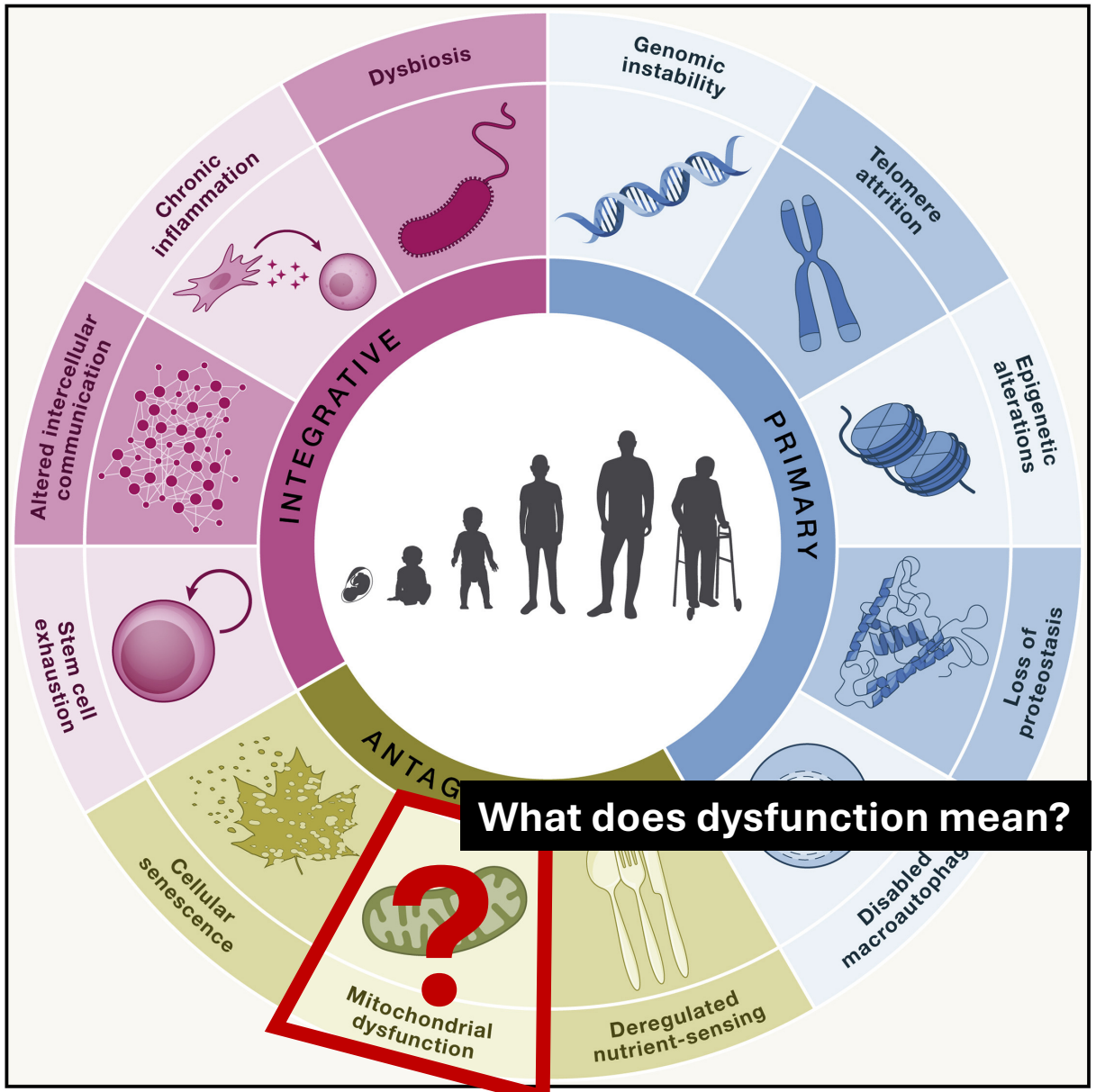

López-Otín et al. 2023 Cell

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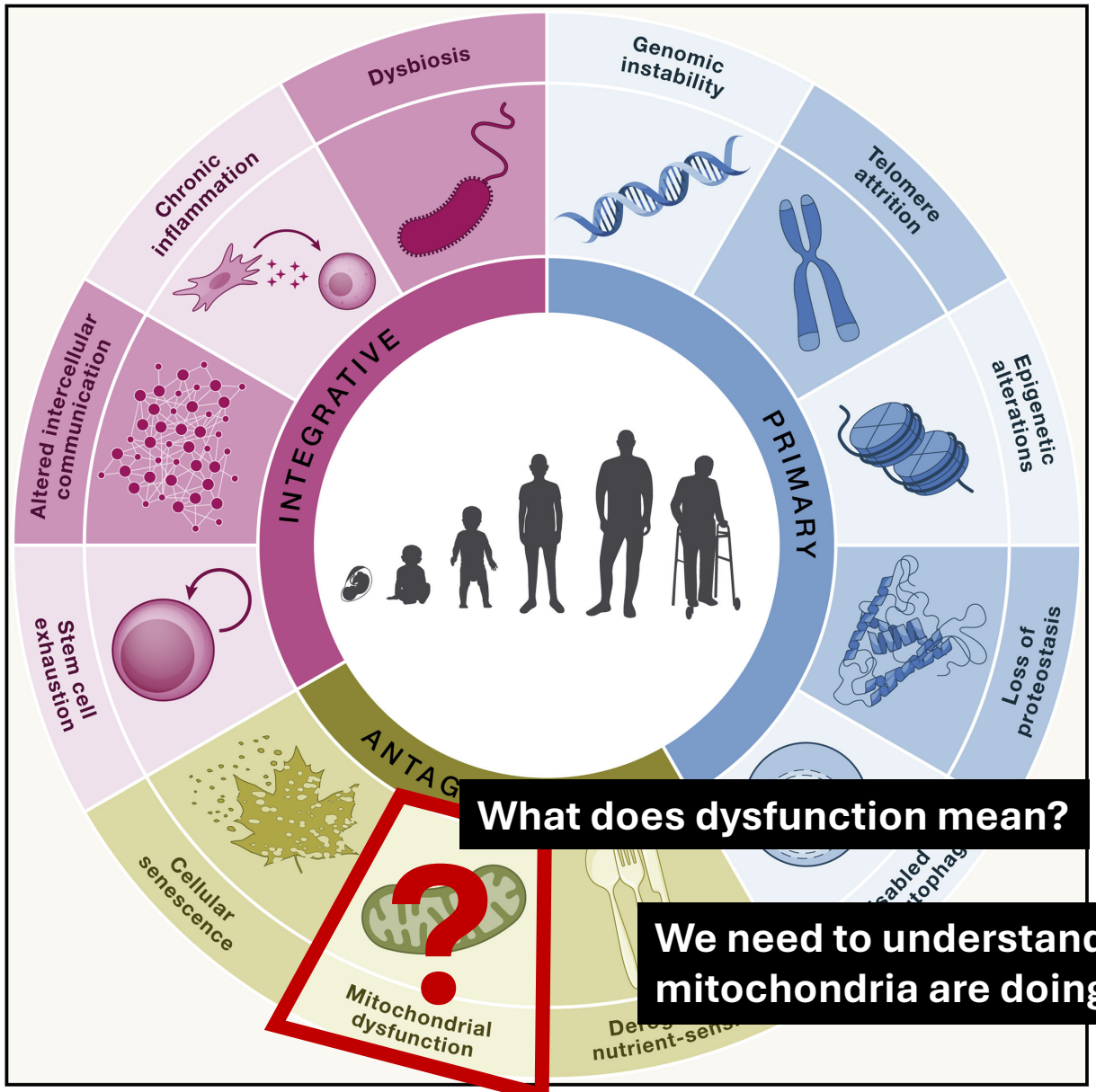

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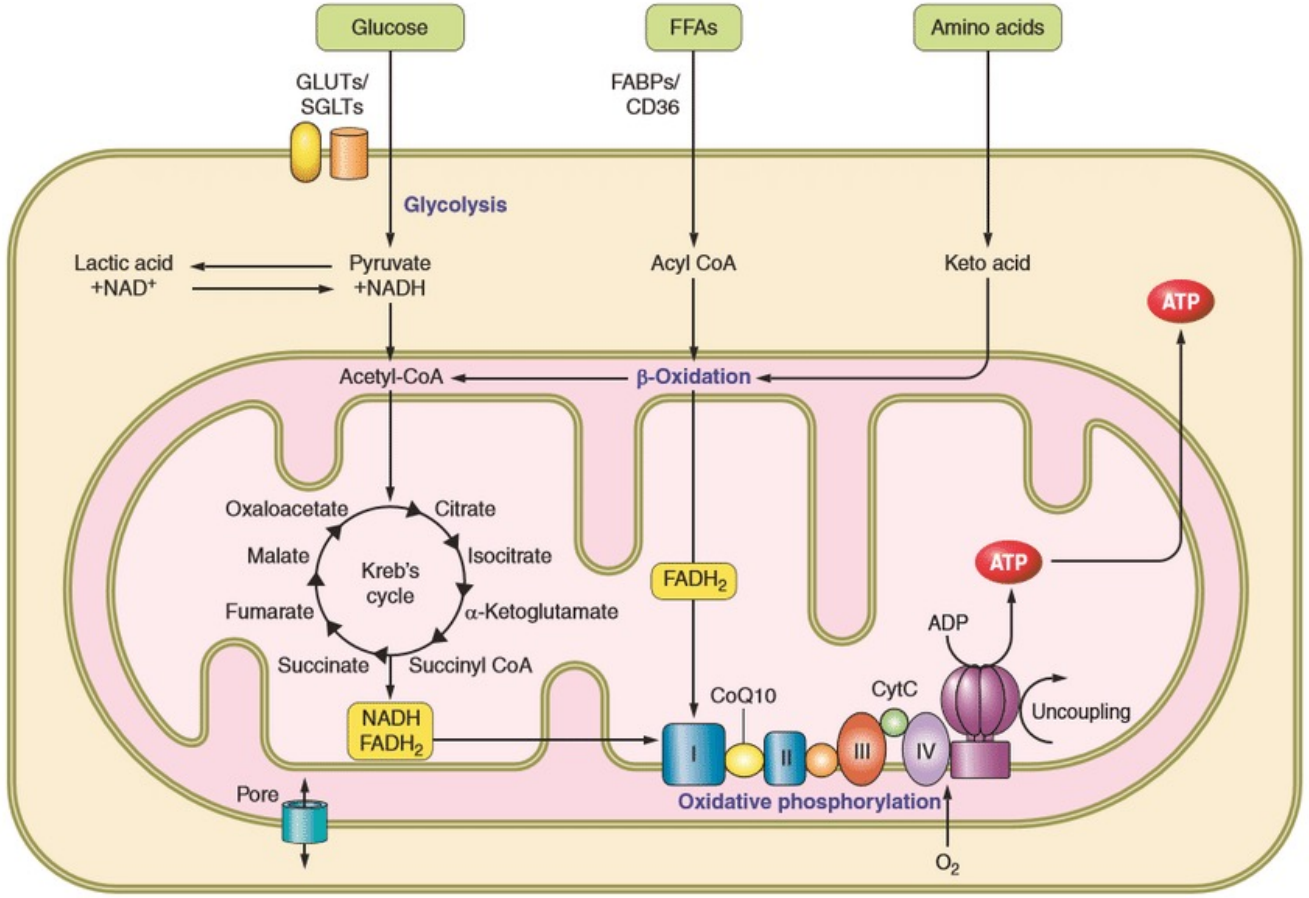
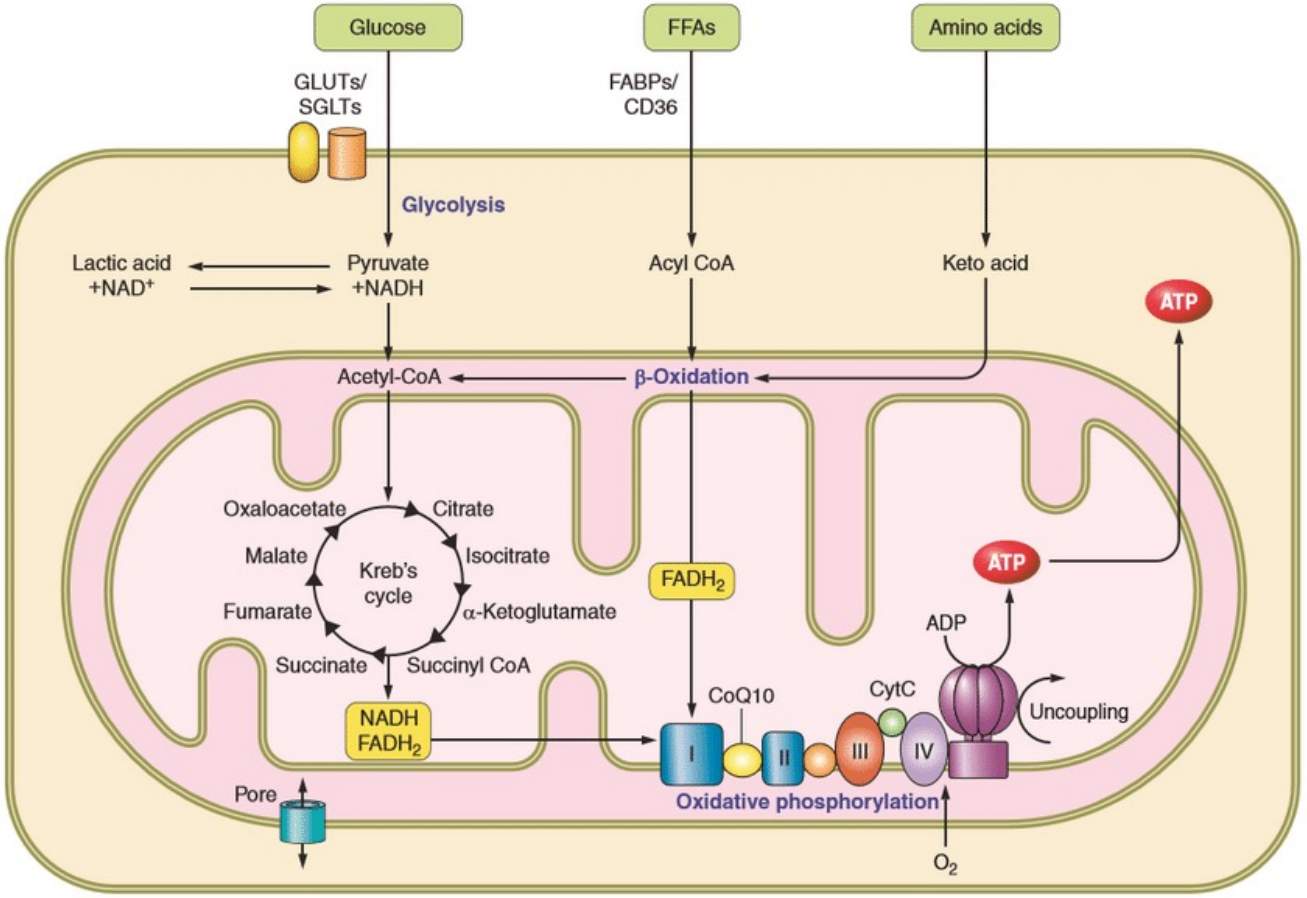
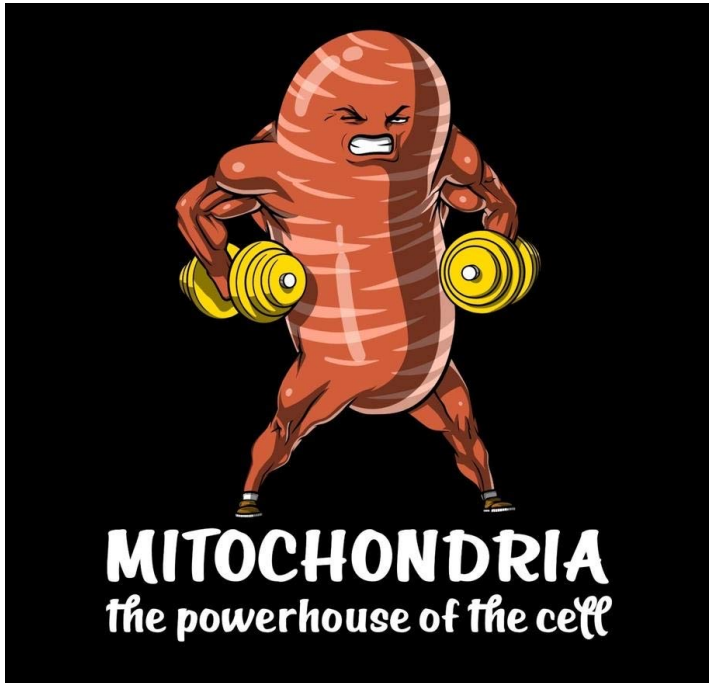
Mitochondrial Function: Energy Production



