The Humble Mitochondrion

Dr. Malay Dave

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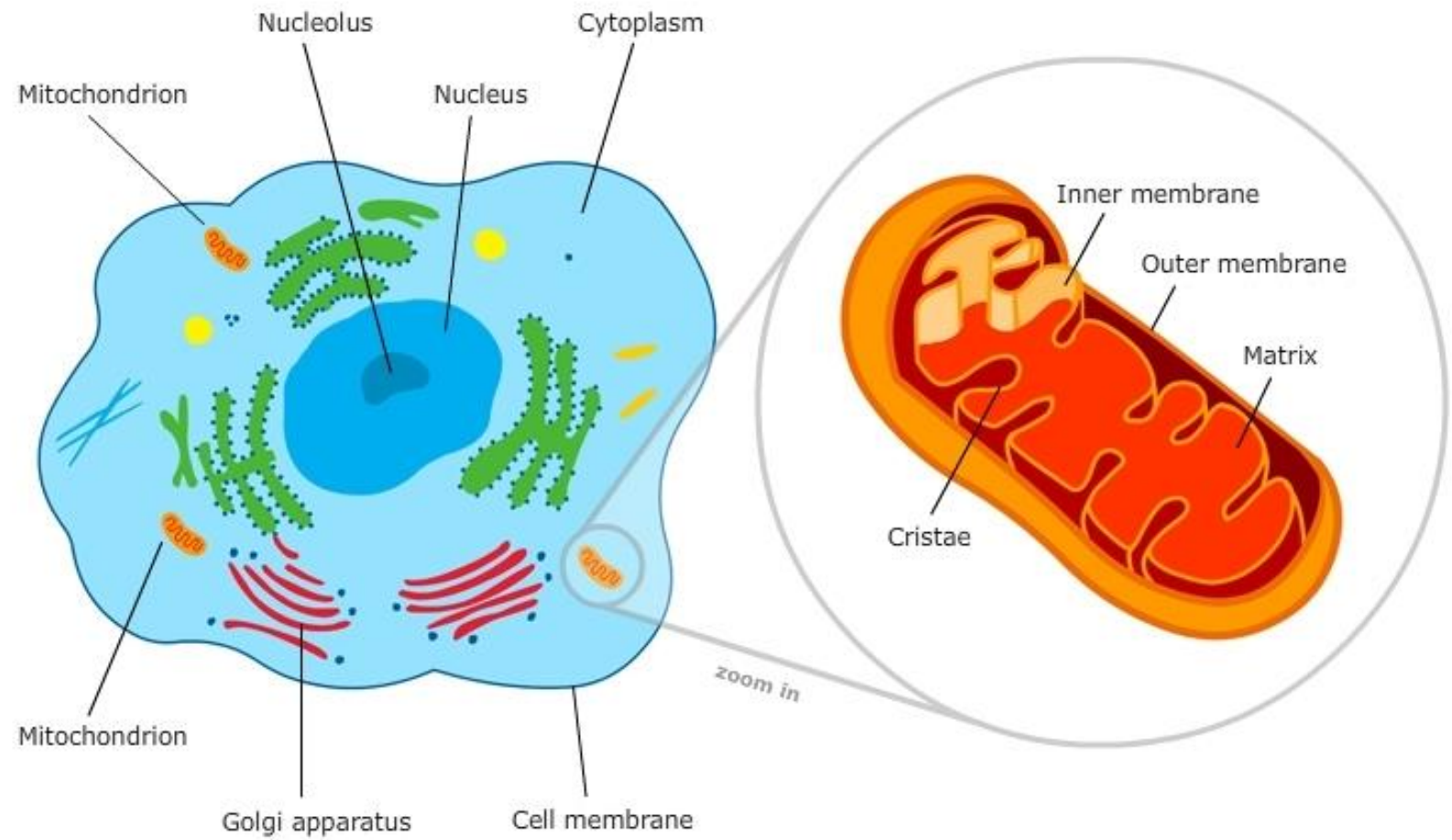
introduction

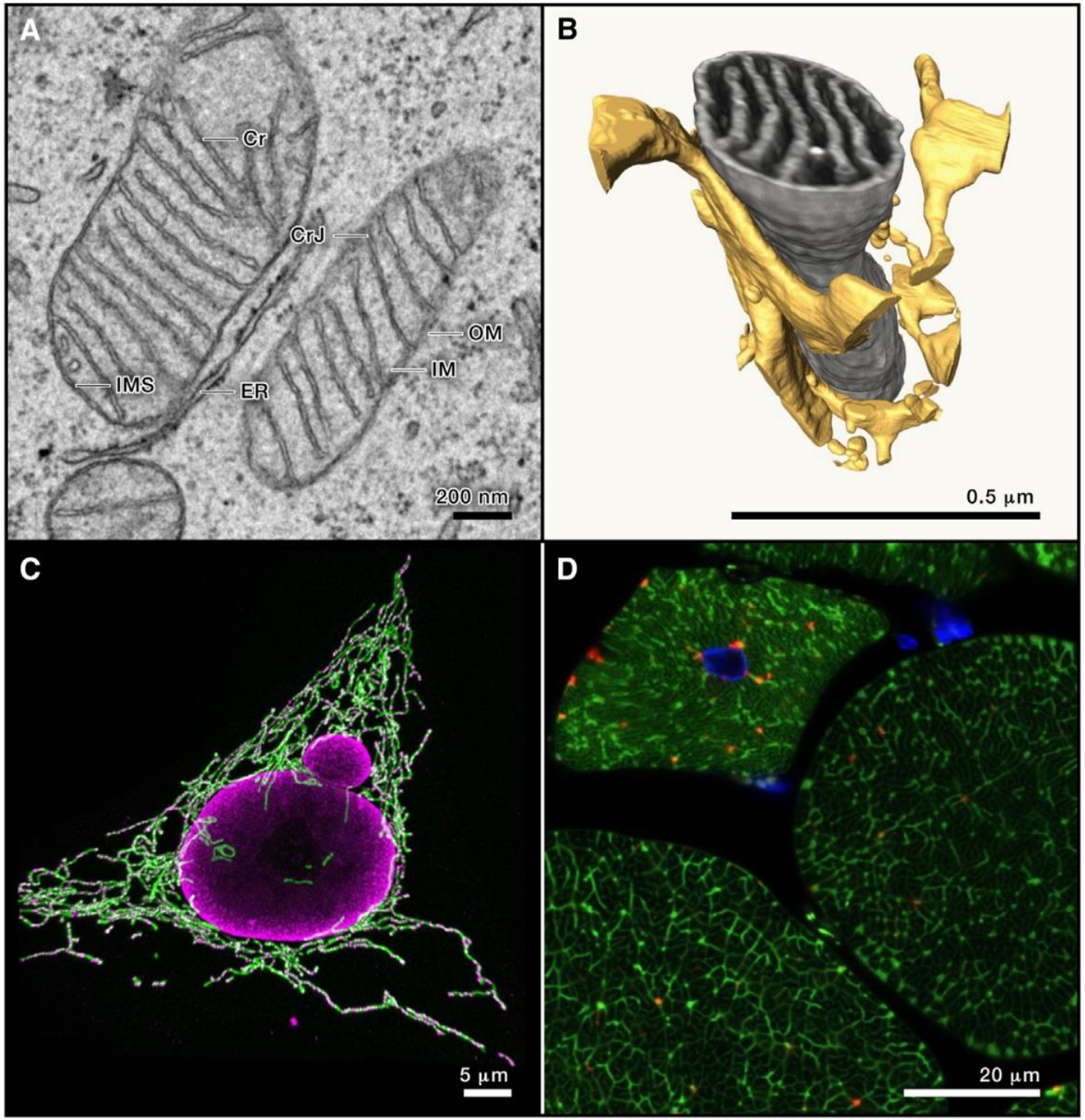


- Double membrane-bound cell organelle - Eukaryotes
- ATP generation - Powerhouse of the cell
- Greek words ‘mitos’ - ‘thread’ and ‘chondrion’ - ‘granule’ or ‘grain-like’
- Richard Altmann discovered mitochondria in 1890 - Bioblasts
- Carl Benda coined the term ‘mitochondrion’ in 1898

https://www.sciencefacts.net/mitochondria.html

- Efficient, adaptable bioenergetic machines - functional and compositional diversity
- Alpha-proteobacterial origin - Endosymbiotic
- One of only two endomembrane systems in addition to the ER
  - Direct and intimate interactions between these two major endomembrane systems
- Form a network which spans throughout the cytosol

Anu Suomalainen and Jodi Nunnari. Mitochondria at the crossroads of health and disease. Cell 187,May 23,2024
Khan, M.; Baussan, Y.; Hebert-Chatelain, E. Connecting Dots between Mitochondrial Dysfunction and Depression. Biomolecules 2023, 13, 695. https://doi.org/10.3390/ biom13040695



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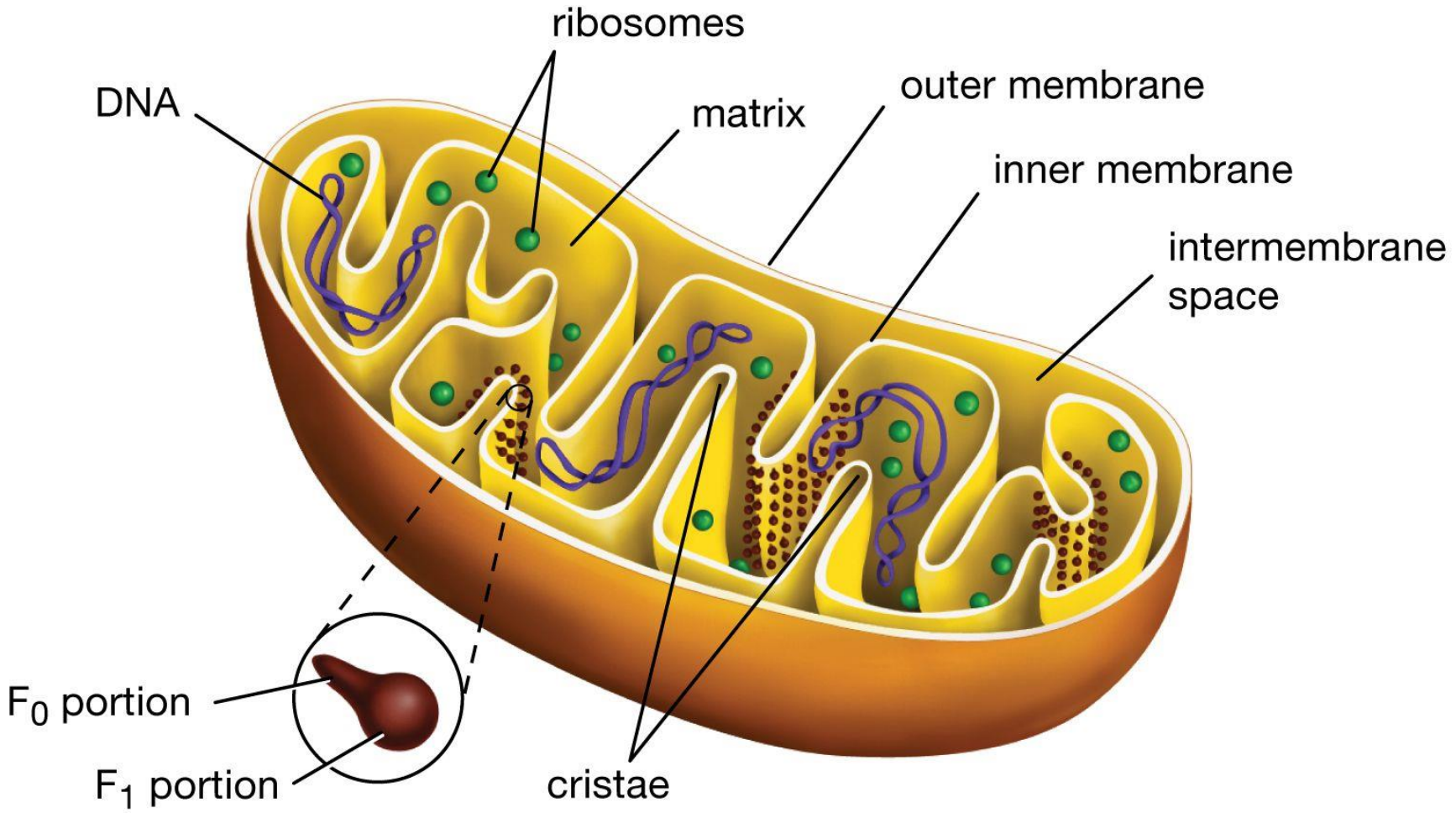
structure



https://www.britannica.com/science/mitochondrion

- 2 distinct membranes: the outer and inner membranes (OM & IM)
- 2 functionally diverse compartments: the intermembrane space (IMS) and the matrix
- **OM**
    - smooth lipid-enriched surface
        - ancestral beta-barrel proteins
        - voltage-dependent anion-selective channels (VDACs) / porins
        - molecules up to 10 kDa in size
    - alpha-helical membrane proteins
        - one transmembrane domain - MFF and MIRO
        - receptors for the mitochondrial division dynamin and motility machinery - mitochondrial behavior and cellular communication

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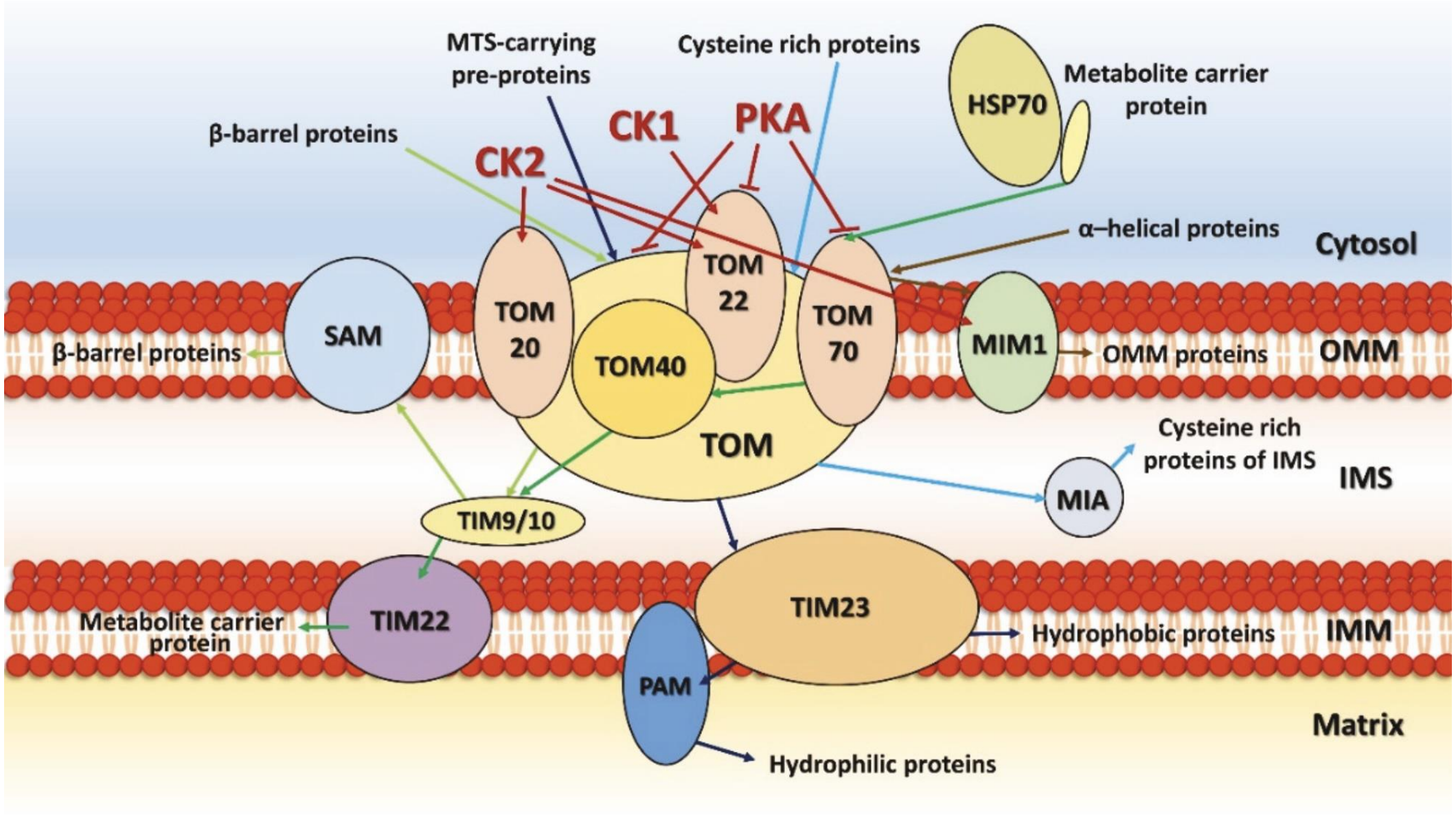

Kotrasova,V et al. Mitochondrial Kinases and the Role of Mitochondrial Protein Phosphorylation in Health and Disease. Life 2021, 11, 82. https:// doi.org/10.3390/life11020082

- **IMS**
  - smallest compartment
  - 5% of the mitochondrial proteome
  - protein and lipid biogenesis, metal homeostasis, redox regulation and oxidative folding, apoptosis, and mitochondrial dynamics / structure

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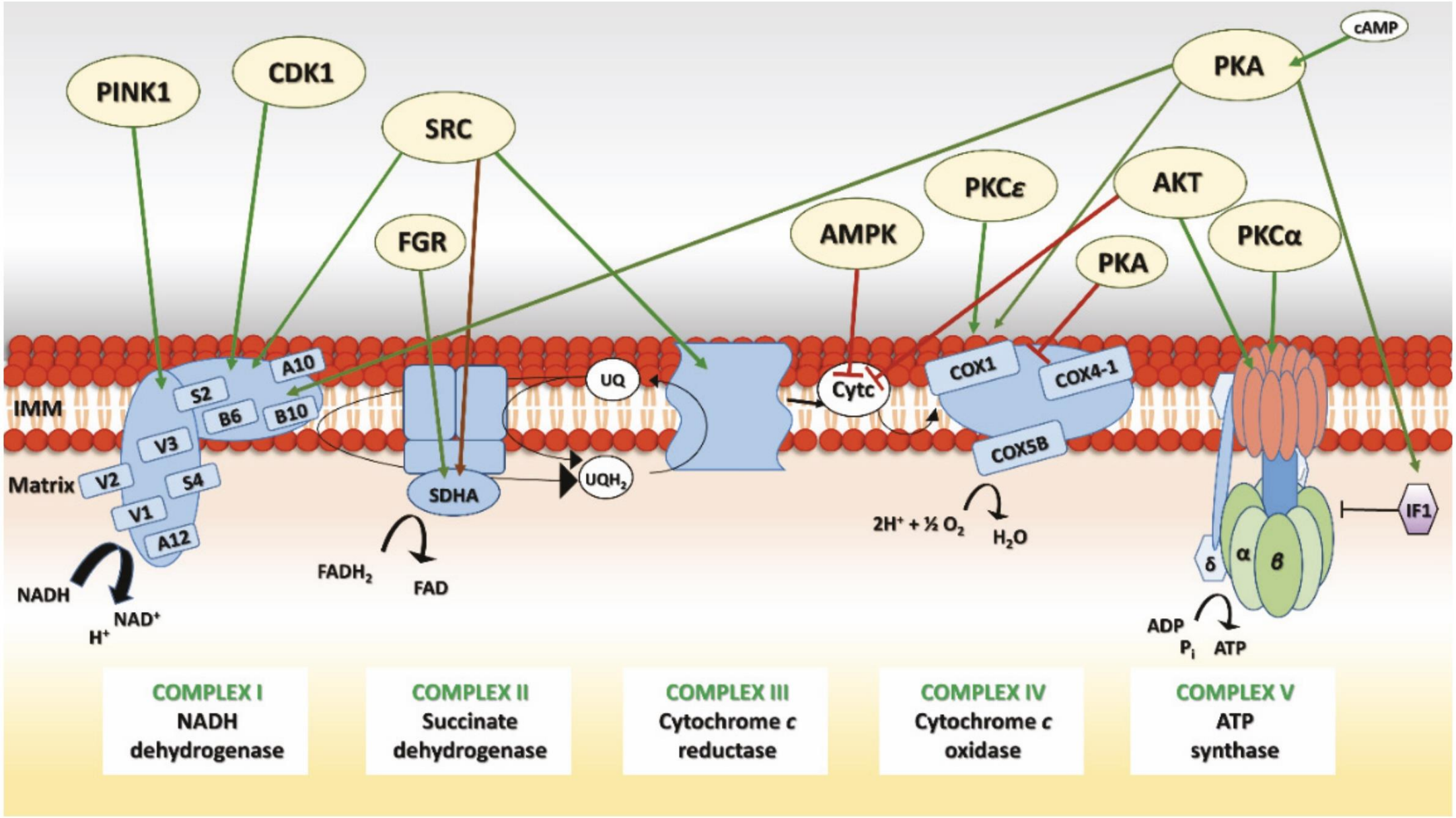

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- **IM**
  - Protein-dense membrane in eukaryotic cells, highly impermeant - cristae
  - The electron transport chain, also called the respiratory chain, with respiratory enzyme complexes (RCs; in humans, complex I–IV) and a turbine-like ATP synthase machine (RC V) that dimerizes to shape and drive the formation of cristae
- **Matrix**
  - biosynthetic reactions, mitochondrial genetic system
  - TCA cycle - oxidizes the carbon backbones of nutrients to NADH- and $FADH_2$-reducing equivalents - used by the RCs to generate chemiosmotic energy for ATP synthesis

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- **Proteome**
  - localized to the IM and matrix
  - metabolism and functioning

- **Lipidome**
  - Over 200 species
    - Glycerolipids
    - Phosphatidylcholine (PC)
    - Phosphatidylethanolamine (PE)
    - Cardiolipin (CL)
  - inherited from its bacterial origins

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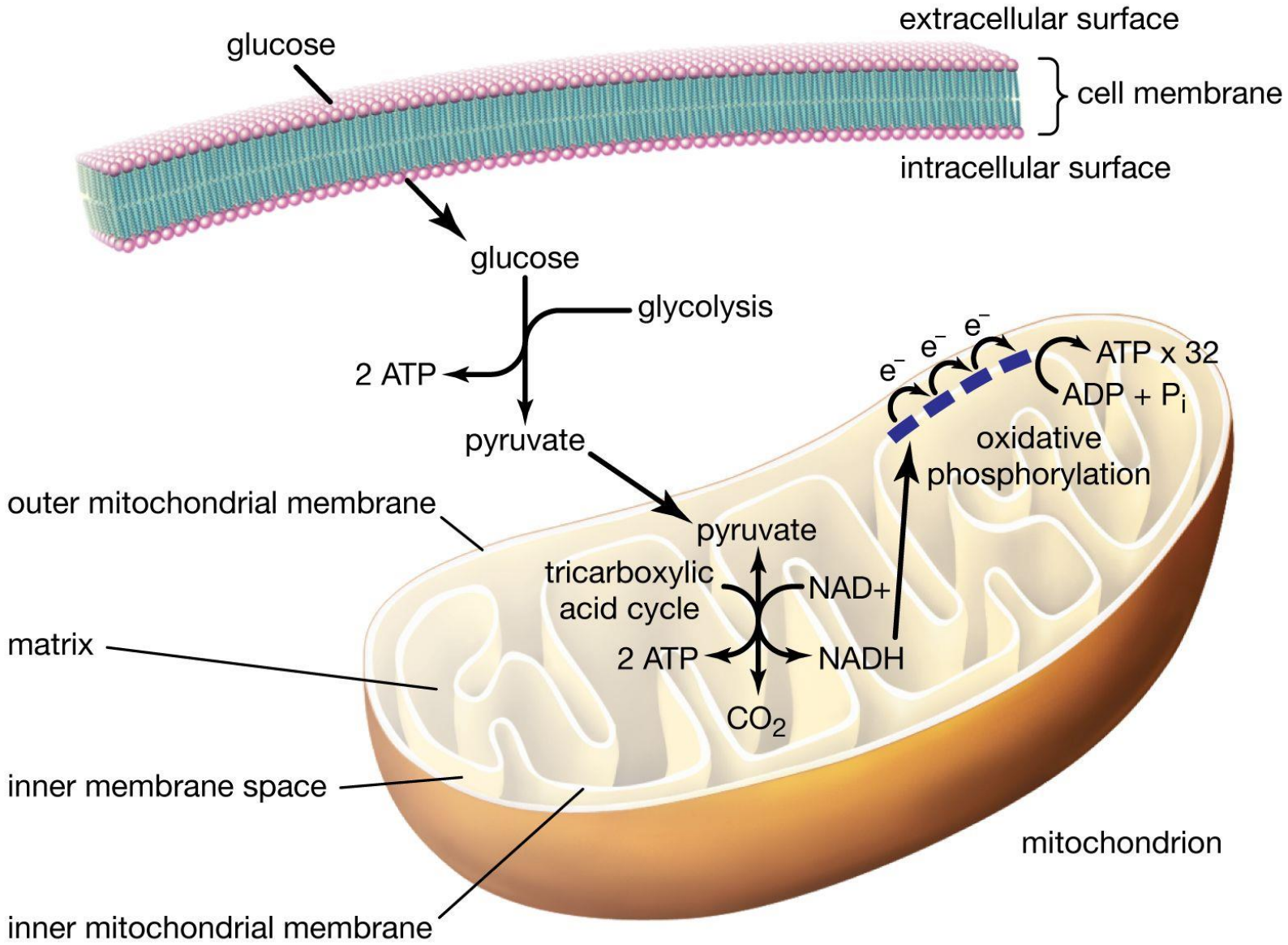
Basic overview of processes of ATP production



https://www.britannica.com/science/mitochondrion

genetics

- Lost most of the bacterial ancestral genome
- Many genes transferred to the nucleus
- Current eukaryotic genomes - > 600 genes of alpha-proteobacterial origin
- 99% of the mitochondrial proteome - encoded by the nuclear genome
- 1000 - 2000 nDNA-coded genes + thousands of copies of the maternally inherited mitochondrial DNA (mtDNA)