Mitochondrial Function: Energy Production





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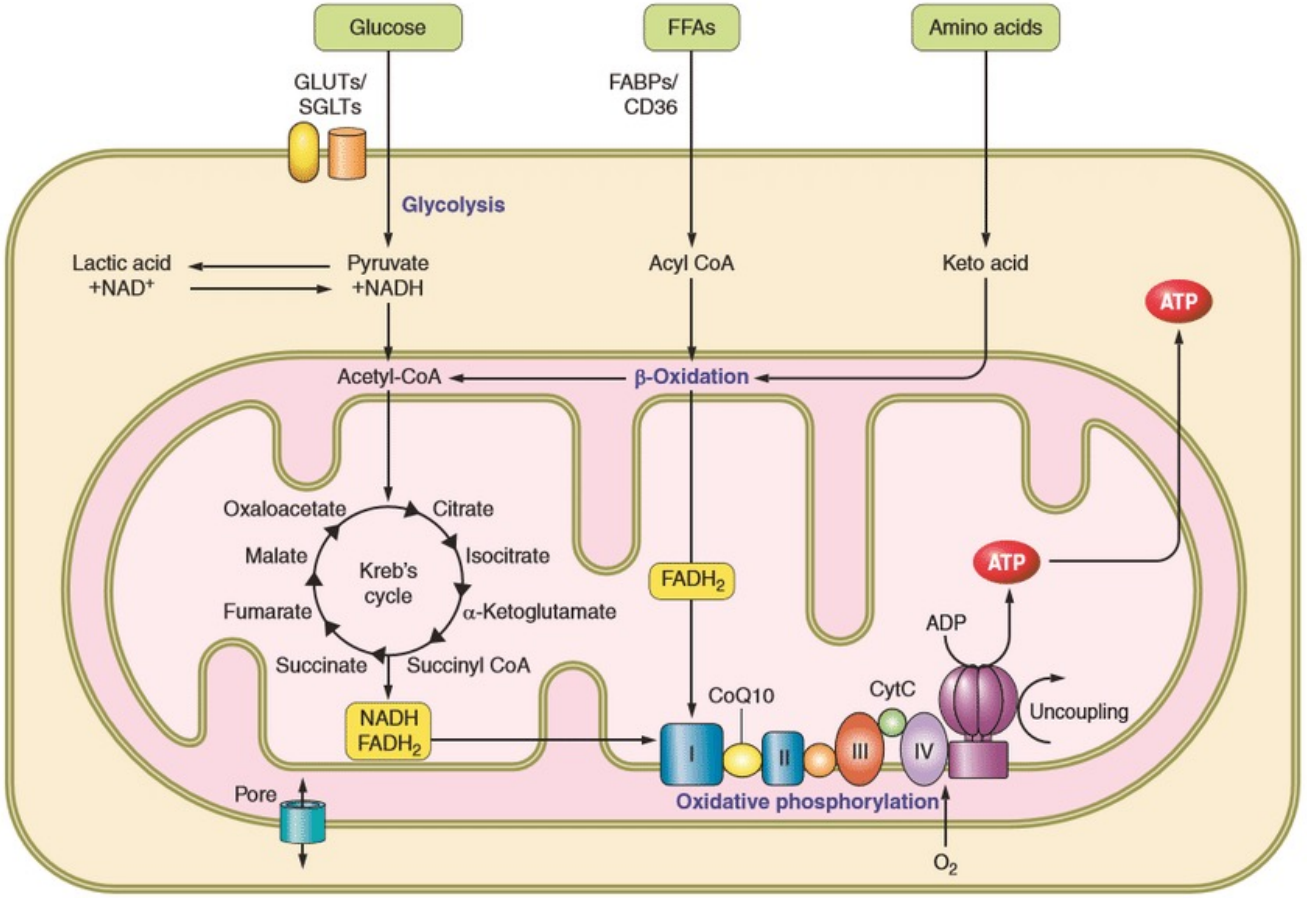

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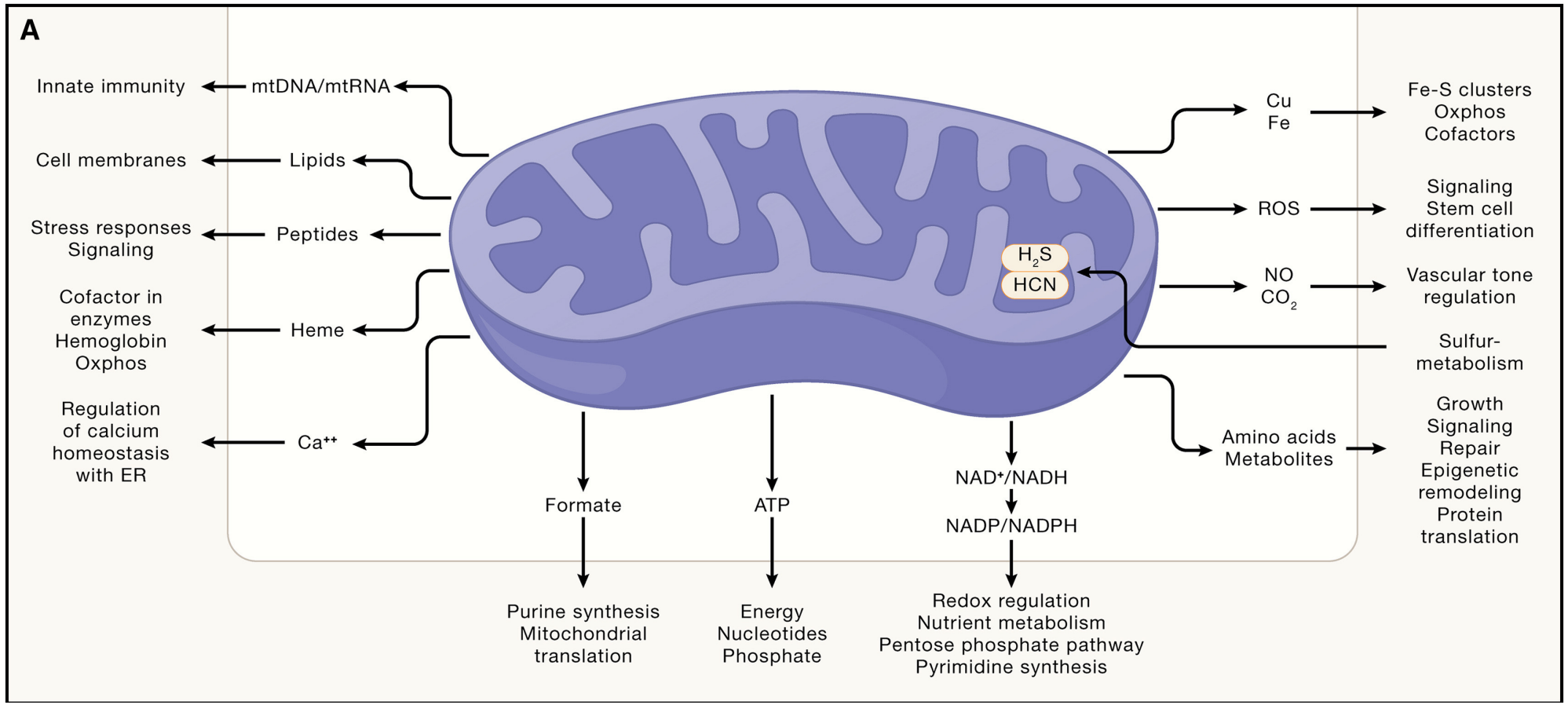
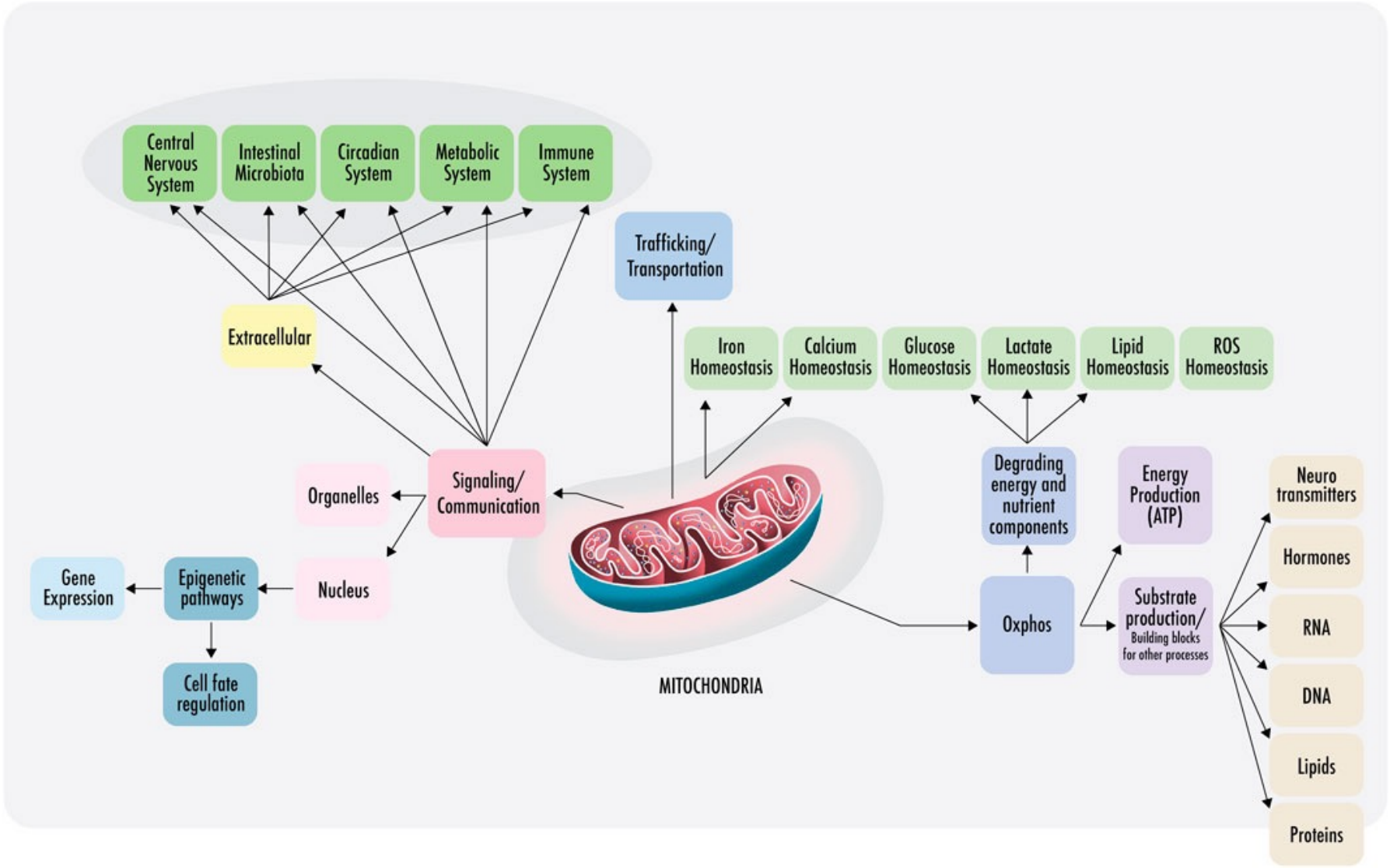
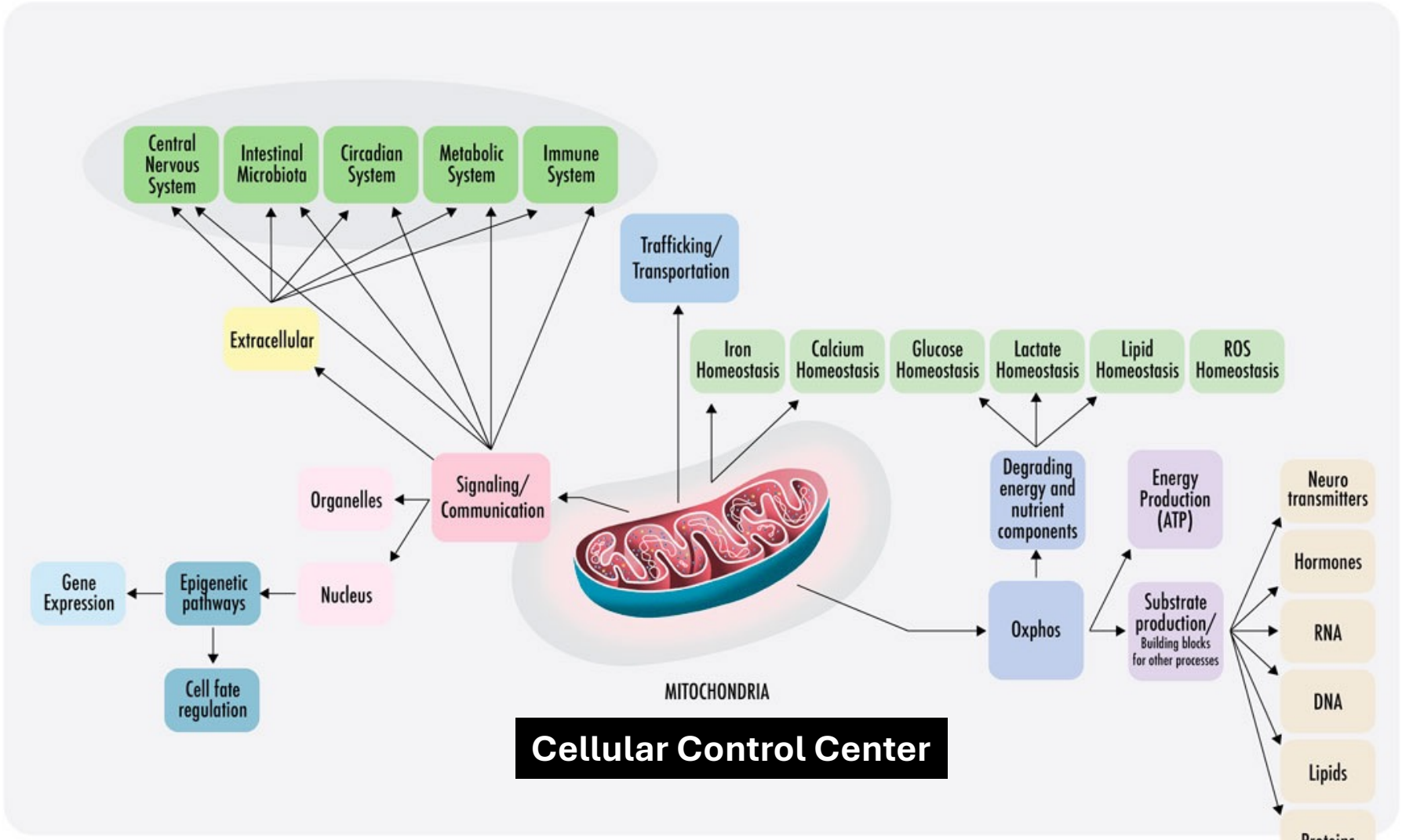
Mitochondrial Functions