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- **The nDNA** - anatomical components of the mitochondrion, for mitochondrial intermediate metabolism and mitochondrial biogenesis, and for the regulation of the mitochondrion

- **The mtDNA - critical genes for OXPHOS and for their expression**
  - 16.6-kb mtDNA - 13 proteins, 12S and 16S ribosomal RNAs, 22 transfer RNAs for mitochondrial protein synthesis
  - Dramatic amplification in cells
  - Transcription and protein translation - the highest consumers of cellular ATP
  - Eukaryotic cells - evolve into relatively large and functionally diverse entities
  - Loss of the ancestral genome - evolution of new pathways for mitochondrial protein and lipid biogenesis

- Mitochondrial gene expression levels vary significantly in humans at both the tissue and individual levels

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- mtDNA variants - ancient adaptive polymorphisms, recent deleterious mutations, and developmental-somatic mutations
- Maternally inherited - male and female mtDNAs do not mix and thus cannot recombine
- Single mtDNA - haplotype, cluster of related mtDNA haplotypes - haplogroup
- mtDNA haplogroup lineages - geographically delineated, indigenous populations
- Adaptation to new environmental factors such as alternative food sources, activity demands, high altitude, warm versus cold regions, and diverse infectious agents
  - Distinctive mitochondrial physiological properties that strongly influence individuals' physiologies

Liming Pei and Douglas C. Wallace. Mitochondrial Etiology of Neuropsychiatric Disorders. https://doi.org/10.1016/j.biopsych.2017.11.018

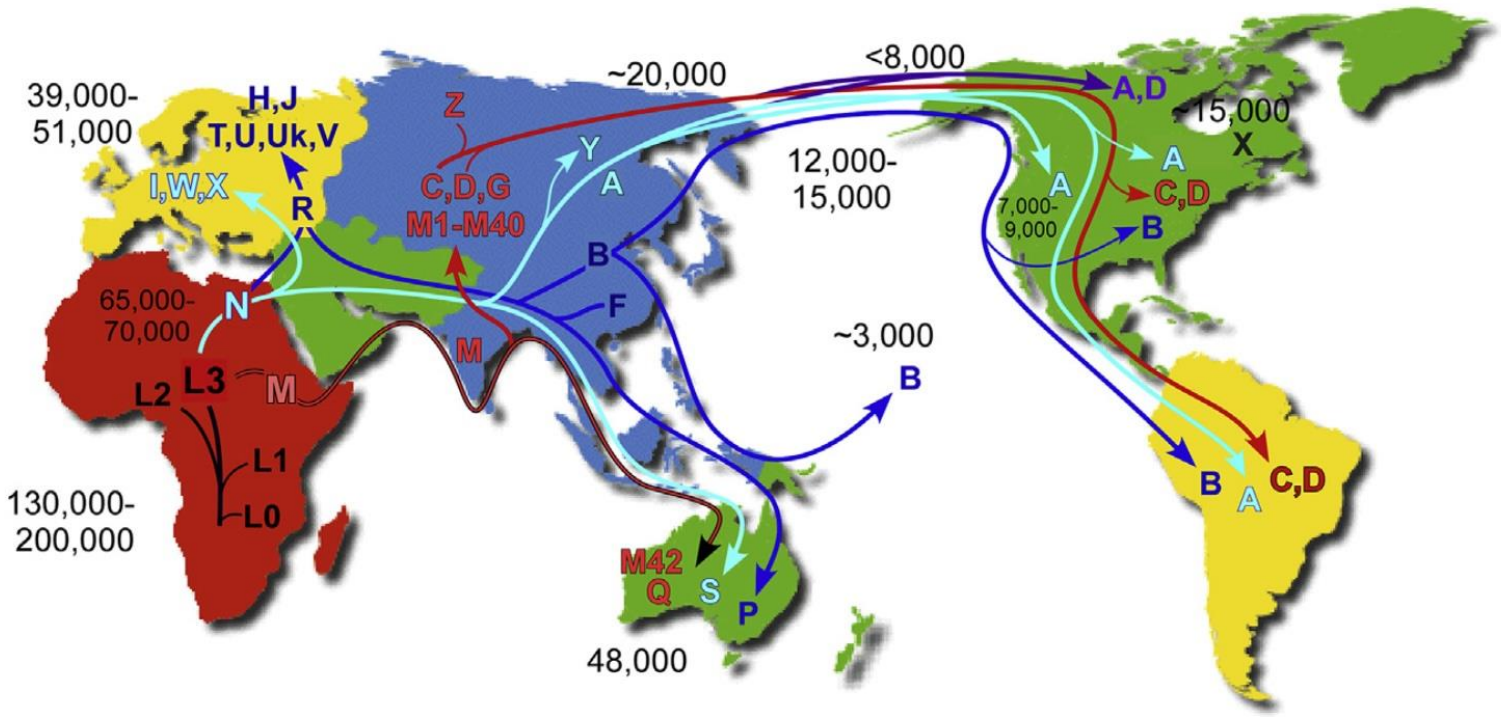

Figure 1. Regional radiation of human mitochondrial DNAs (mtDNAs) from their origin in Africa and colonization of Eurasia and the Americas implies that environmental selection constrained regional mtDNA variation. All African mtDNAs are subsumed under macrohaplogroup L and coalesce to a single origin about 130,000–170,000 years before present. African haplogroup L0 is the most ancient mtDNA lineage found in the Koi-San peoples, and L1 and L2 in Pygmy populations. The M and N mtDNA lineages emerged from Sub-Saharan African haplogroup L3 in northeastern Africa, and only derivatives of M and N mtDNAs successfully left Africa, giving rise to macrohaplogroups M and N. N haplogroups radiated into European and Asian indigenous populations, while M haplogroups were confined to Asia. Haplogroups A, C, and D became enriched in northeastern Siberia and were positioned to migrate across the Bering Land Bridge 20,000 years before present to found Native Americans. Additional Eurasian migrations brought to the Americas haplogroups B and X. Finally, haplogroup B colonized the Pacific Islands. Reproduced with permission from MITOMAP (www.mitomap.org).

- Mitochondria are related to bacteria - mtDNA replication and transcription enzymes originate from bacteriophages
- Phage polymerases - high processivity - maintain the high mtDNA copy number
  - The viral origin of POLG has relevance for medicine
- MtDNA copy number per cell varies depending on the cell type and is highly regulated during cell fate transitions
- mtDNA is inherited uniparentally via the maternal lineage

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- Paternal mitochondria
  - actively degraded by mitophagy
  - nuclear localization of a spermatoid cell-specific form of TFAM destabilized sperm mtDNA leading to its loss during sperm maturation

- The human oocyte - 200,000 copies of mtDNA, distributed after fertilization during division to cells forming the early embryo - mtDNA replication only resumes at the blastocyst stage

- During oocyte development, there is an mtDNA “bottleneck,’’ which selects against pathogenic variants, especially protein-coding variants of mtDNA

- Mitochondrial replacement therapy - tool to prevent mtDNA-transmitted diseases

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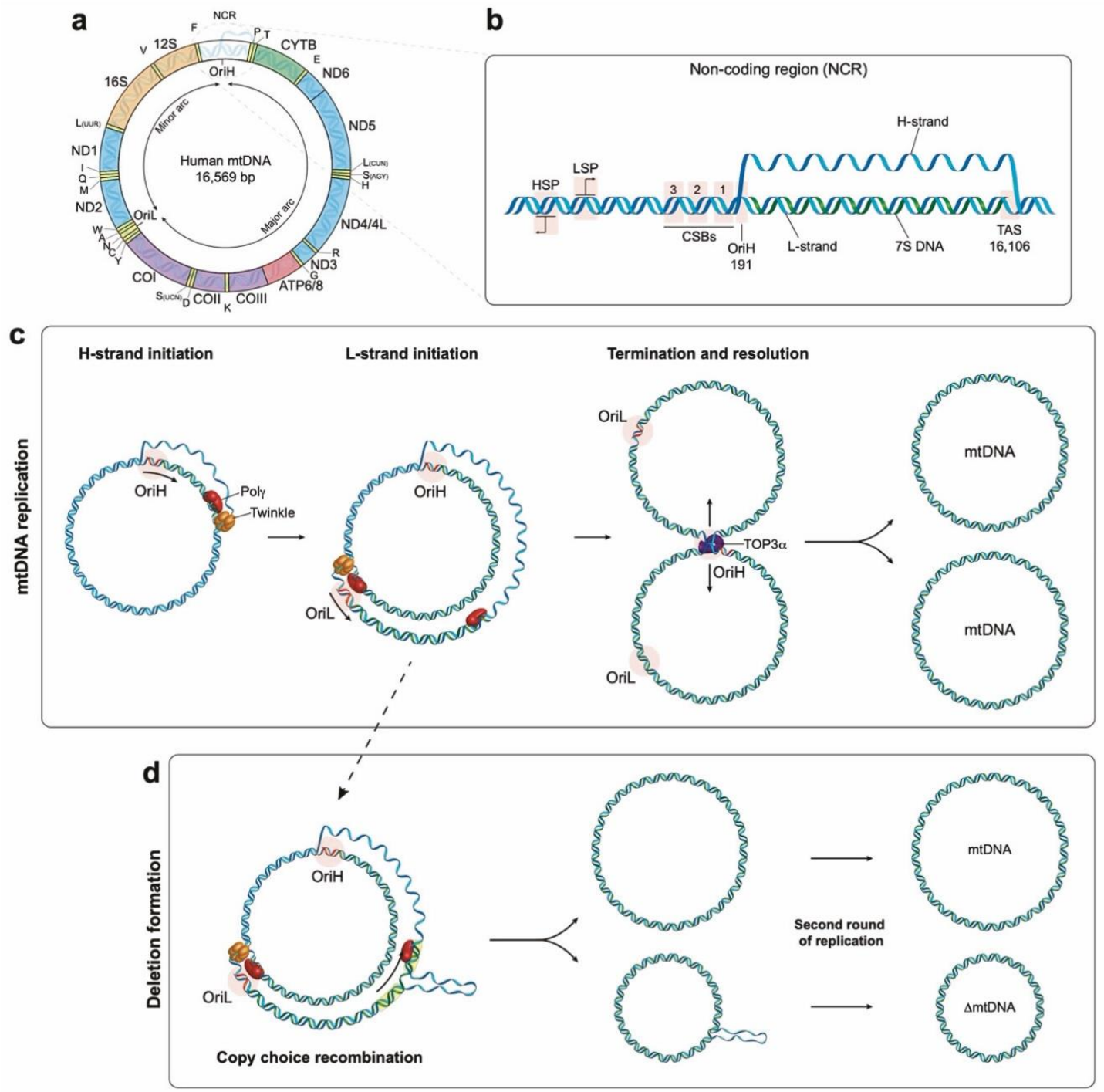
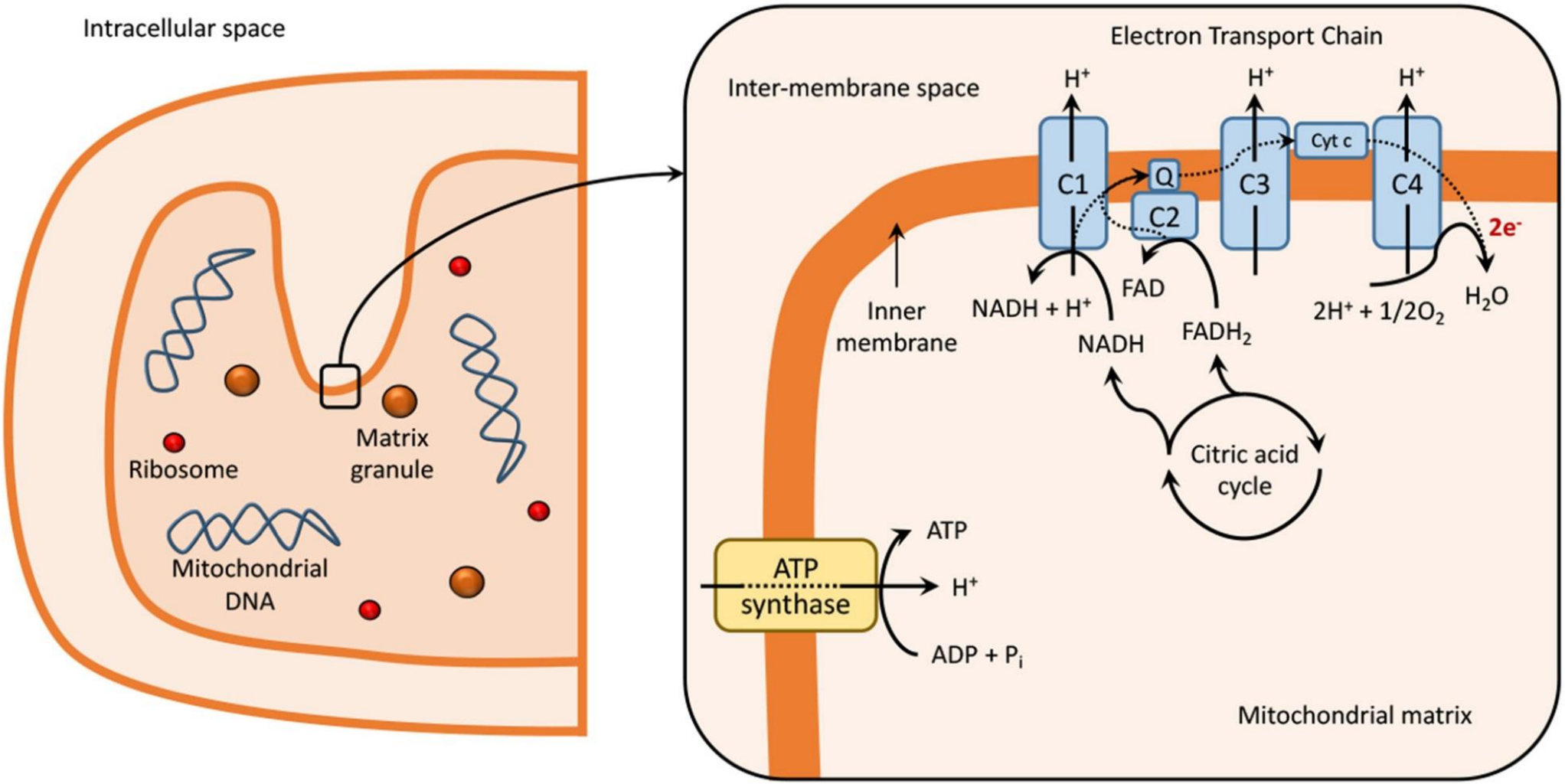