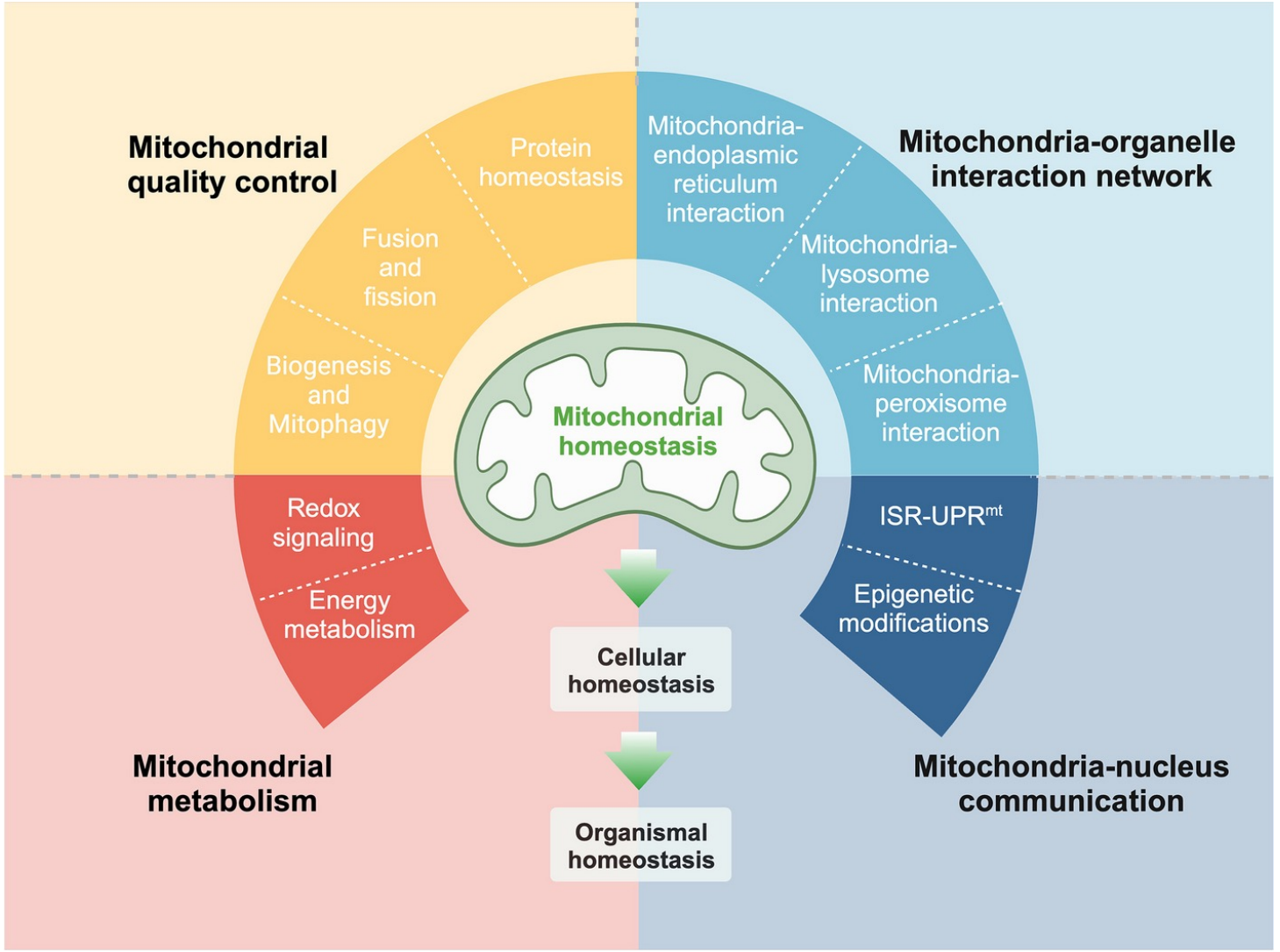
Mitochondrial Functions



Mitochondrial Functions

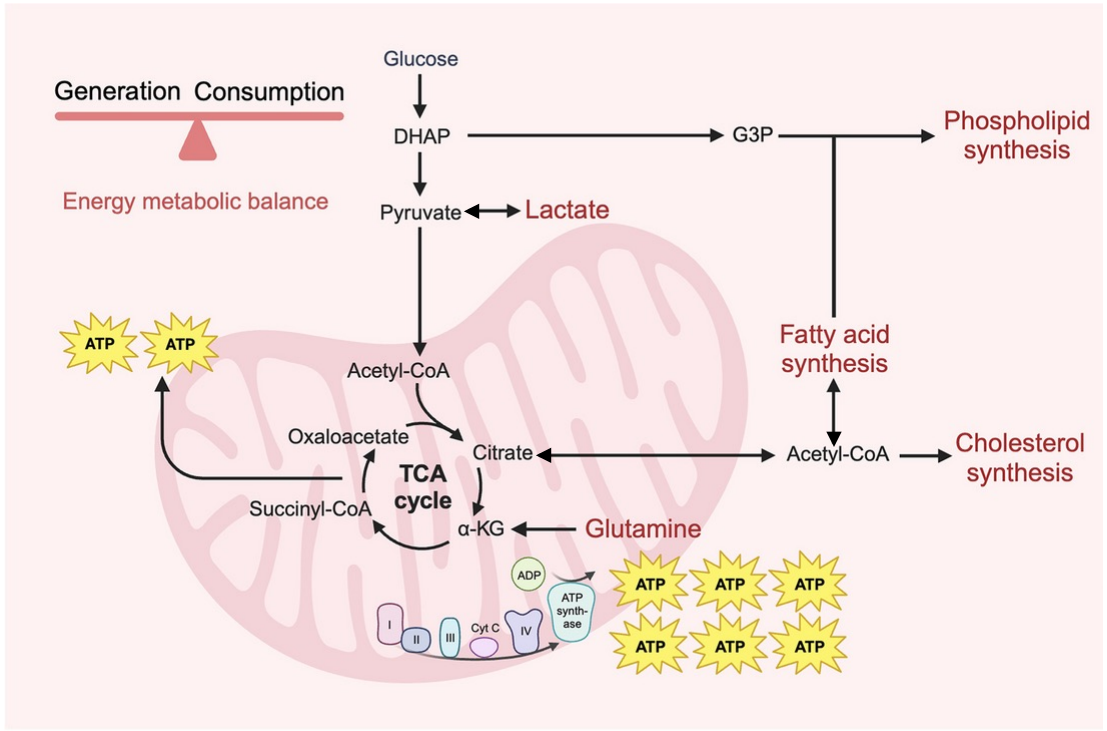


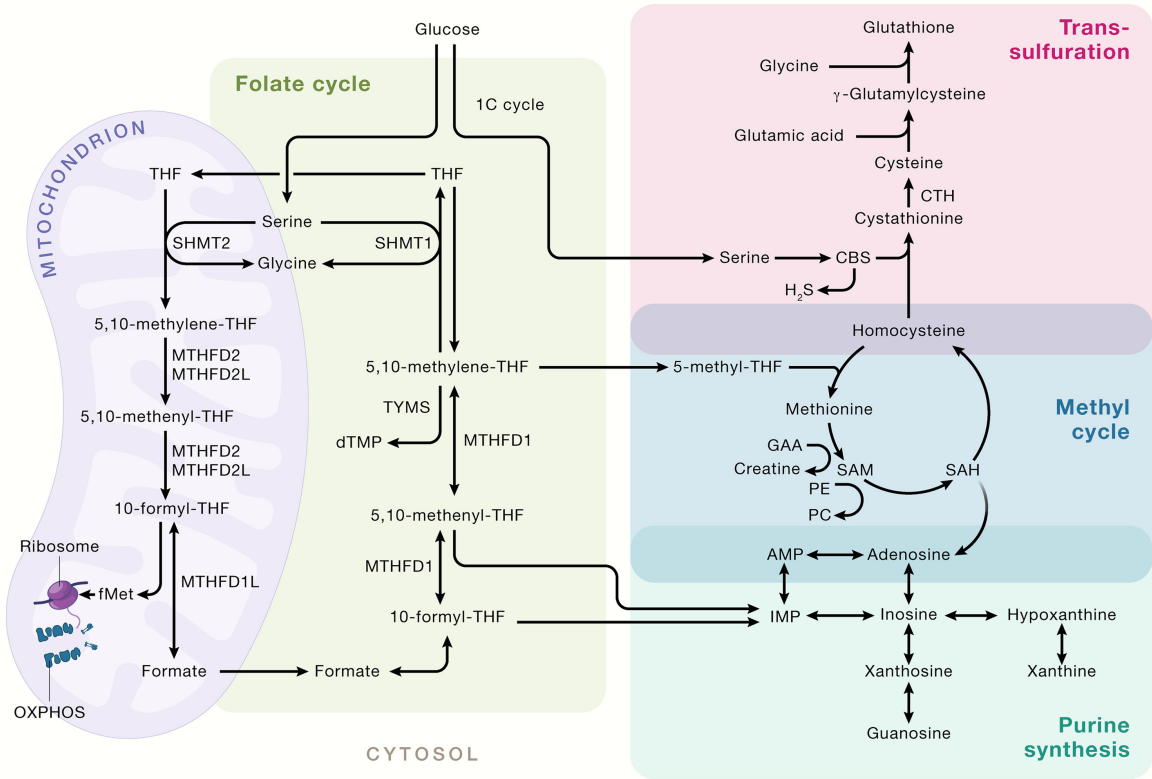
Mitochondrial Homeostasis



Li et al. 2024 Current Medicine

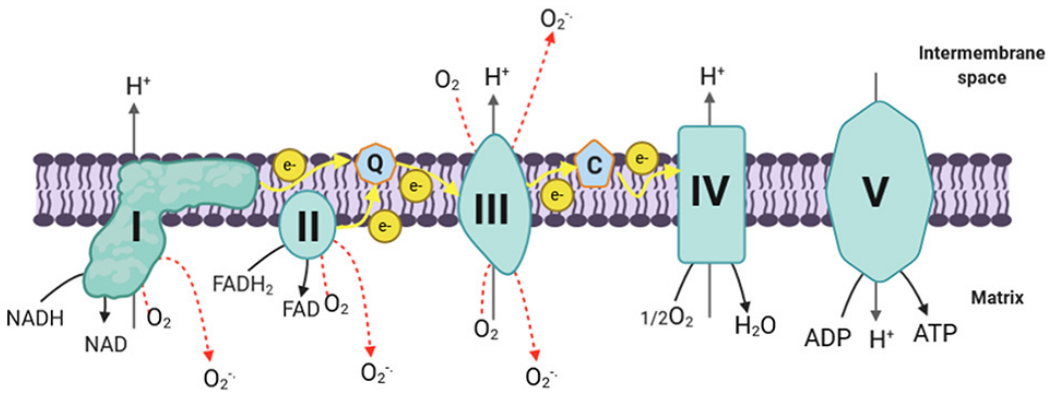
Mitochondrial Metabolism

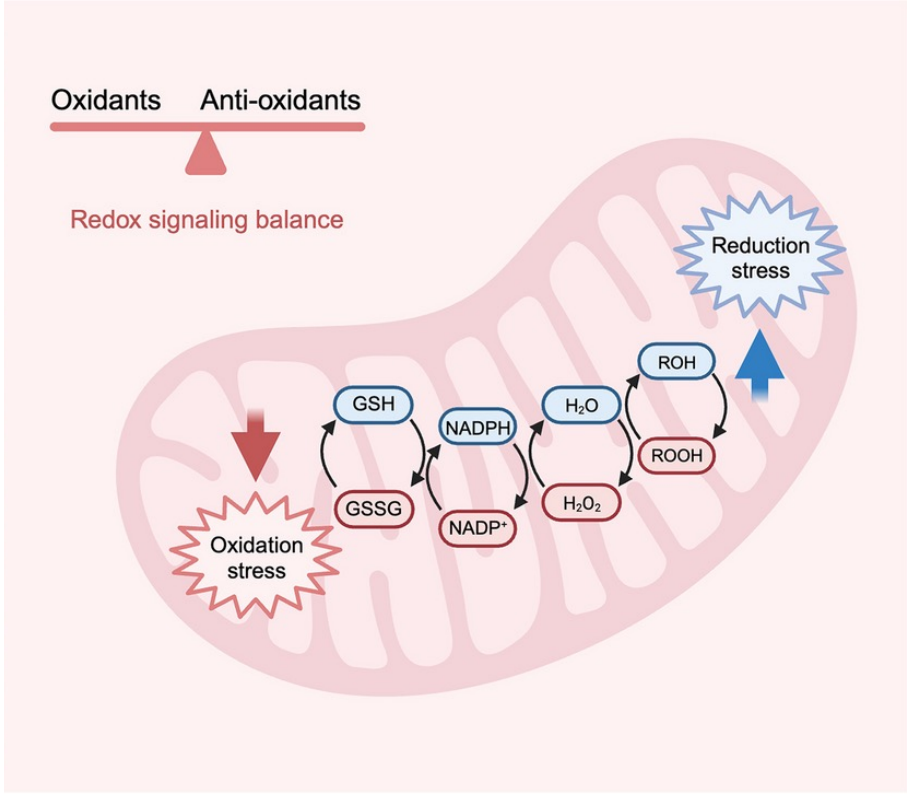




Maintenance of Adequate Metabolic Flux

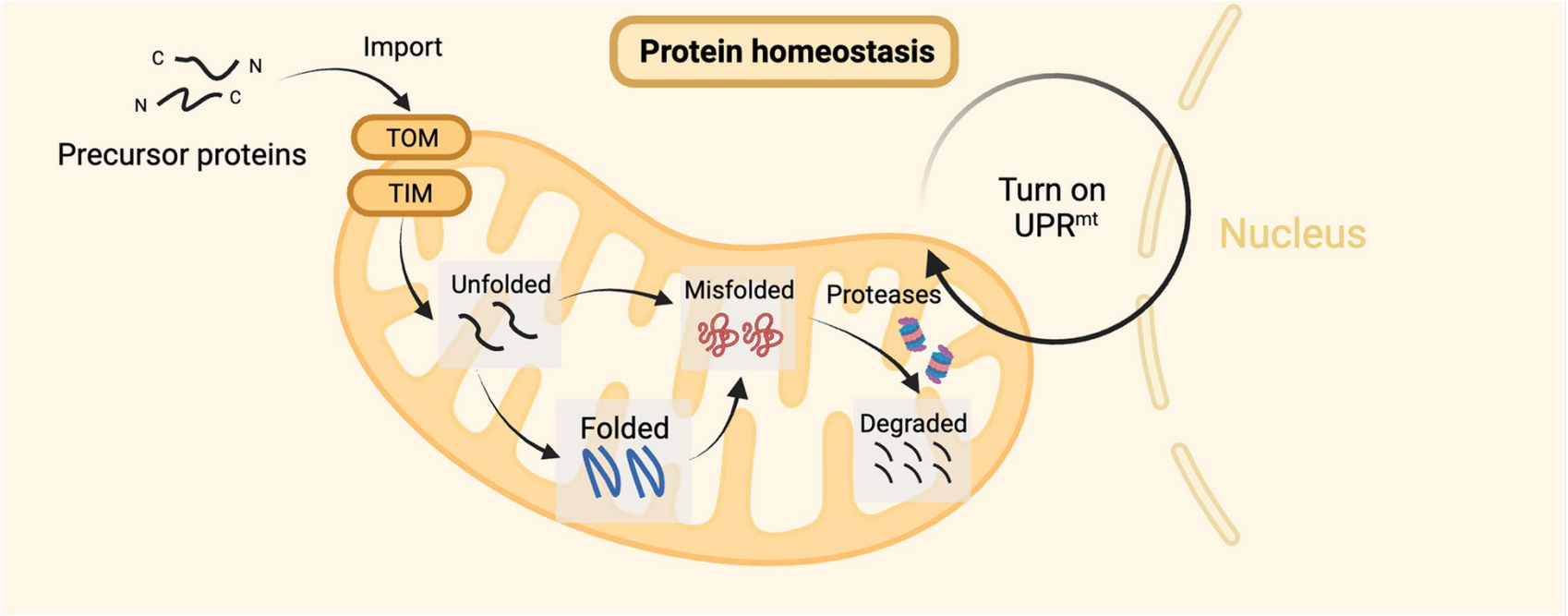
Mitochondrial Metabolism





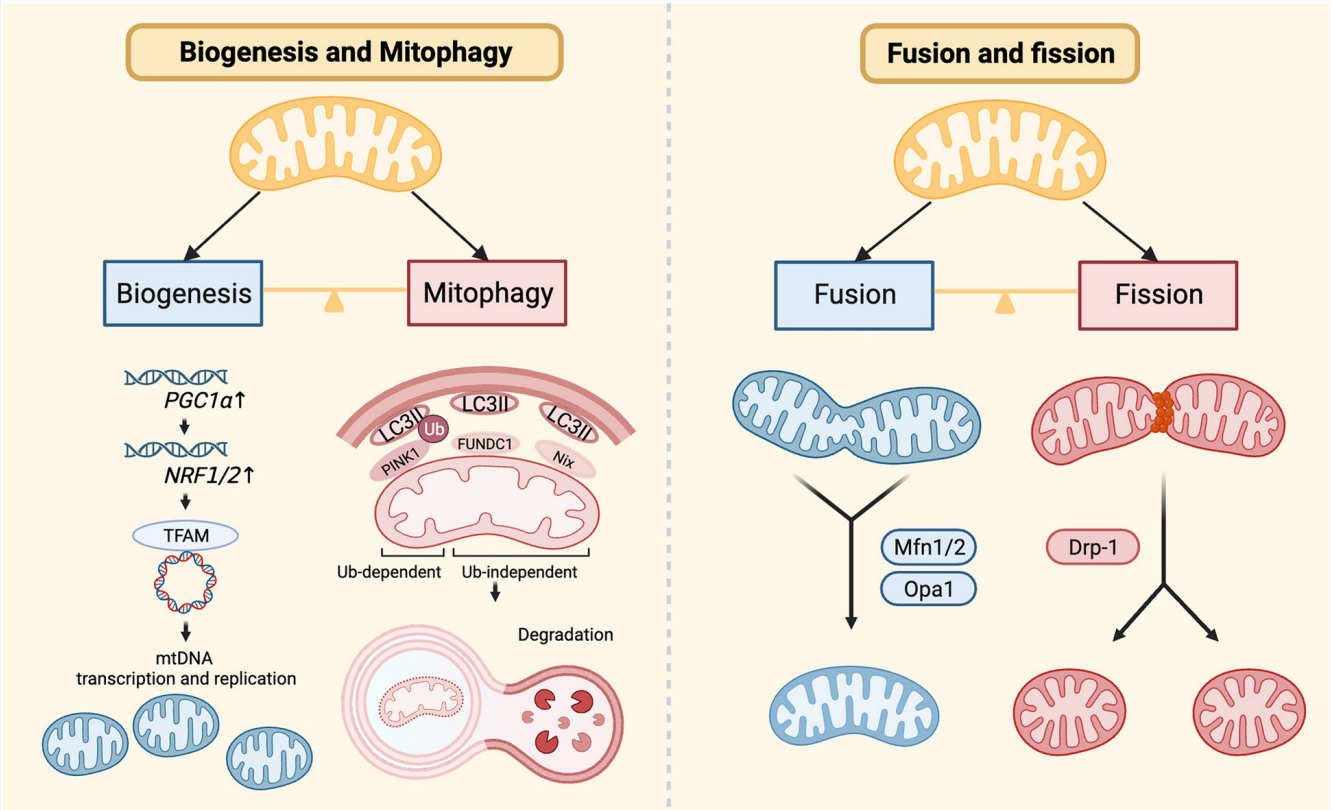