James Chapman et al. The Maintenance of Mitochondrial DNA Integrity and Dynamics by Mitochondrial Membranes. Life 2020, 10, 164; doi:10.3390/life10090164

mechanisms



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- Complex I, or nicotinamide adenine dinucleotide (NAD+), and/or complex II (succinate dehydrogenase) - begin the process of oxidative phosphorylation by catalyzing the transfer of electrons from NADH and FADH2, respectively, to coenzyme Q (or ubiquinone)

- The transfer of electrons - conducted through complex III (ubiquinol: cytochrome c oxidoreductase), cytochrome c and complex IV (cytochrome c oxidase), to the terminal acceptor, generating an electrochemical proton gradient that enhances ATP production in complex V *via* oxidative phosphorylation

- Single-electrons can escape and produce a single-electron reduction of O_2, forming superoxides and other ROS

- Impaired functioning of ETC - excessive ROS production, which leads to the damage of DNA, lipids, proteins, and other molecules - oxidative damage

- The generation of ROS is also related to signaling physiological processes - synaptic plasticity and memory

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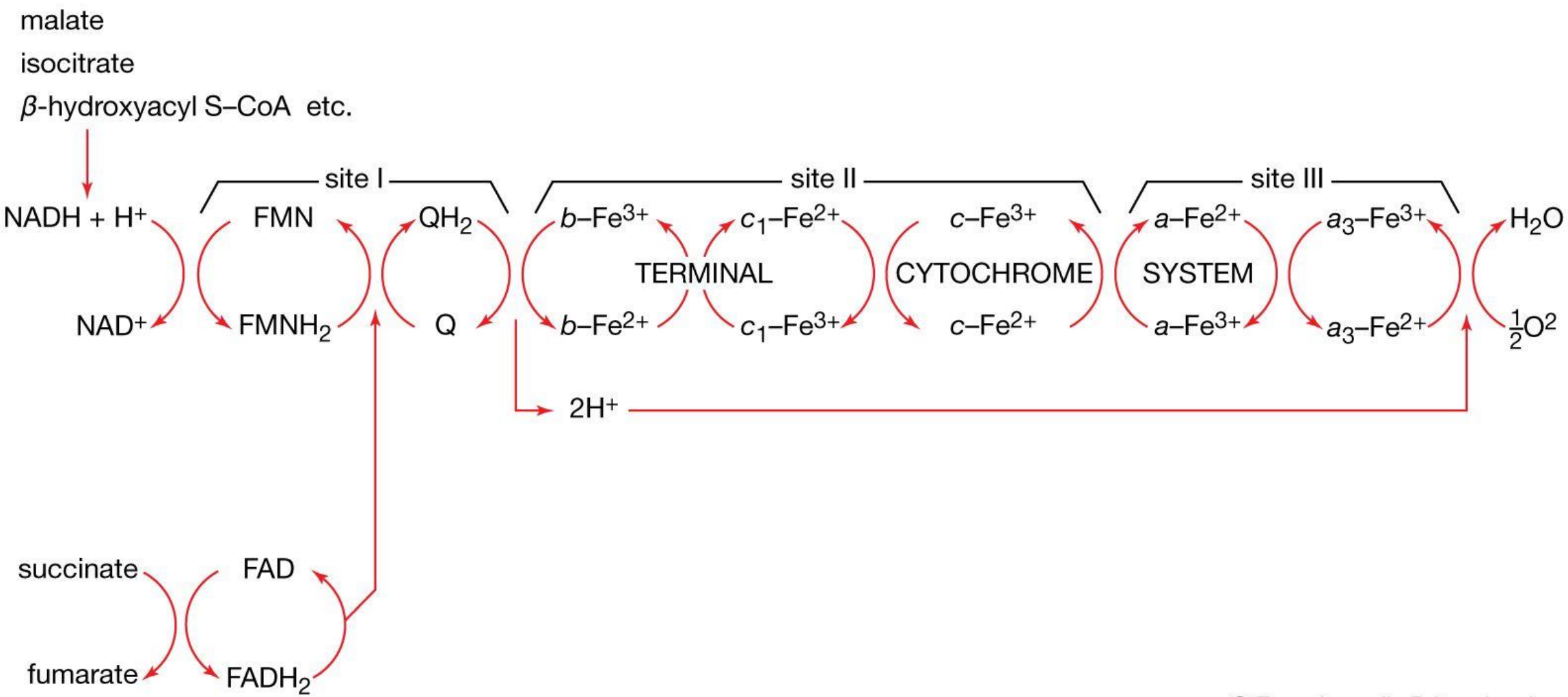

https://www.britannica.com/science/mitochondrion

- Setting metabolic programs - providing the necessary energy and molecular precursors for various cellular functions and influencing gene expression and signaling pathways - based on nutrient, stress, and differentiation status of cells

- The RCs can function as solitary units - also assemble into defined supercomplexes - increase the efficiency of respiration

- Electron transfer by RCs is coupled to proton transport - generates a tremendous electrochemical potential of 150–200 mV across the IM

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Electrochemical potential

- Power the rotary turbine-shaped engine, complex V, ATP synthase - ATP
- Mitochondrial fusion and protein import
- Sentinel for mitochondrial health
  - Decreases impede the import of nuclear-encoded mitochondrial proteins – initiation of cellular stress responses
  - Mitochondrial integrated stress response (ISRmt) - metabolically buffers the cell to promote recovery
  - PINK1-mediated mitophagy - initiates the degradation of mitochondria that are beyond repair
  - Loss - cell death via the opening of the mitochondrial permeability transition pore (mtPTP) and BCL associated X (BAX)-mediated cytochrome *c* release during apoptosis
  - Hypoxia - ATP synthase can run in the reverse direction

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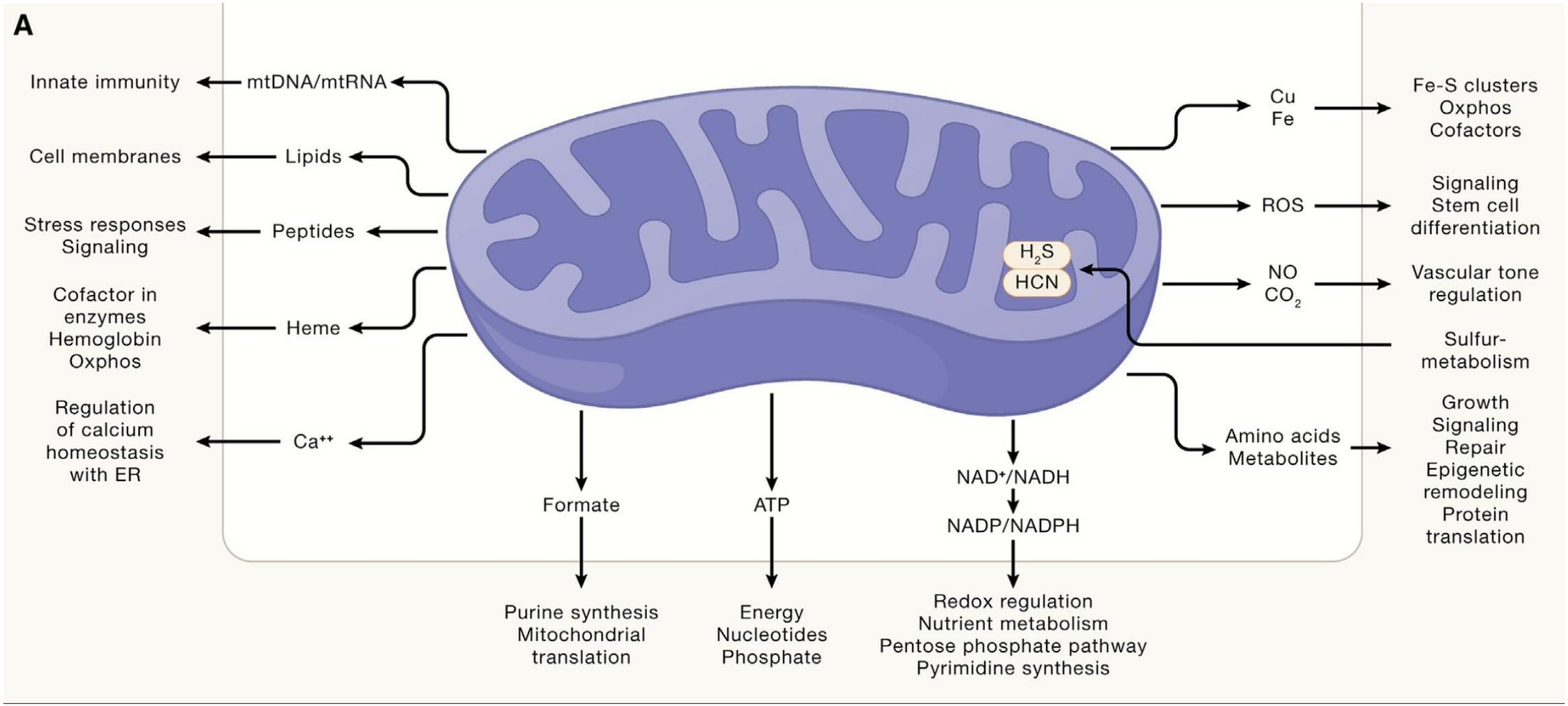

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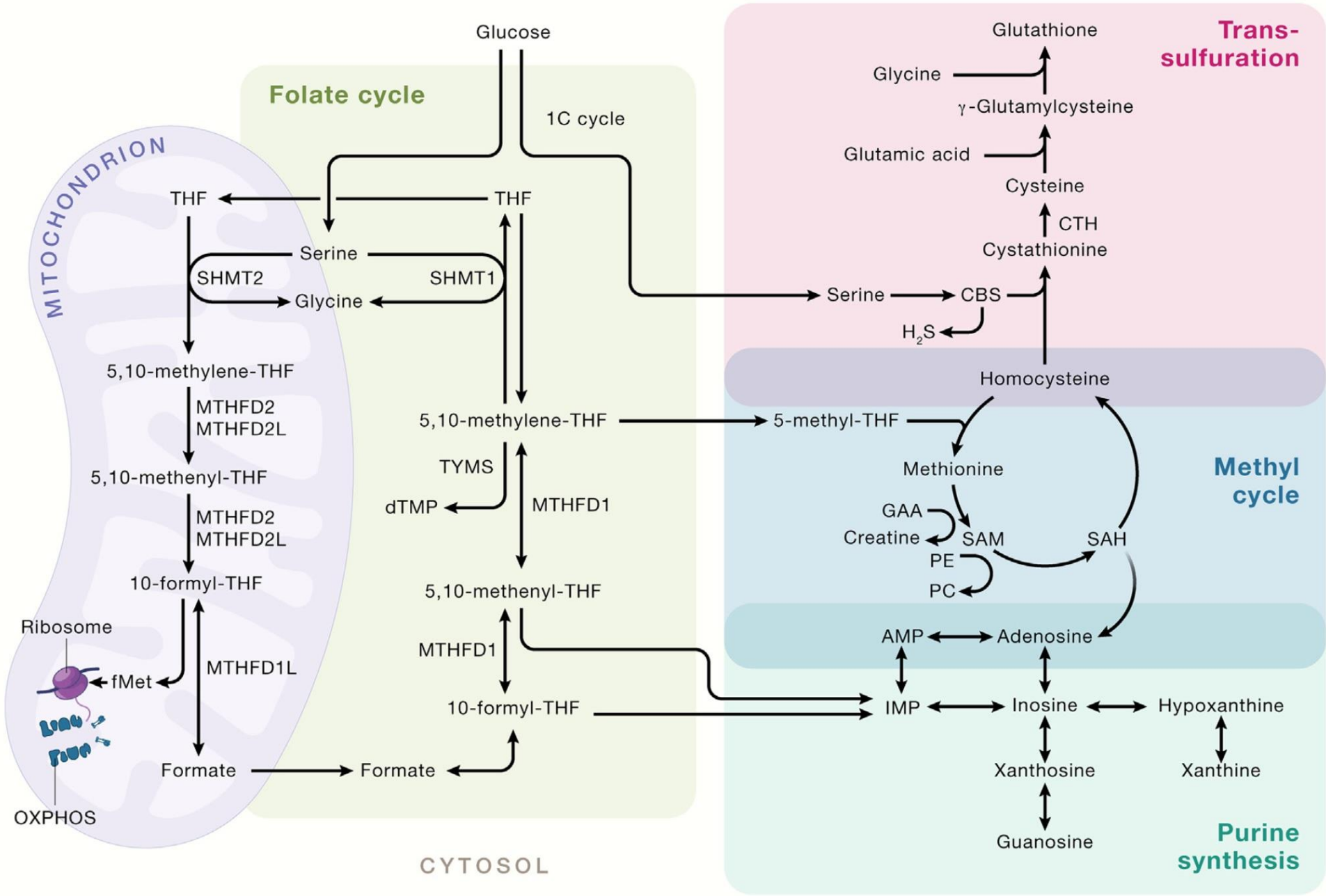

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- Mitochondrial shape and distribution
  - Concerted actions of the mitochondrial division, fusion, and motility machines

- Glycolytic pluripotent embryonic stem cells - mitochondria are fragmented and underdeveloped in their internal cristae structure
  - As stem cells differentiate, mitochondria undergo concerted changes - switch to oxidative phosphorylation for energy production and smaller elongated mitochondria and form networks with extensive cristae

- Mitotypes
  - in brown fat cells, where mitochondria-contacting lipid droplets are specialized for lipid storage, whereas unassociated mitochondria are active in oxidative phosphorylation

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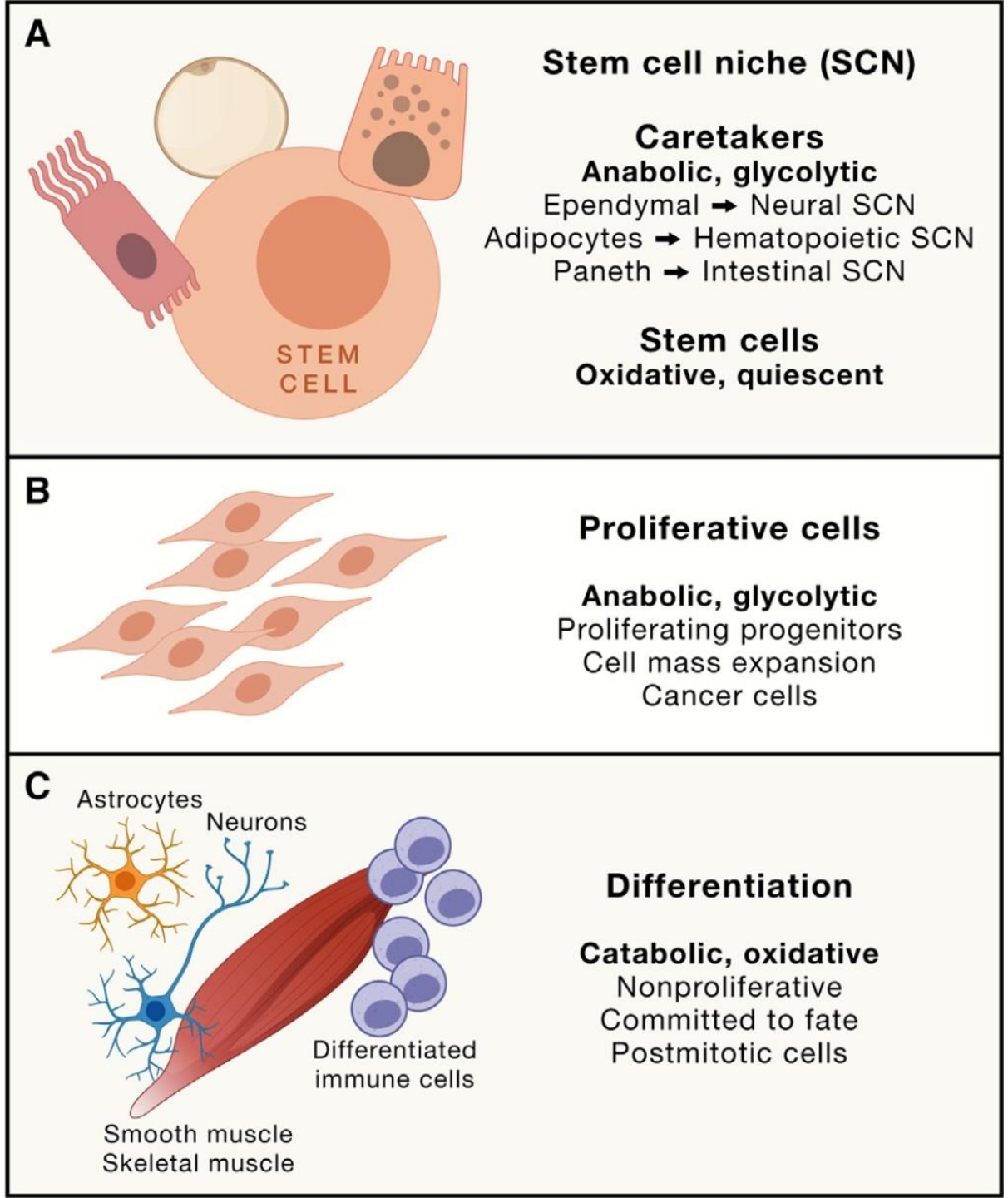

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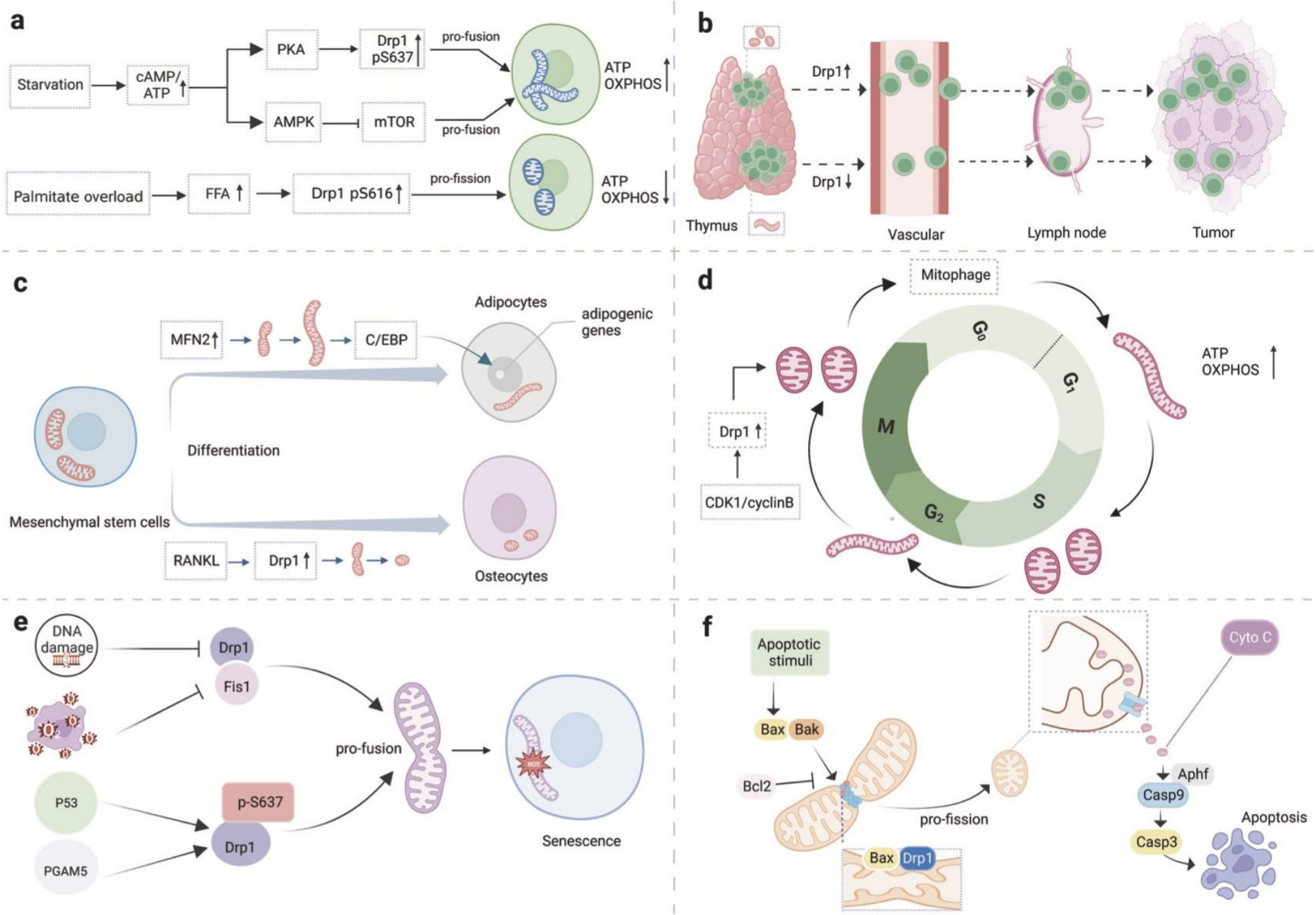

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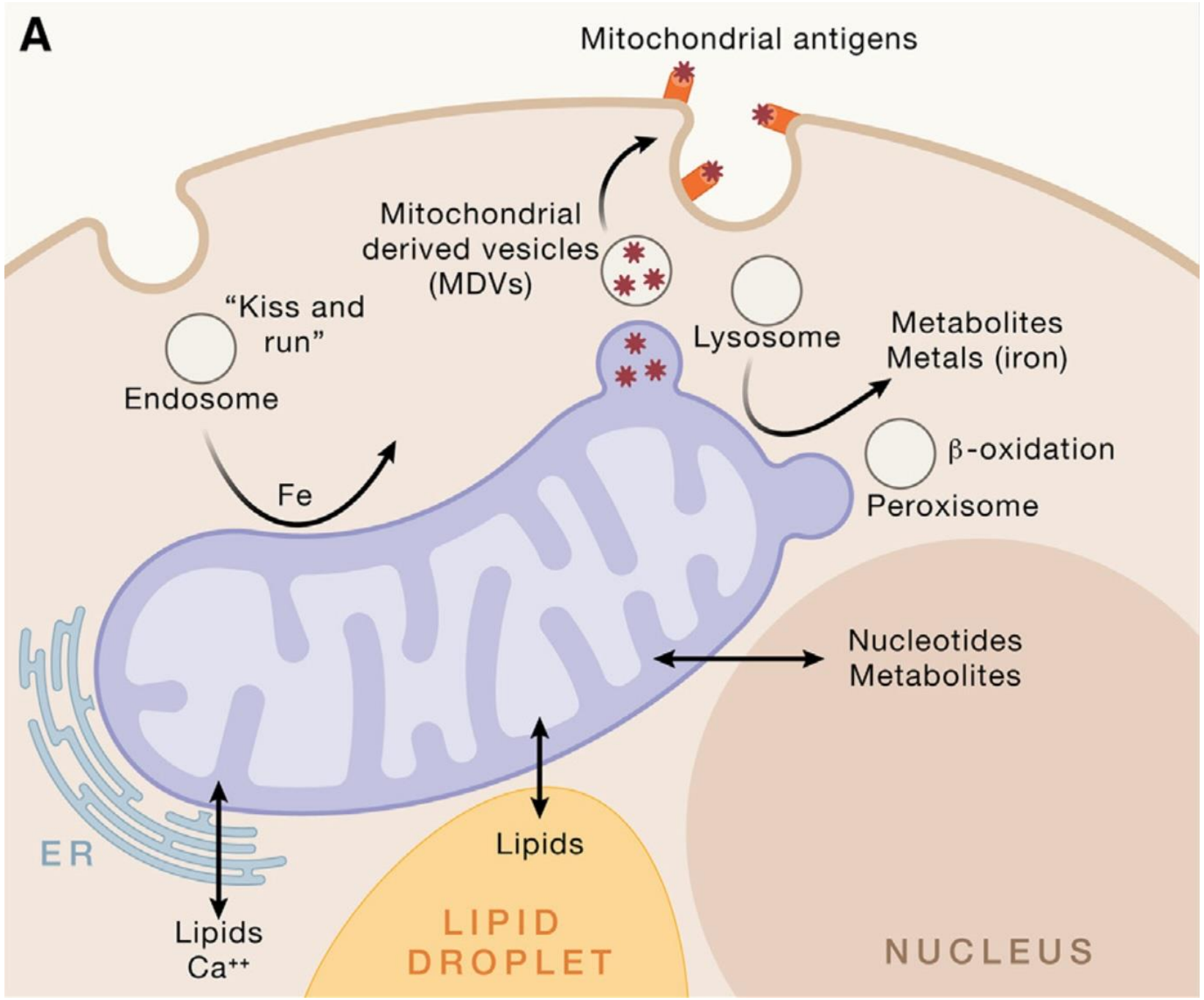