Prevention of Oxidative Stress/Damage

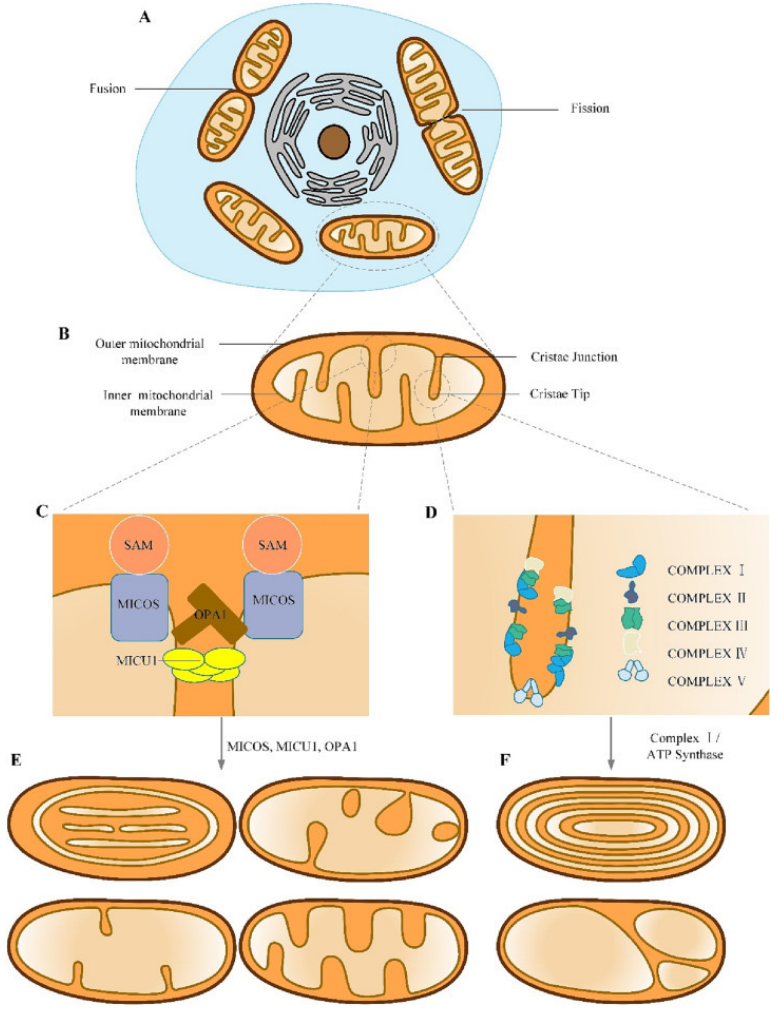
Mitochondrial Quality Control



Guarantee Availability of the Right Set of Proteins at the Right Time

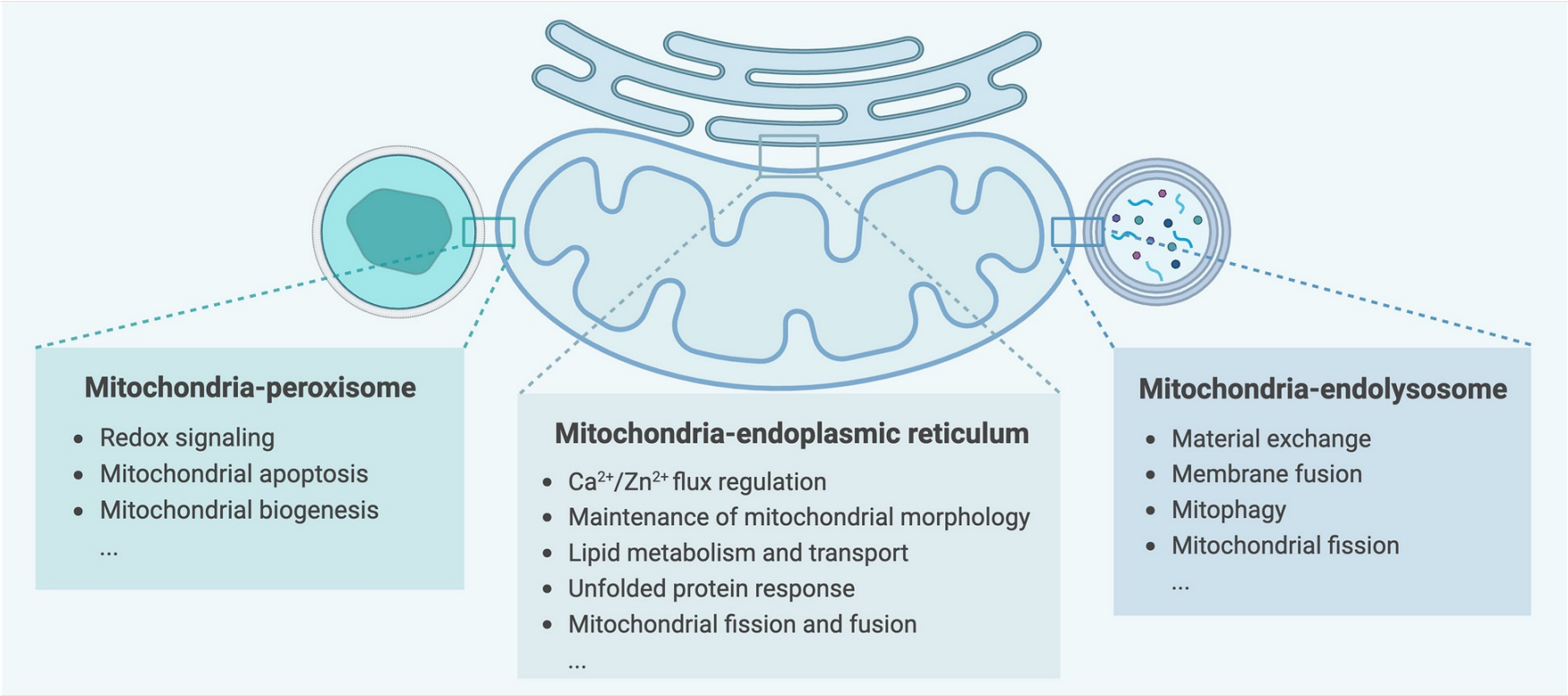
Mitochondrial Quality Control





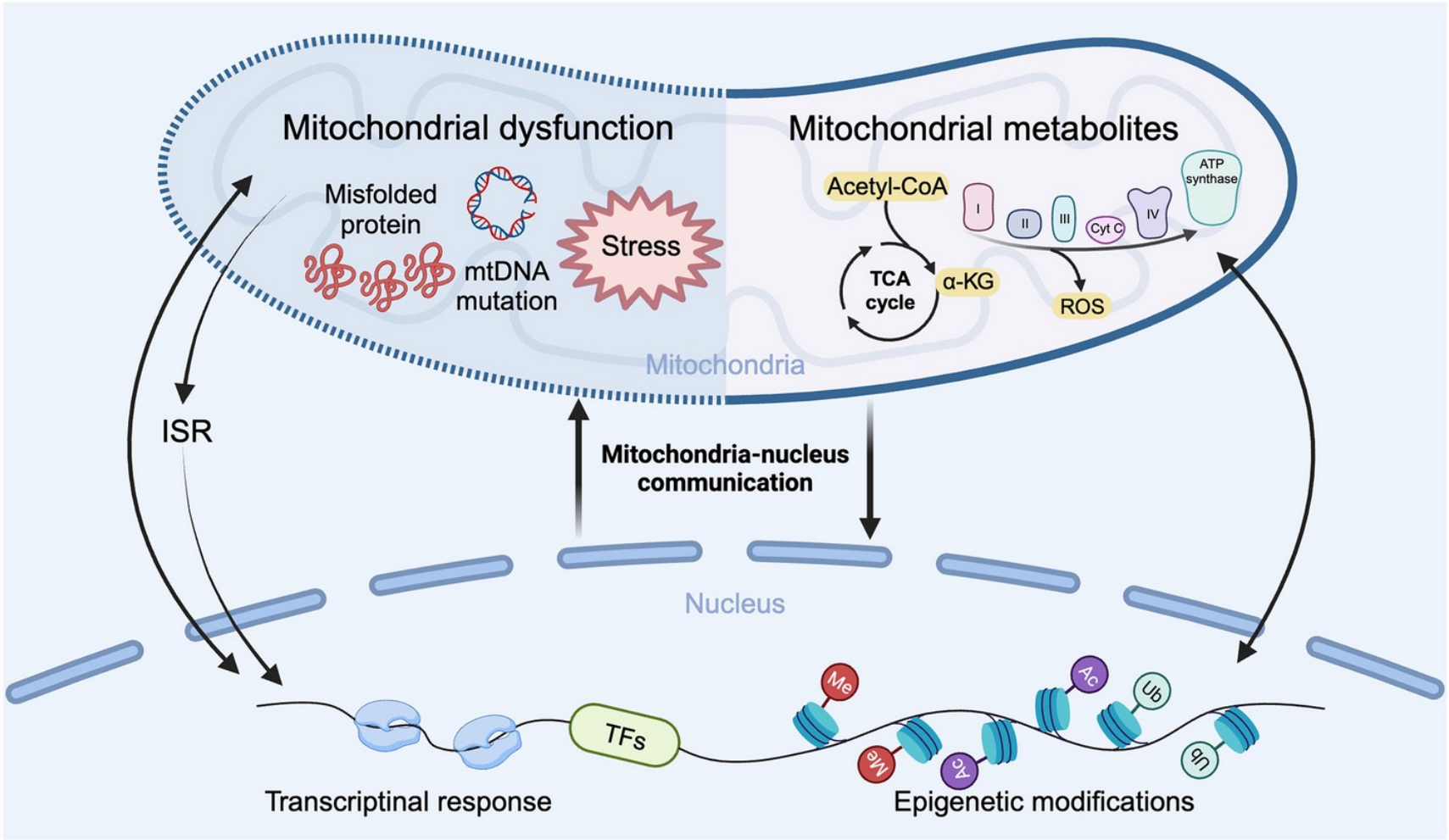
Control of Amount, Volume and Architecture

Mitochondria-Organelle Interaction Network

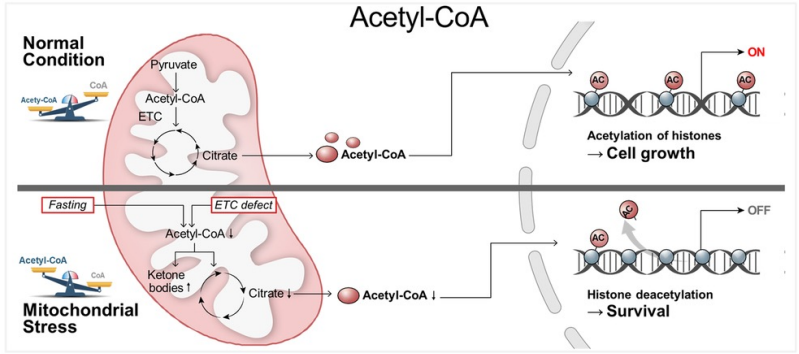


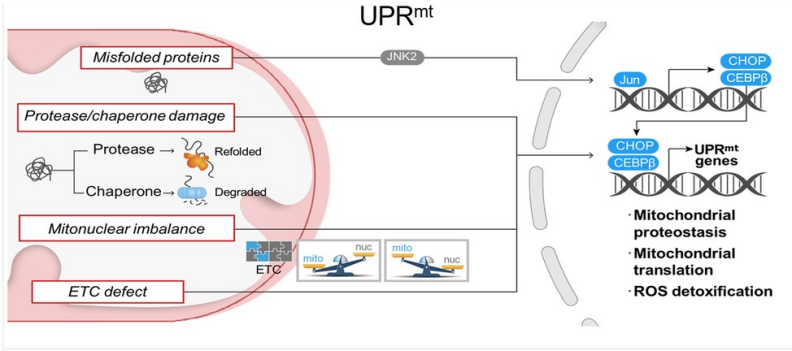
Maintaining Connectivity is Key for Functionality