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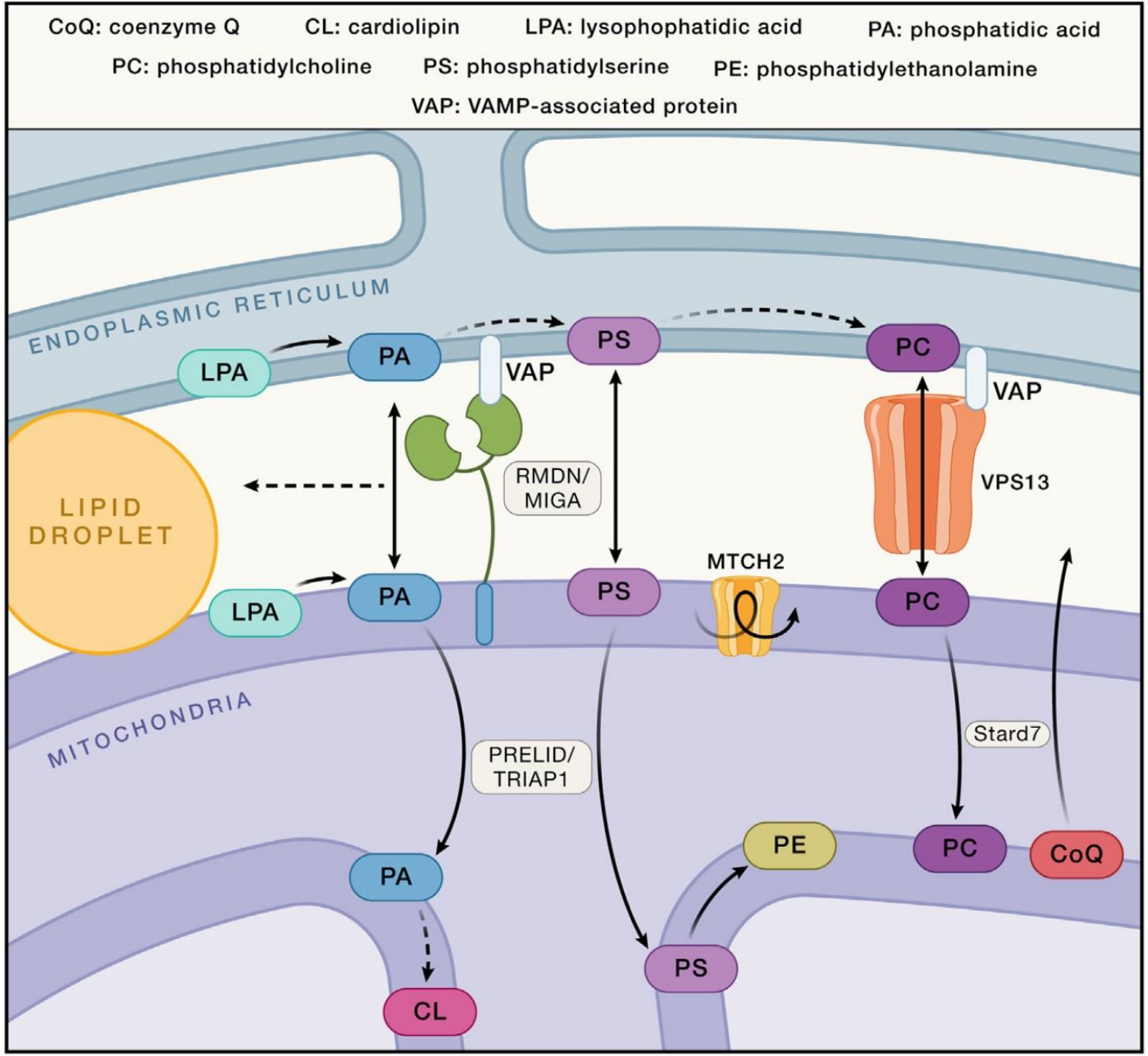

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self management

- Fusion and fission between individual organelles

- **Fission**
  - GTPase dynamin-1-like protein (Drp1)
  - Required for mitochondrial quality control

- **Fusion**
  - Mitofusin 1 (Mfn1), Mitofusin 2 (Mfn2) and Optic Atrophy-1 (OPA1)
  - Transfer of mitochondrial proteins, lipids, metabolites and mitochondrial DNA (mtDNA) between individual mitochondria

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- The primary fusion factors involved are Opa1, MFN1, and MFN2, which bind to the inner and outer membranes of mitochondria (IMM and OMM)

- Fission is mainly mediated by Drp1, which binds to the OMM and forms a ring-like structure around the organelle, resulting in its division into two separate ones

- Mitophagy
  - PINK / parkin target damaged mitochondria to the lysosome for degradation
  - Mitochondrial transport along microtubules is facilitated by TRAK/ Miro motor adapter complex

- Drp1: dynamin-related protein 1; MFN1/2: mitogenic protein 1/2; Opa1: optic atrophy protein 1; Fis1: protein fission 1; Mff: mitochondrial fission factor, PINK: PTEN-induced kinase 1, Miro: mitochondrial rho GTPase

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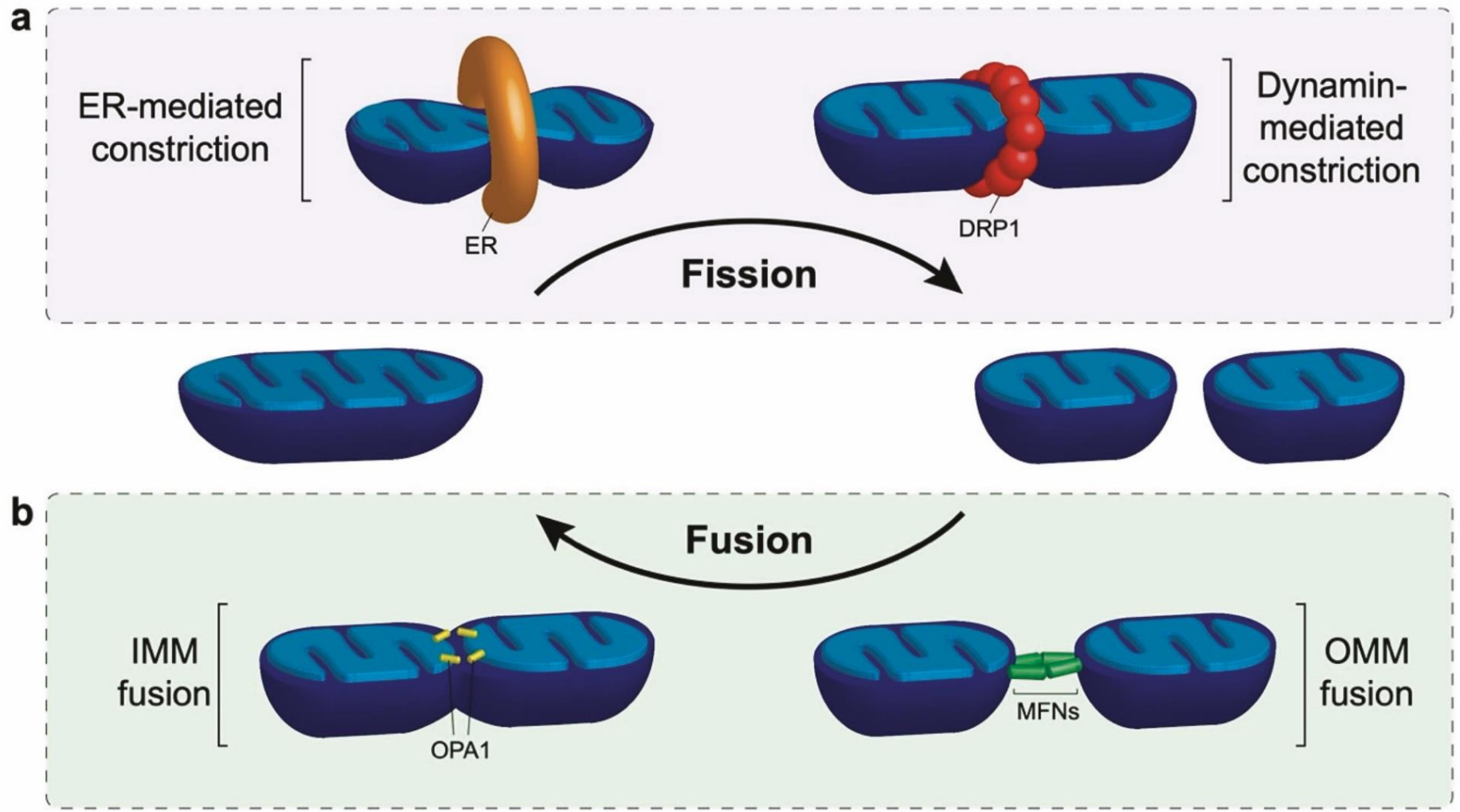

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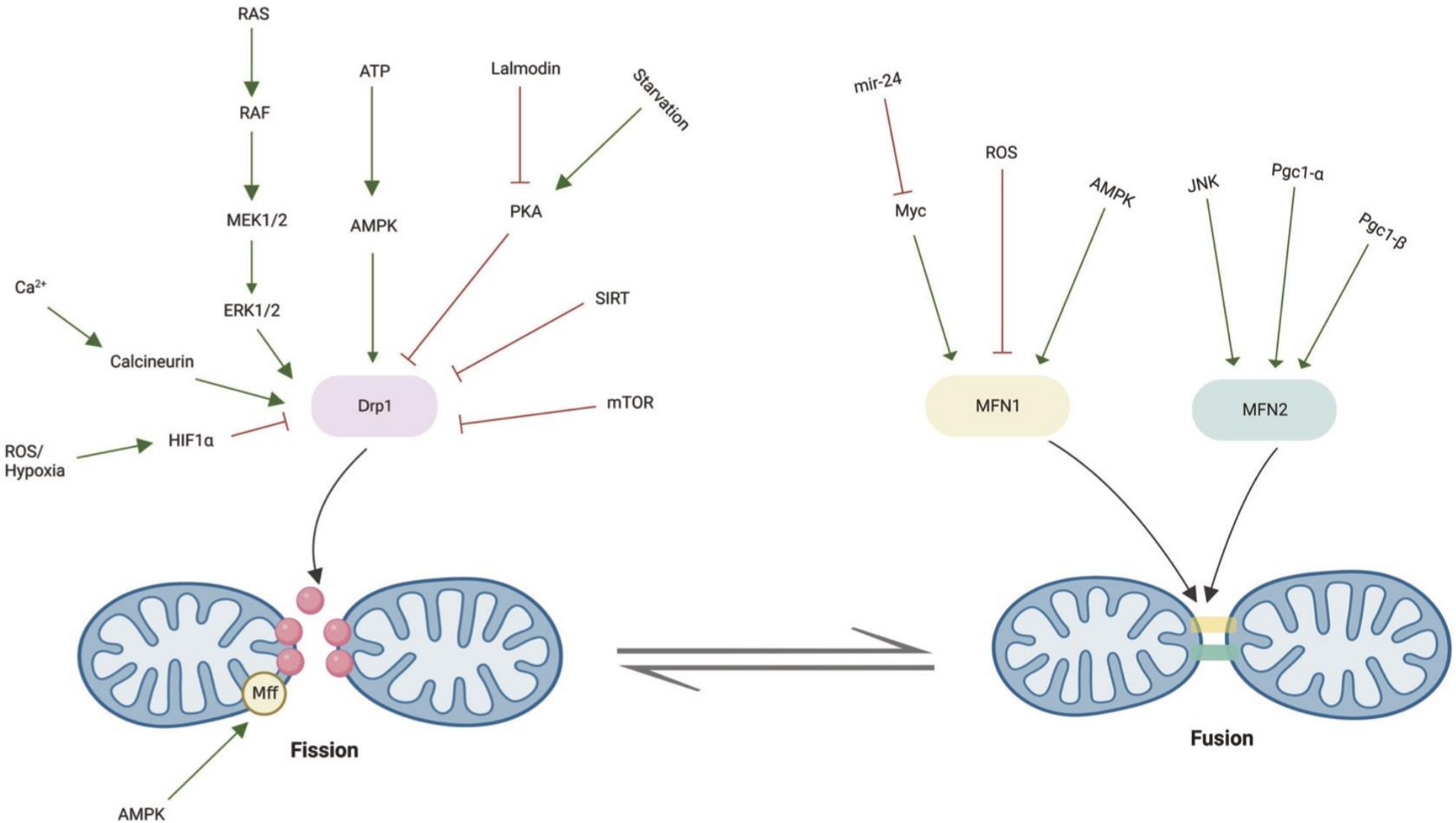