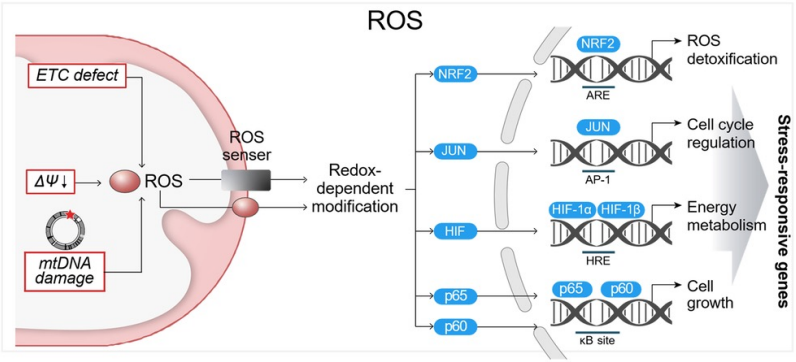
Mitochondria-Nucleus Communication

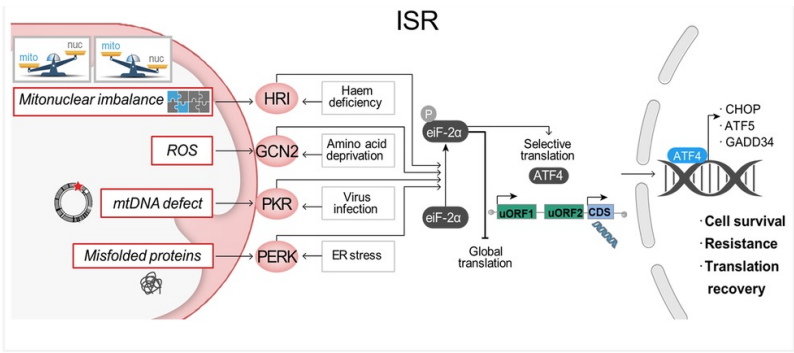


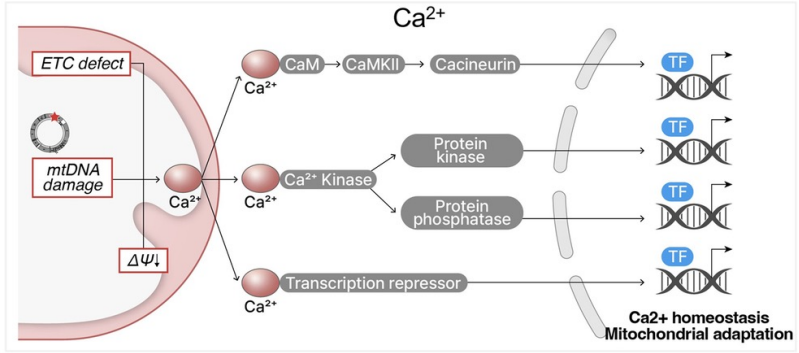
Mitochondria Retrograde Signaling





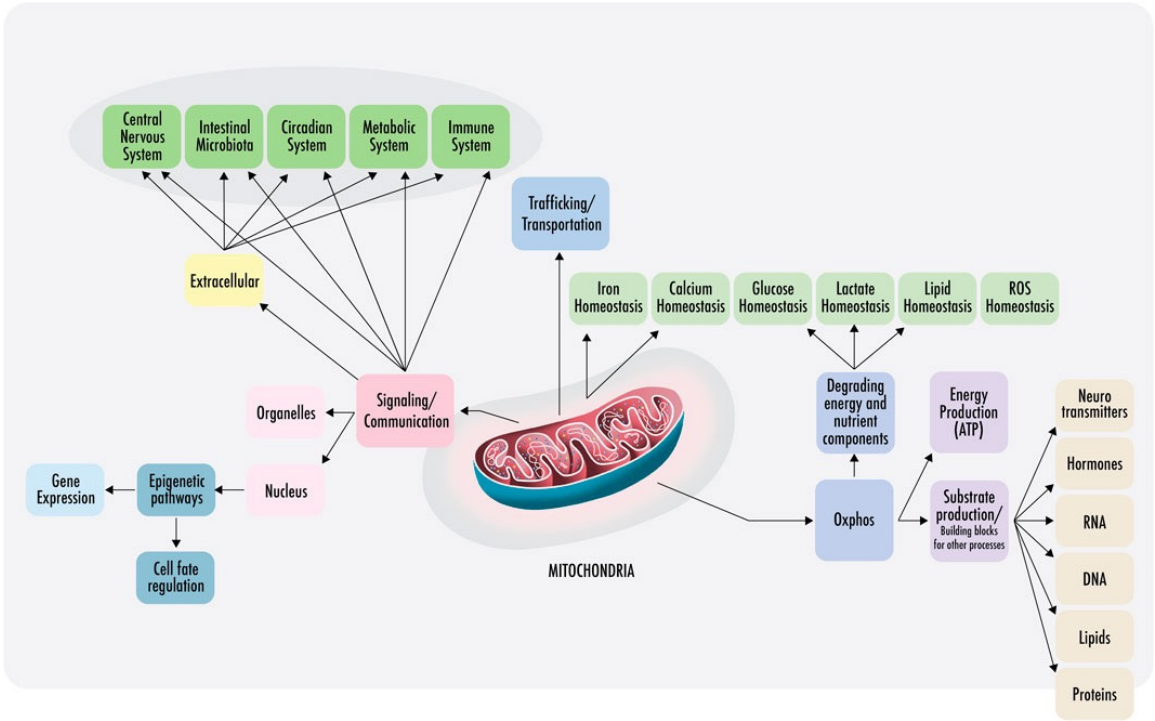


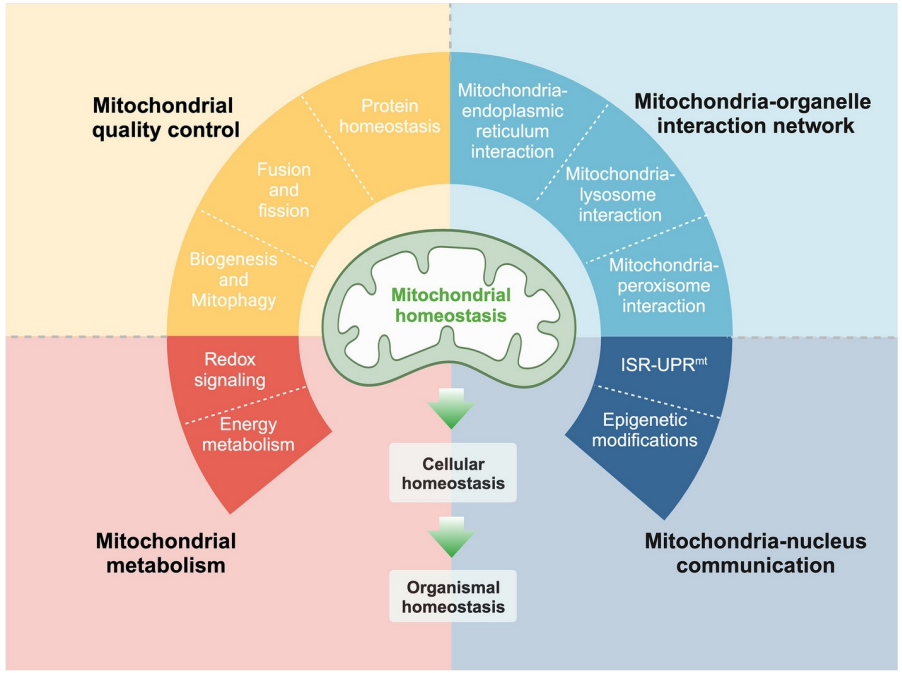




Specialized Routes of Communication to Tune Mitochondrial Adaptation

Mitochondrial Functions are Safeguarded by Homeostatic Networks





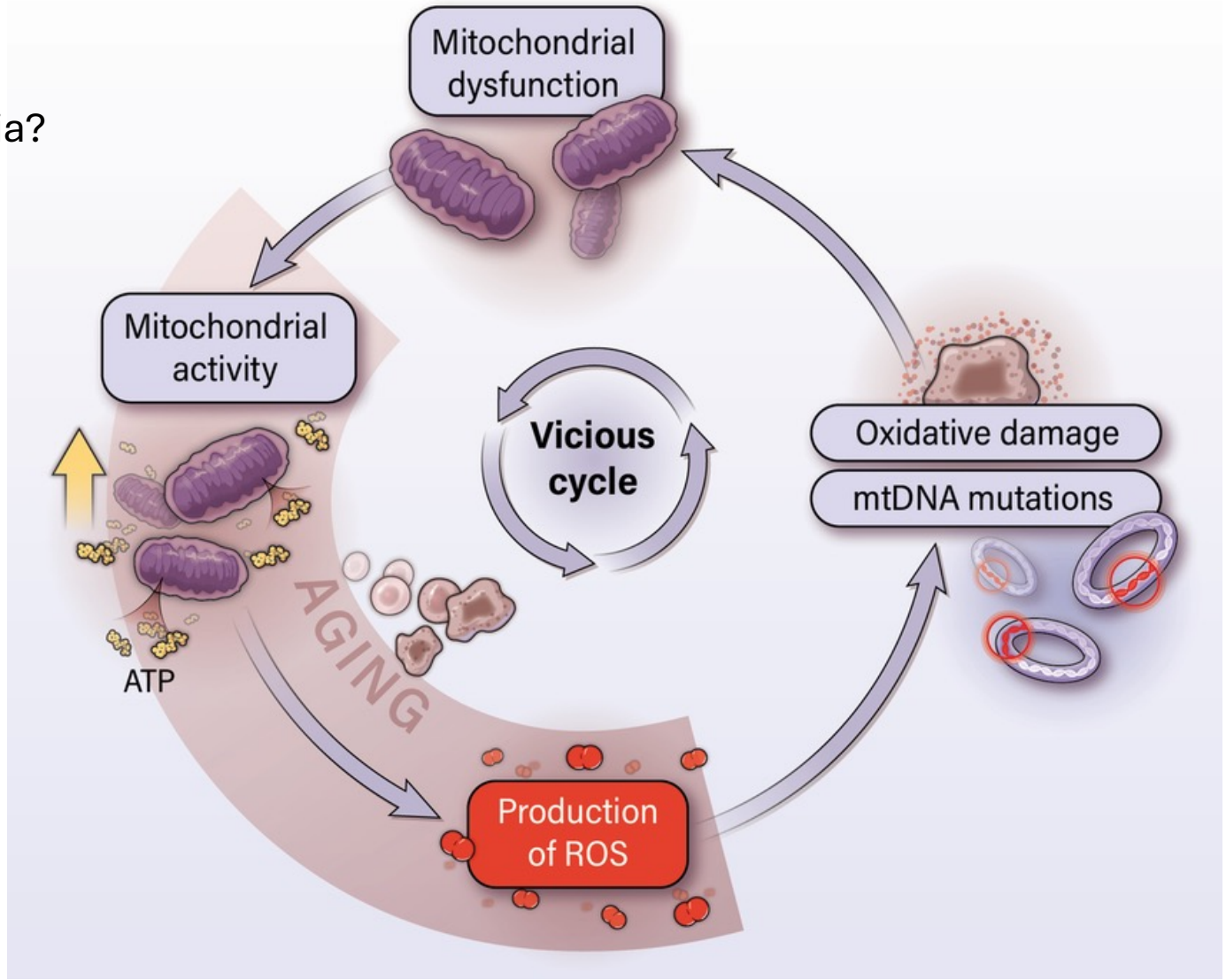
Mitochondrial Dysfunction is Complex, Interdependent and Context-Specific

How is Mitochondrial Homeostasis Challenged During Aging?

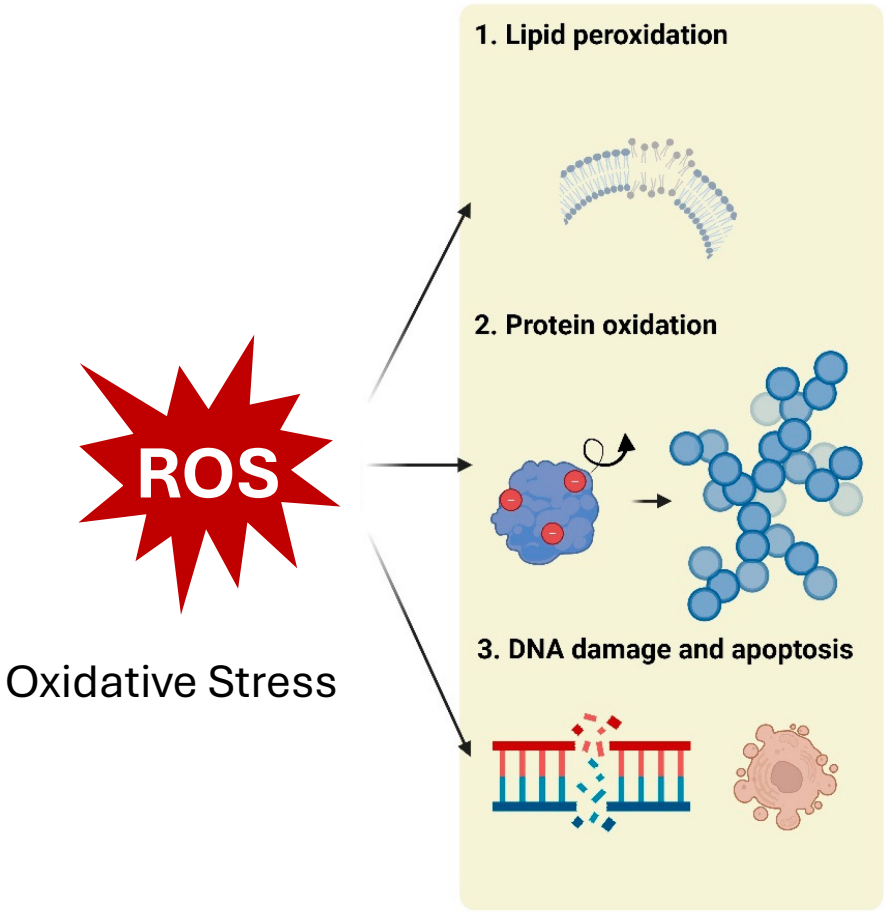
What are the Physiological Consequences?

Mitochondrial Free Radical Theory of Aging

Postulated in 1972
by Denham Harman
The Biologic Clock: The Mitochondria?



Consequences of Increasing Oxidative Stress



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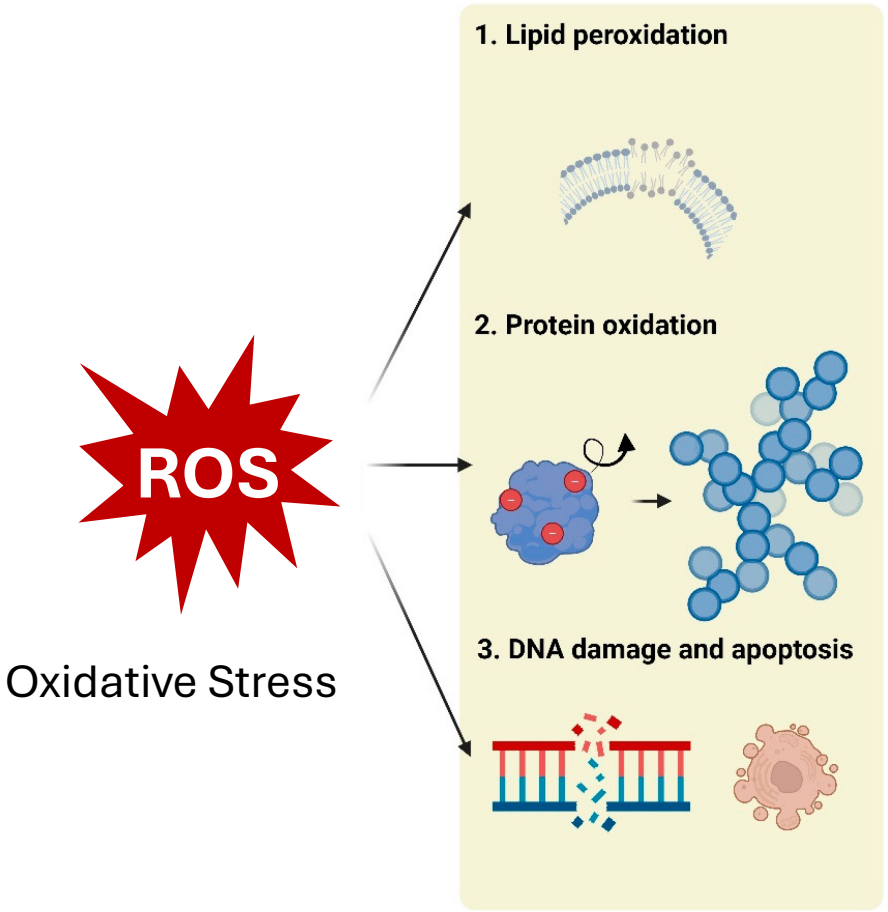
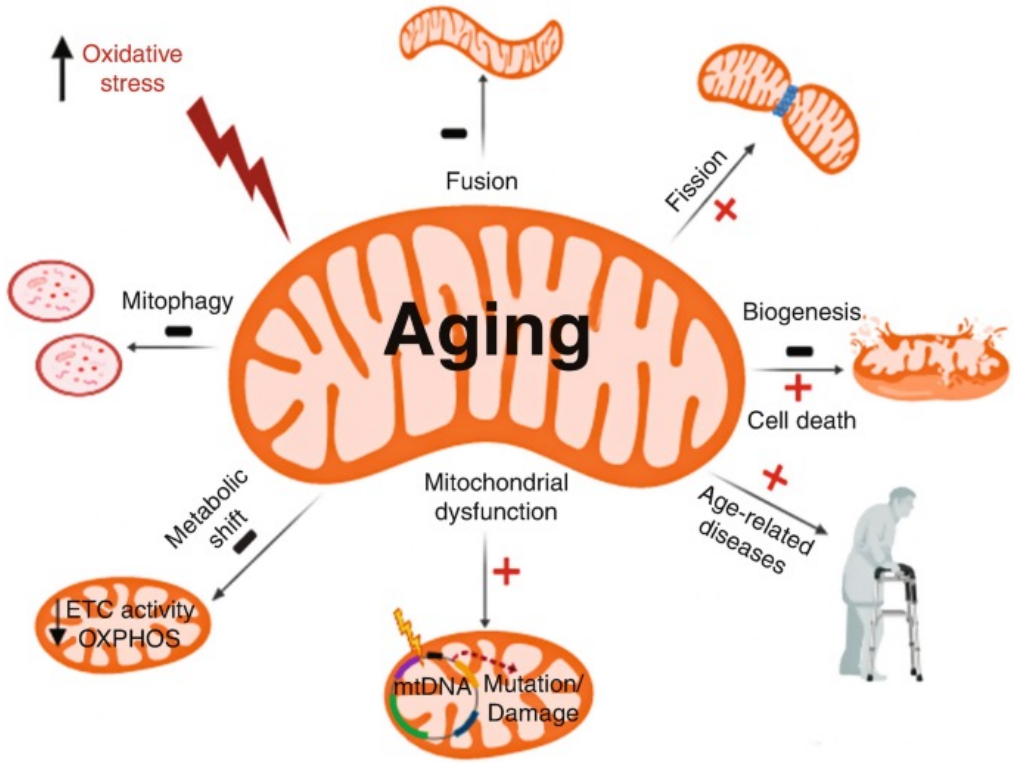
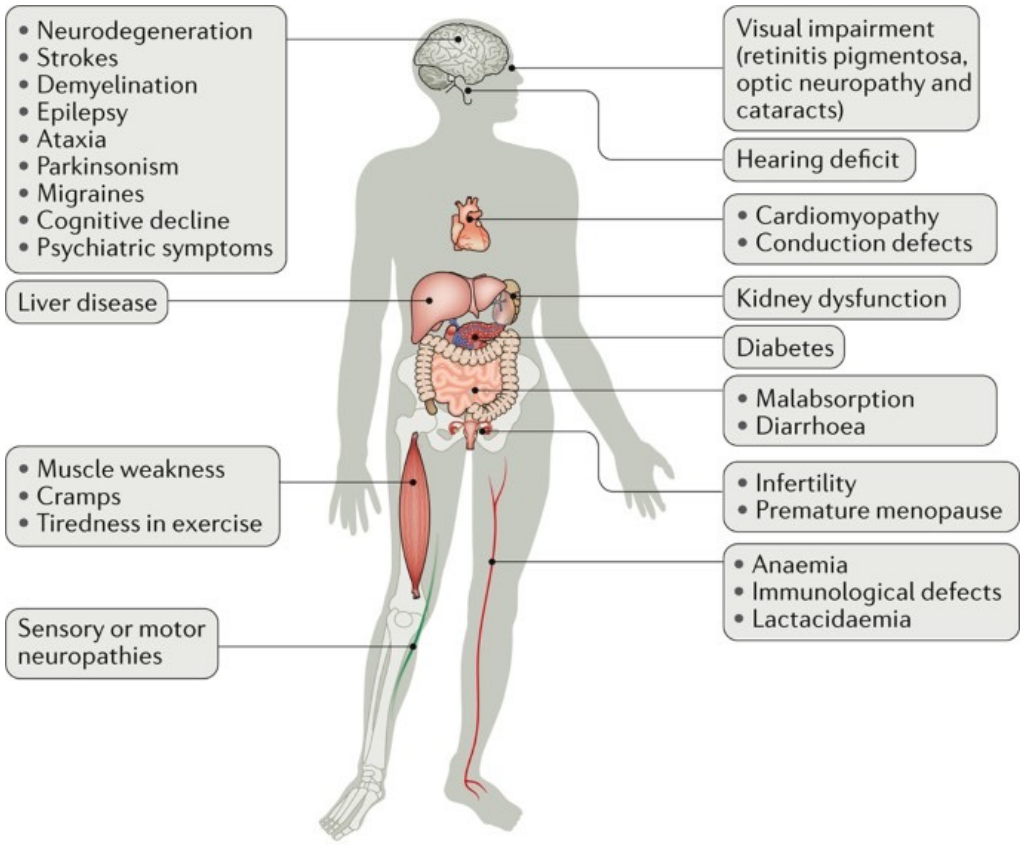