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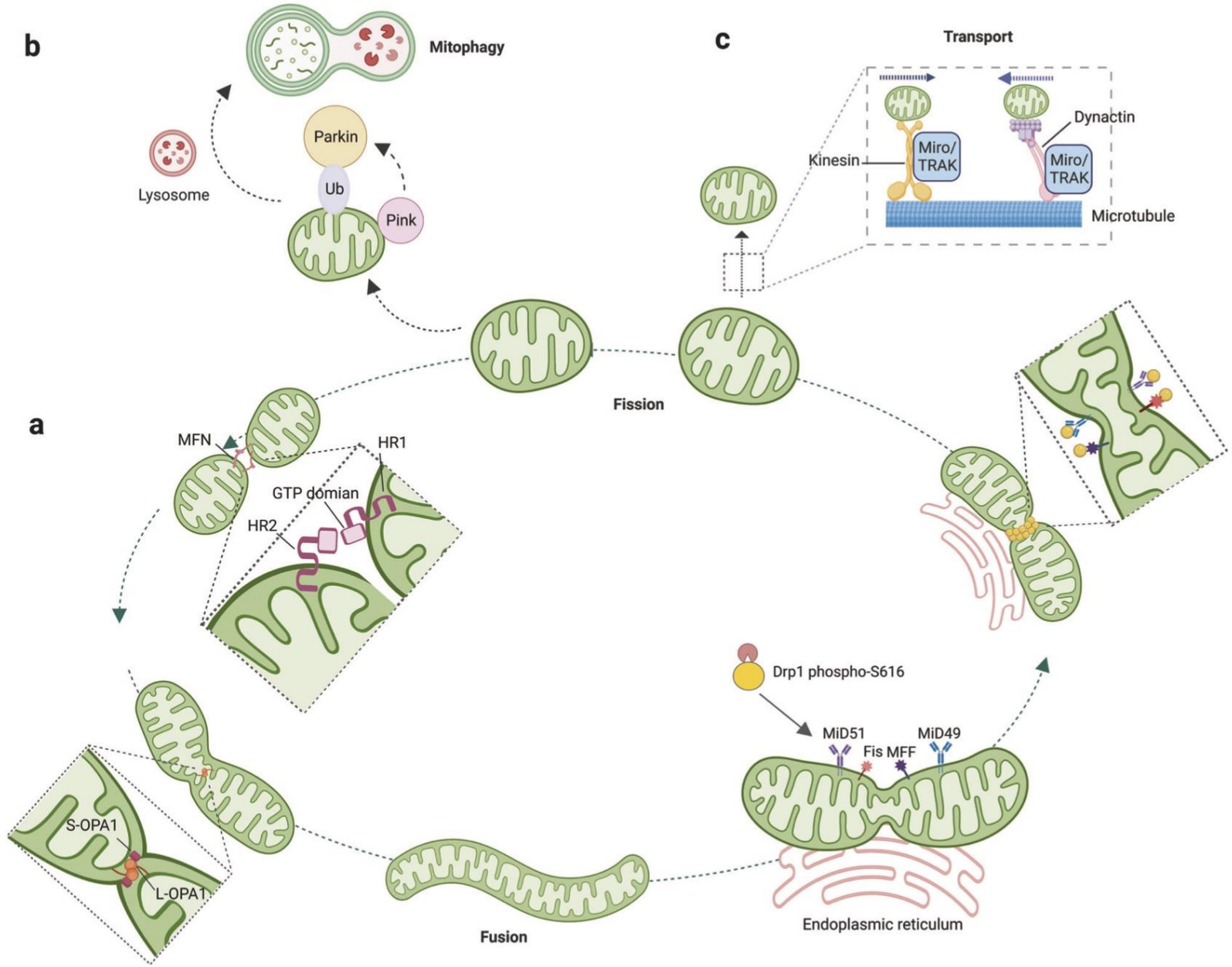

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- Nuclear-encoded mitochondrial protein biogenesis
  - **Transcriptional control of mitochondria**
    - Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha Protein (PGC-1a)
  - **Translational control of mitochondria**
    - Localized mRNA synthesis of mitochondrial proteins - mitochondrial biogenesis and stress responses - neurons
  - **Post-translational control of mitochondrial functions**

- Mitochondrial lipid biogenesis

- Mitochondrial lipid transport at membrane contact sites

- Mitochondrial contact sites as organizers of mitochondrial behavior and signaling

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- Mitochondrial dysfunctions are signaled in a retrograde manner to elicit corresponding stress responses that progress in stages
  - Remodeled metabolic pathways that promote repair to removal of damaged proteins by microautophagy, mitophagy, and mitochondrial-derived vesicle-mediated pathways

- When the capacity of these pathways is exceeded, the cells die by apoptosis, ferroptosis, or pyroptosis, depending on a signal and cell / tissue context

- Mitochondrial proteases
  - First-line responders for mitochondrial quality control
  - AAA proteases are localized to the IMS, IM, and matrix and are associated with import and assembly machinery where they monitor, extract, and degrade misfolded, misassembled, and damaged proteins

- Vesicle-mediated mitochondrial turnover and mitophagy
  - Compartmentalization of proteins to budding membranous vesicular structures (MDVs)

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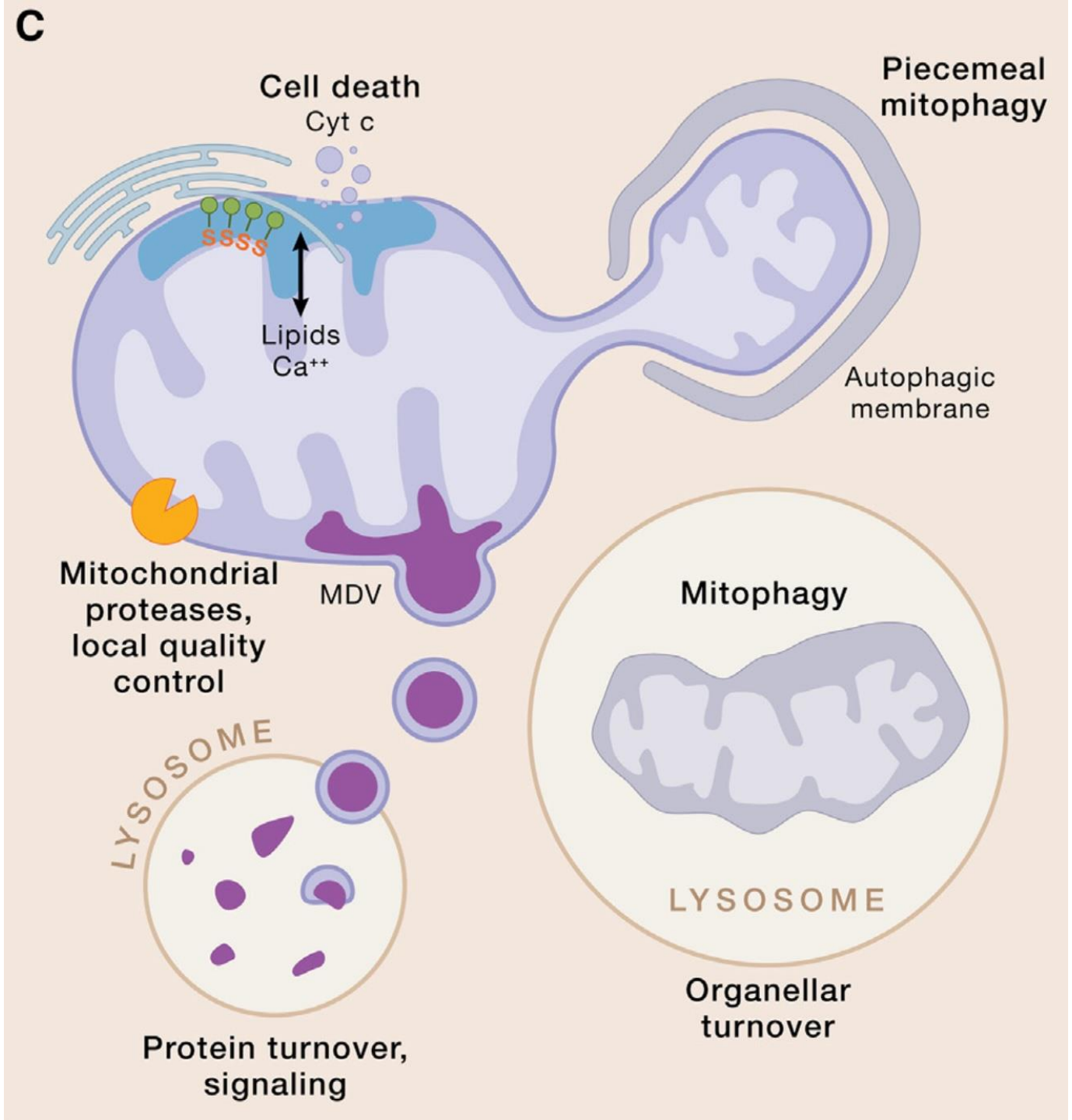

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Innate Immunity And Inflammation

- Tissue damage - mitochondrial antigen release to extracellular sites
- Virus infection - trigger mitochondria to release its components into cytoplasm
  - Elements of the mitochondrial genetic system - mitochondrial DNA, RNA, and mitochondrial-derived formyl peptides (mDAMPs)
- Activation of cellular pattern recognition receptors (PRRs)
  - double-stranded DNA-sensor cyclic GMP-AMP synthase (cGAS)
  - stimulator of IFN genes (STING) pathway
  - dsRNA sensor RIG-I
- Downstream cascade of an innate immunity response

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- Upregulation of nuclear transcription programs and a type-I IFN response
  - cytokine release to counteract the infection
- Under physiological conditions
  - Mitophagy - safeguard against the release of mDAMPs
- Capacity of these quality-control systems is exceeded, or defective
  - inflammation can drive pathogenesis
- Mitokines

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- Mitochondrial functions - altered with aging - tissue-specific manner
- Chronic shift toward mitochondrial biosynthetic repair functions at the cost of ATP production
- Changes in transcription and translation and cell-extrinsic factors
- Recognized as contributors to most age-related degenerative diseases
- Altered metabolism can also cause adverse drug effects

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dysfunction & pathology

- No coherent pathophysiological etiology for psychiatric disorders
- What do “brain” diseases have to do with congenital heart disease and metabolic disorders ?
- Assumed that if a symptom emanates from an organ, then the “cause” of the problem must be a defect in that organ - Problems with behavior, learning, and memory relate to the brain
- The brain is 2% to 3% of body weight - expends 20% of mitochondrial energy
- The milder the bioenergetic defect - the more brain-specific the symptoms
- Mitochondrial diseases present at any age, in any organ system, in a highly tissue-specific or multisystemic manner and display any inheritance pattern

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- The mtDNA has a very high mutation rate
- Hence, new mutations arise regularly, initially giving rise to mixtures of mutant and normal mtDNAs (heteroplasmy)
- Changes in the heteroplasmy percentage of a mutant can give graded defects and variable phenotypes
- Because multiple genes code for each of the enzyme complexes of OXPHOS, multiple different gene alterations can result in similar bioenergetic defects and related phenotypes
- Heart, kidney, muscle, and endocrine systems - high energy demand tissues
- Mild mitochondrial dysfunction – a/w diabetes and metabolic syndrome