Mitochondrial, Cellular, Tissue, Organismal Dysfunction

Age-Associated Diseases with Underlying Mitochondrial Dysfunction



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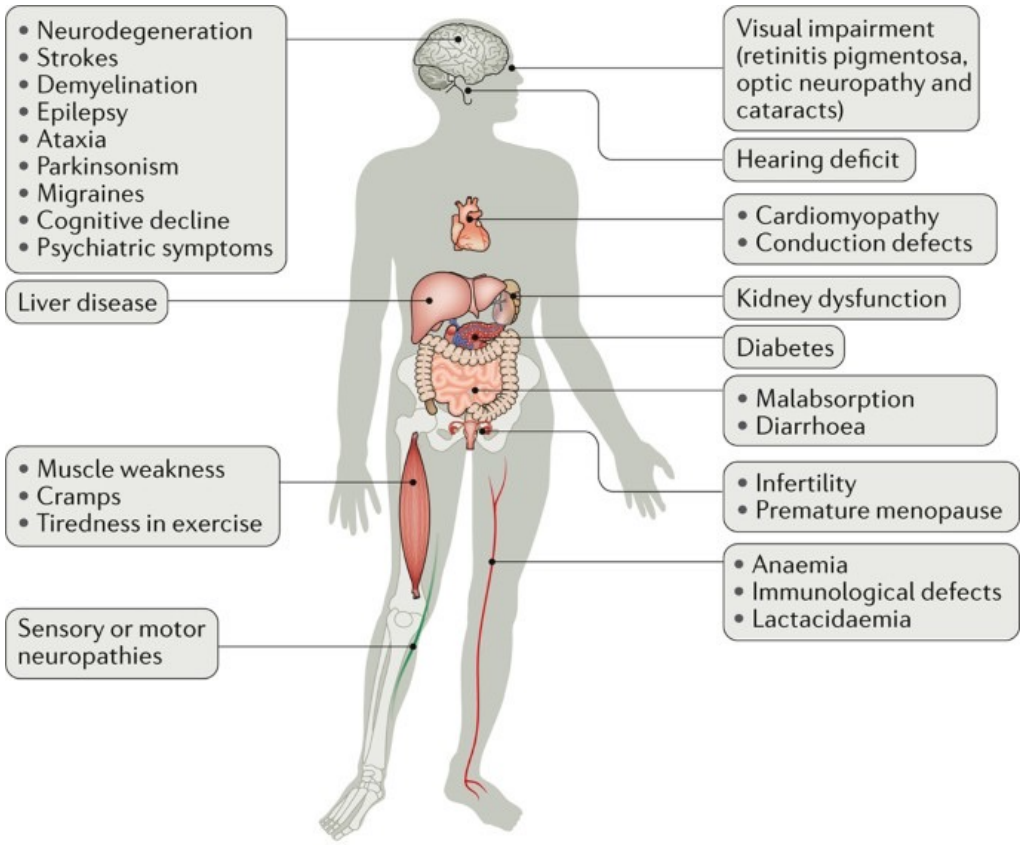
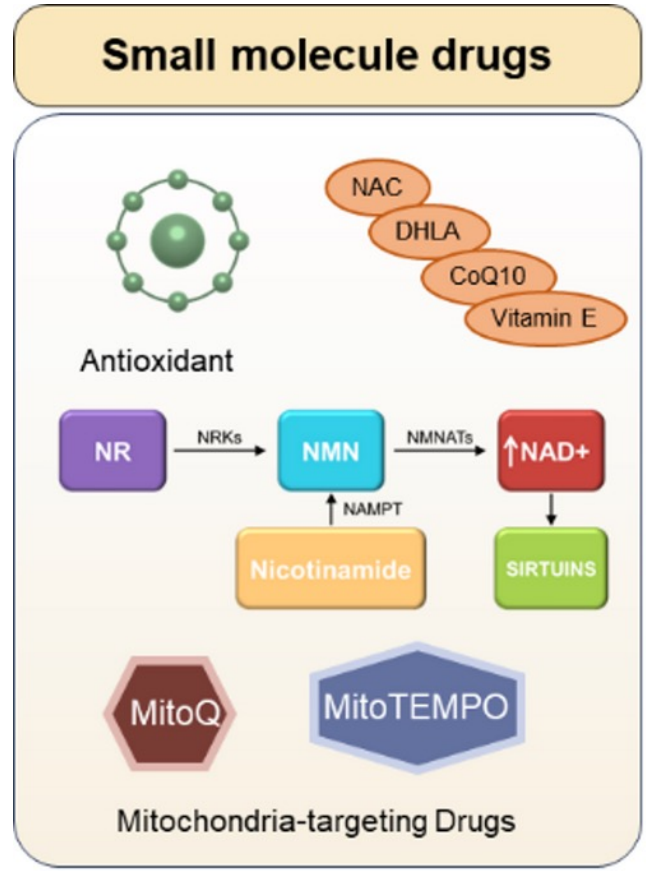
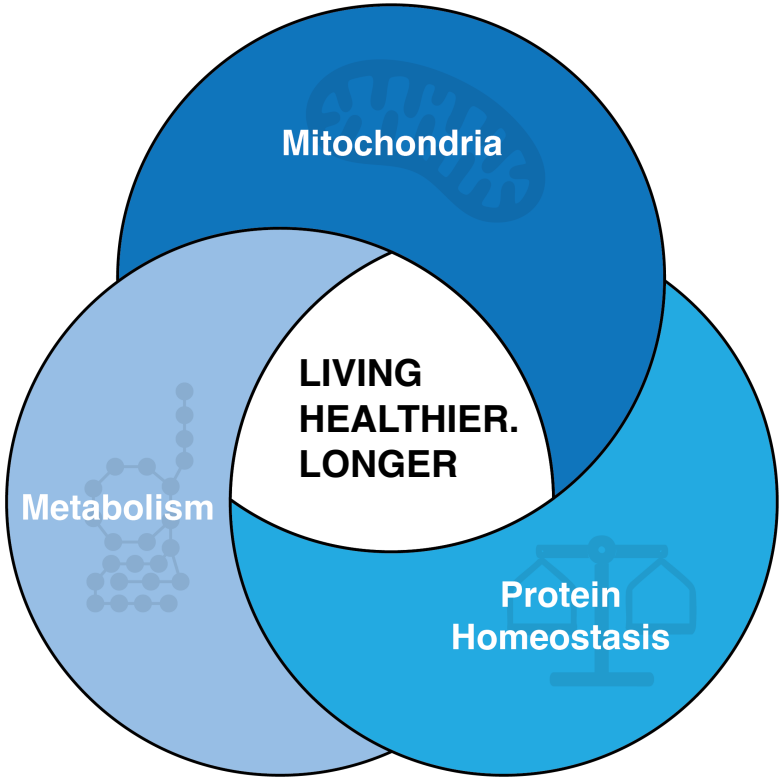


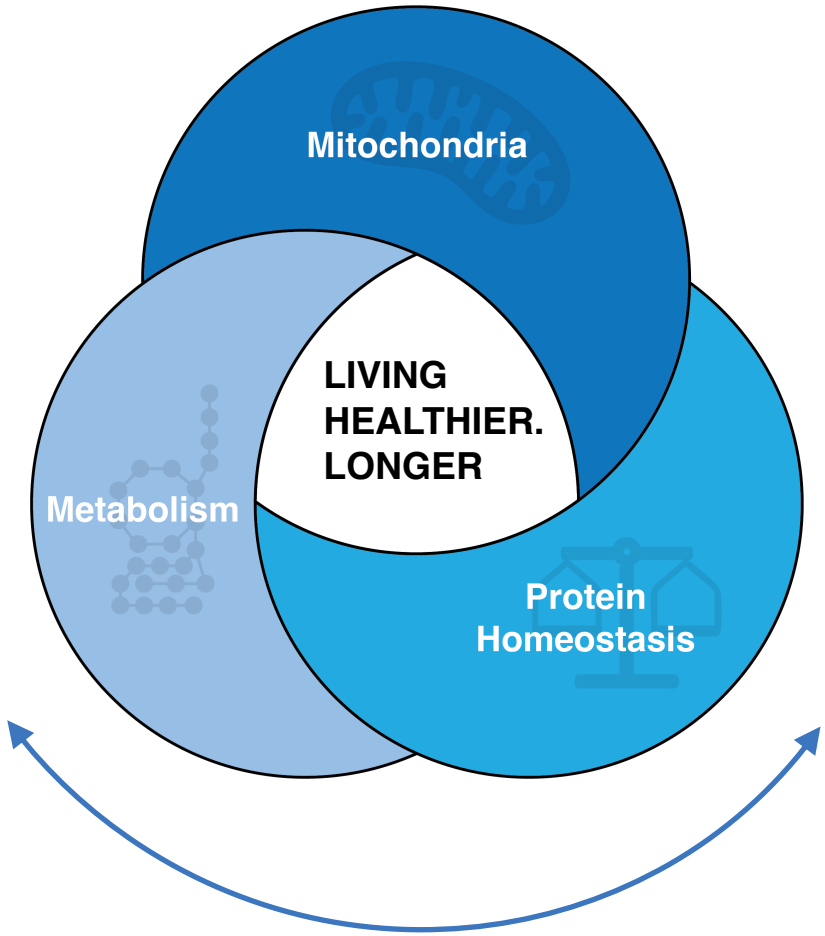


Fundamental Research Areas of Interest



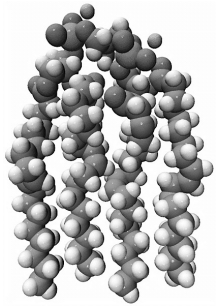
Fundamental Research Areas of Interest

REWIRING
Physiology
Age and Disease

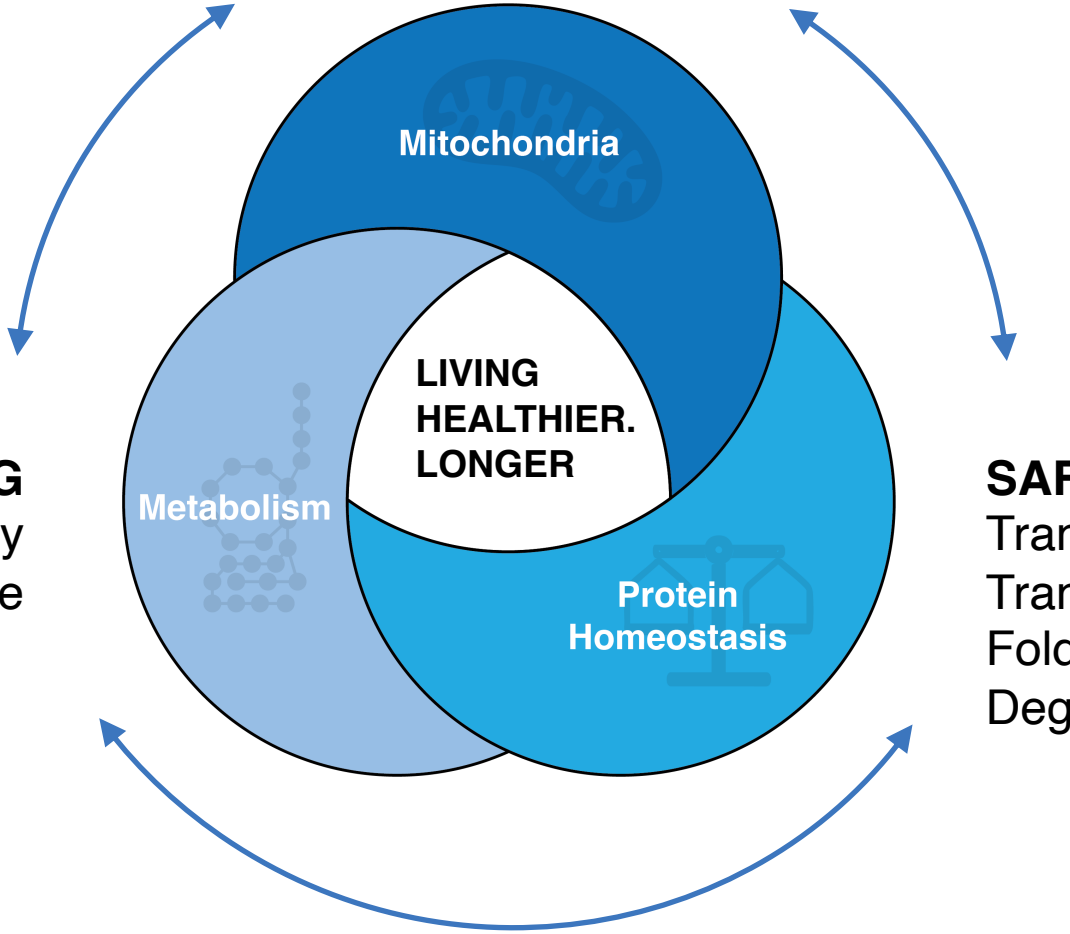


SAFEGUARDING
Transcription
Translation
Folding
Degradation

Fundamental Research Areas of Interest



CARDIOLIPIN DYNAMICS



REWIRING
Physiology
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SAFEGUARDING
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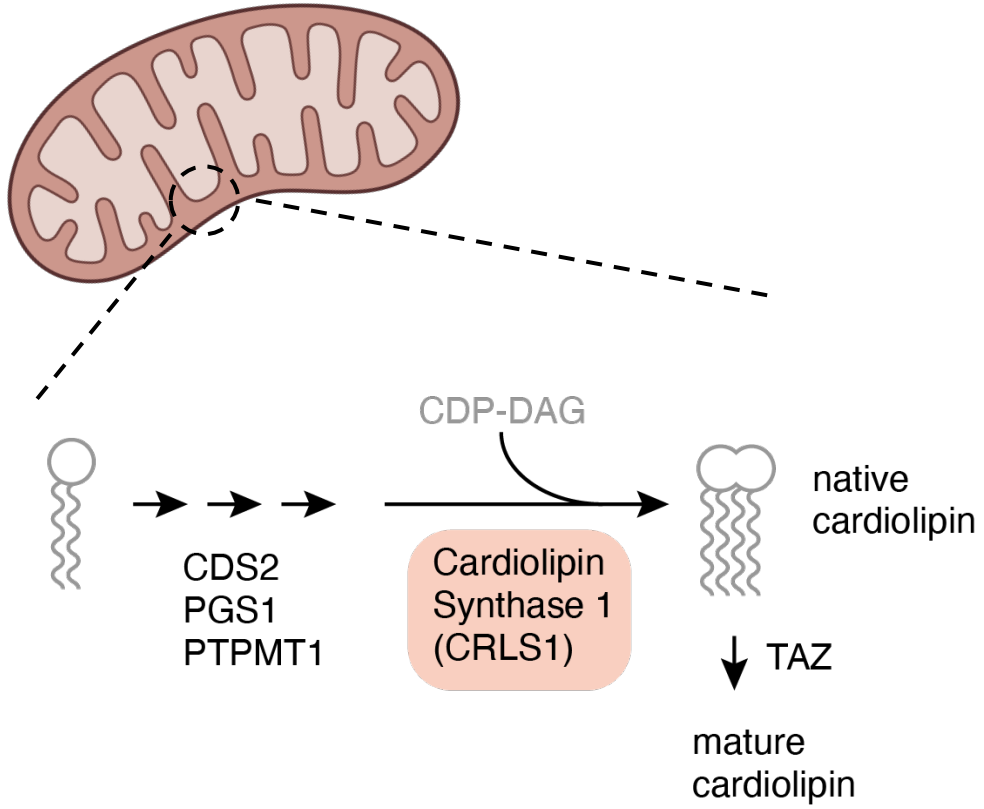
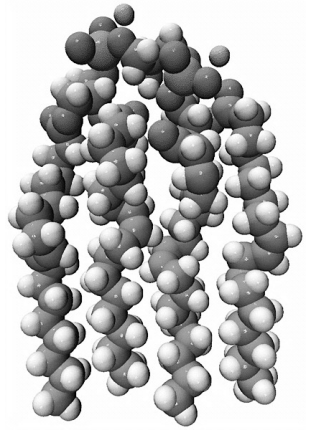
Cardiolipin: A Phospholipid at the Heart of Mitochondrial Structure and Function

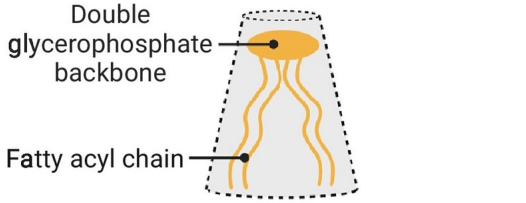




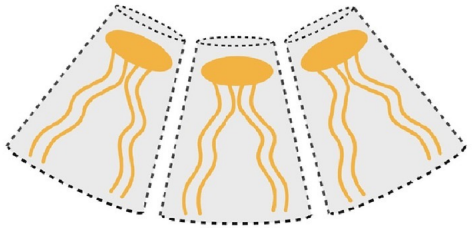
- Cristae formation
- Supercomplex formation
- Protection against ROS
- Apoptosis
- Mitochondrial biogenesis
- Fusion/fission dynamics
- Buffering proton gradient

adapted from Paradies et al. 2014

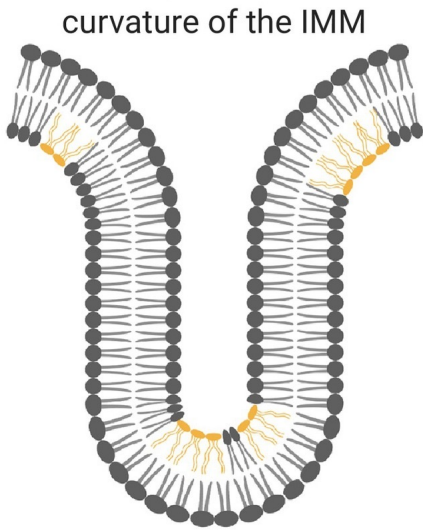
Cardiolipin: A Phospholipid at the Heart of Mitochondrial Structure and Function



CL aggregation favors negative curvature of membranes



adapted from Falabella et al. 2021



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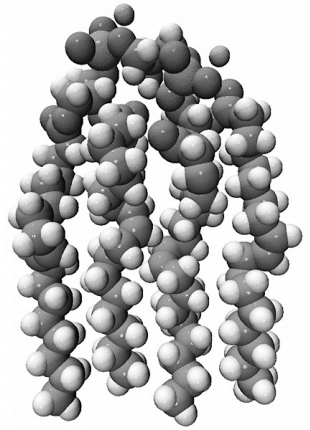

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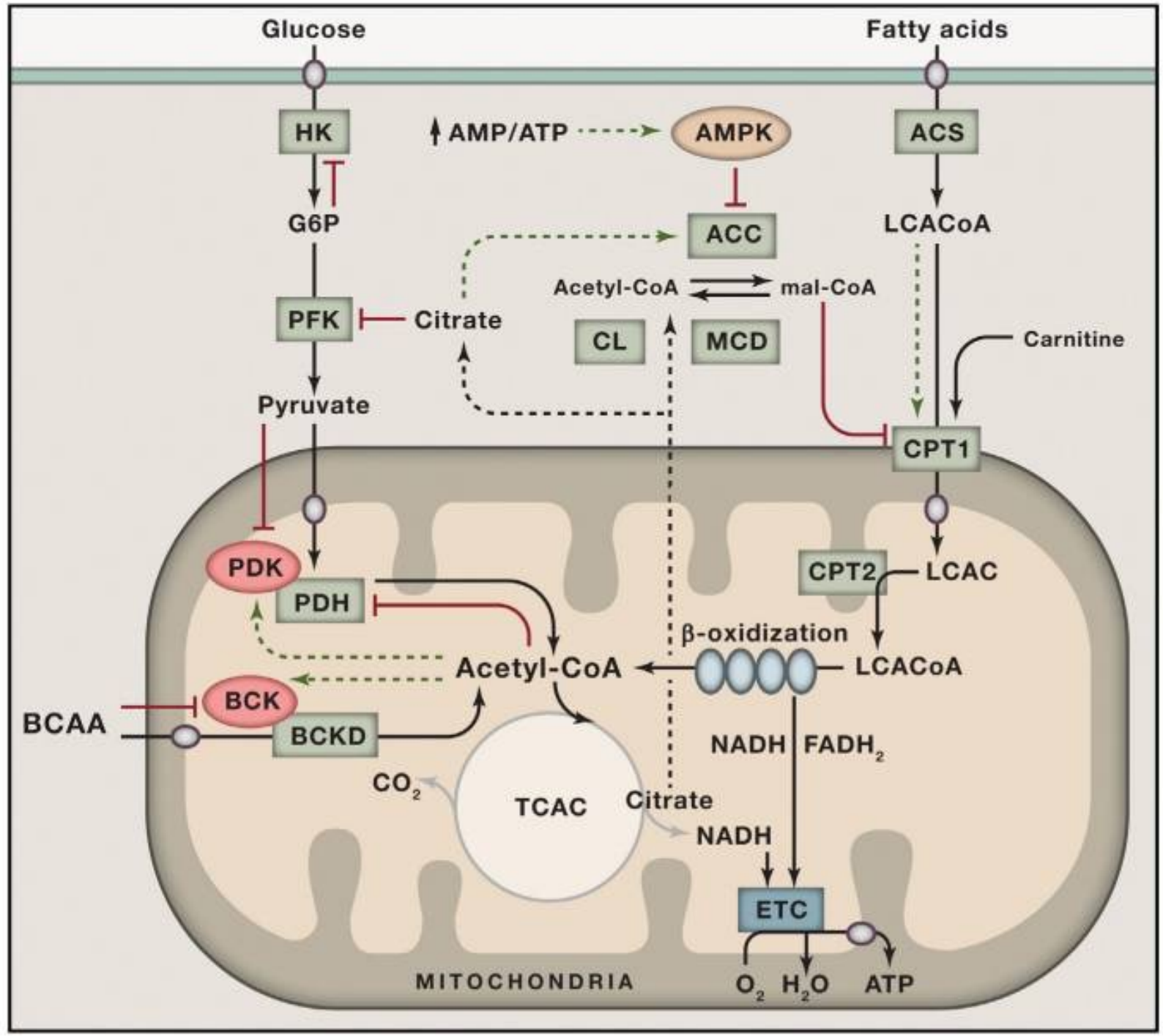
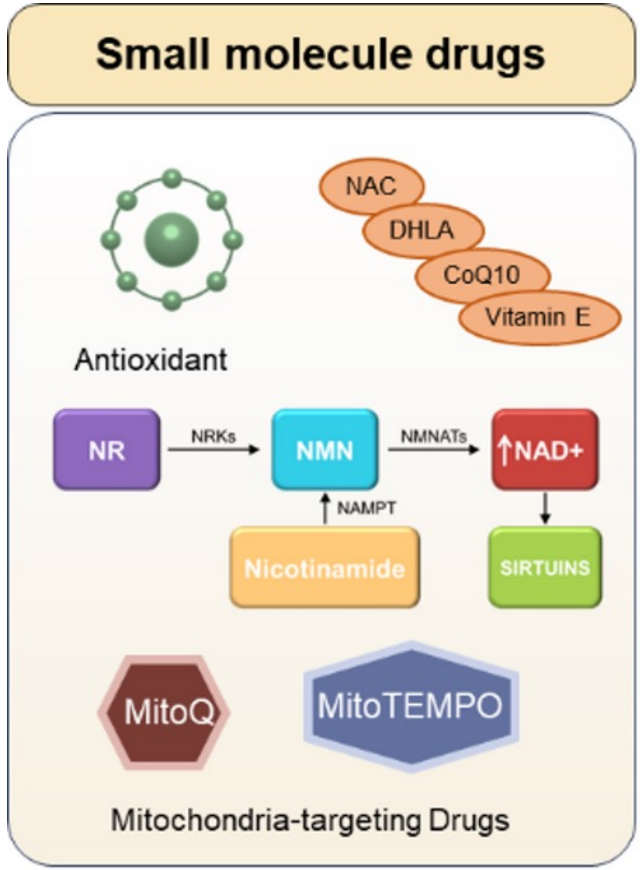

Glucose
Fatty acids
HK
AMP/ATP
AMPK
ACS
G6P
ACC
LCACoA
Acetyl-CoA
mal-CoA
PFK
Citrate
CL
MCD
Carnitine
Pyruvate
CPT1
PDK
CPT2
LCAC
PDH
β-oxidization
Acetyl-CoA
LCACoA
BCK
BCAA
BCKD
NADH
FADH2
CO2
TCAC
Citrate
NADH
ETC
MITOCHONDRIA
O2
H2O
ATP

Table 1 Therapeutic interventions

Drug	Mechanism	Adaptation symptoms	References
Alpha lipoic acid	Activates signaling pathways such as AMPK and SIRT1 and reduces oxidative stress	Neurodegenerative Disorders	[344]
CoQ10	Improvement of cellular energy metabolism by promoting energy production through the electron transport chain	Cardiovascular diseases	[345]
NMN	Managing mitochondrial metabolism in NK cells	Cancer	[346]
SS-31	Mitochondria-targeted antioxidant peptide improves myocardial function and reduces oxidative damage	Diabetes Mellitus and Alzheimer's disease	[347, 348]
Curcumin	Scavenging of ROS	Metabolic Disease	[349]
Melatonin	Increased number of mitochondria	Lung cancer and neurodegenerative disorders	[350, 351]
Resveratrol	Scavenging of ROS; activation of antioxidant signaling pathways	Fatty liver disease	[352]
Rapamycin	Inhibition of mTOR signaling pathway	Alzheimer disease	[353]
Urolithin A	Removes damaged mitochondria	Metabolic syndrome	[354]
Cordycepin	Mitochondrial metabolism	Alzheimer disease	[355]
MIC	DAF-12/FXR to enhance mitochondrial function	Alzheimer disease	[356]
MitoTam	Cycle-breaking ATP synthase kills senescent cells	Cancer	[357]
Phenylboronic acid	Inhibition of PDKs in mitochondria	Cancer	[358]
SGLT2 Inhibitors	Improvement of mitochondrial function	Attenuate vascular inflammation and arterial stiffness	[359]



Mitochondrial Diversity as Key to Understand Sensitivity towards Dysfunction