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- Ancient mtDNA lineages harboring function variants (haplogroups)
  - eg. the mtDNA tRNA^{Gln} gene at nucleotide 4336A>G

- Heteroplasmic mtDNA tRNA $^{Leu(UUR)}$ nucleotide 3243A>G mutation
  - 10% to 30% 3243G mutation - type 1 or type 2 diabetes or autism
  - 50% to 90% 3243G - multisystem neurological, cardiac, and muscle disease
  - 100% mutant as pediatric lethality

- Mitochondrial DNA mutations
  - accumulate with age in tissues, resulting in the age-related decline in mitochondrial function

- Progressive mitochondrial defects
  - can exacerbate inherited nDNA or mtDNA mitochondrial gene defects

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Ancestral factors

- Long-term evolutionary co-existence of viruses and prokaryotes
- Mitochondria may continue to serve as a prime focus for virus infection
  - the virus may then have direct access to the nuclear genome
- Intracellular transport of mitochondrial mtDNA as nuclear-mitochondrial segments (NUMTs) is an evolutionarily ancient phenomenon

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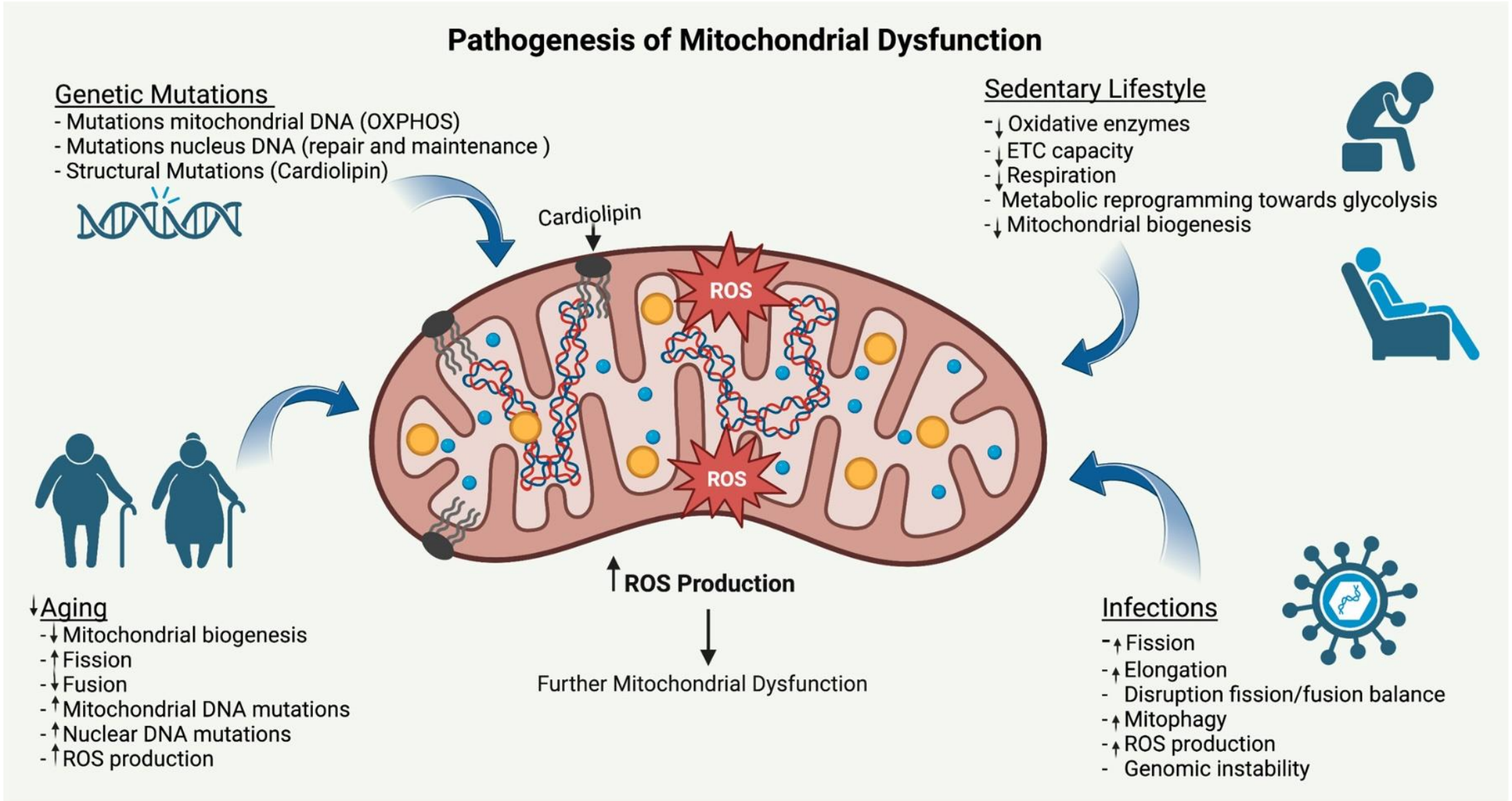

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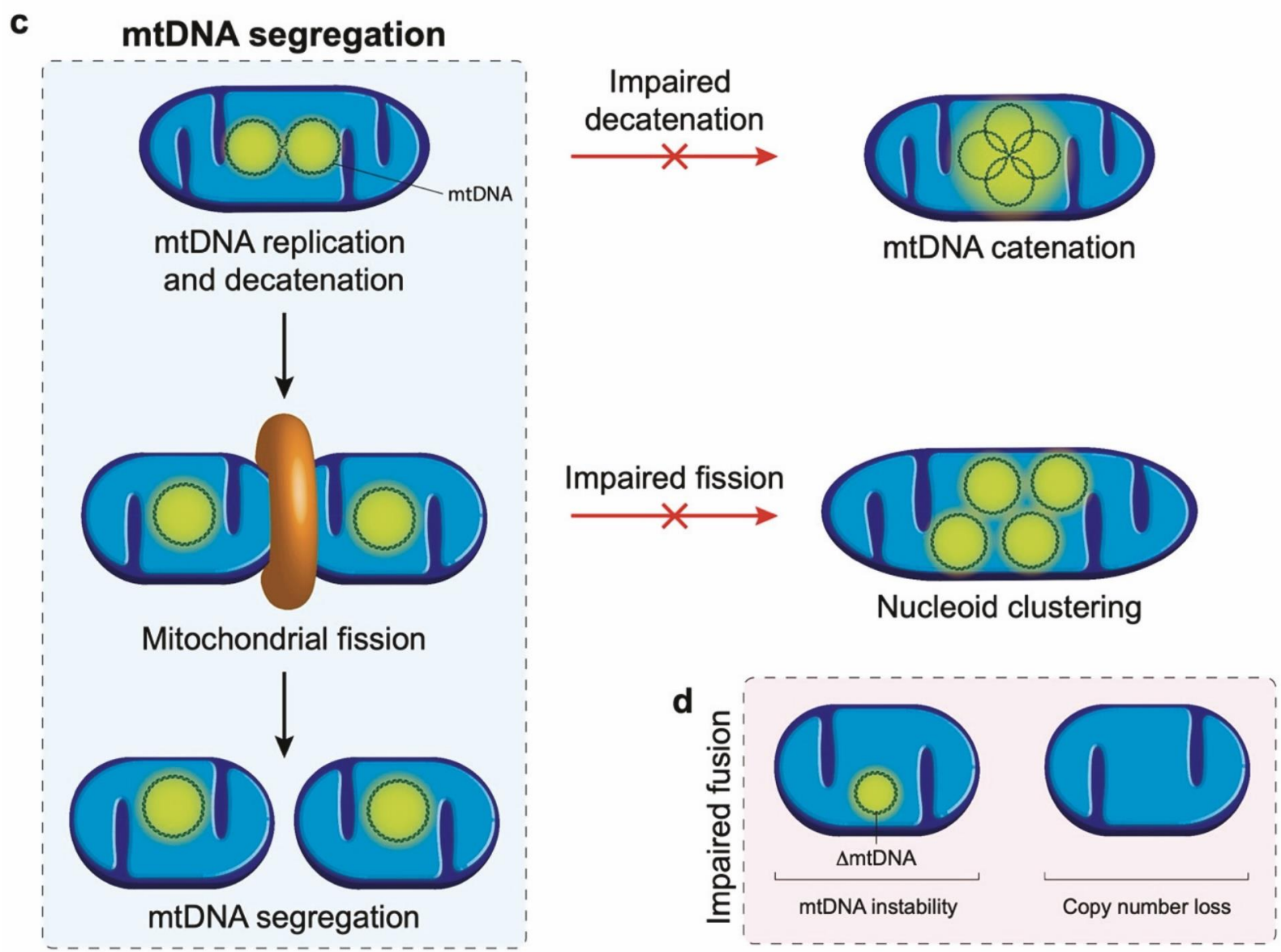
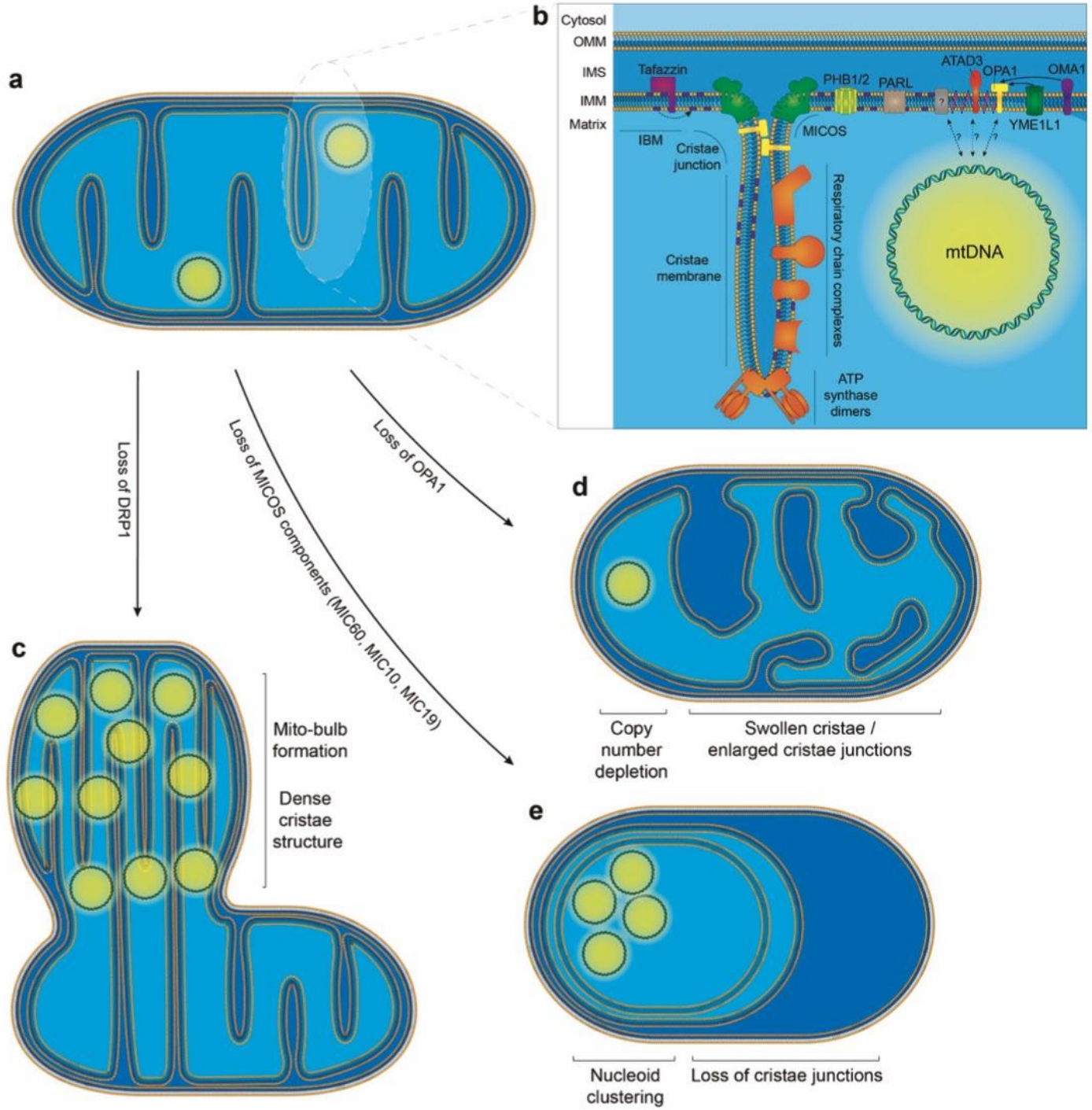


James Chapman et al. The Maintenance of Mitochondrial DNA Integrity and Dynamics by Mitochondrial Membranes. Life 2020, 10, 164; doi:10.3390/life10090164



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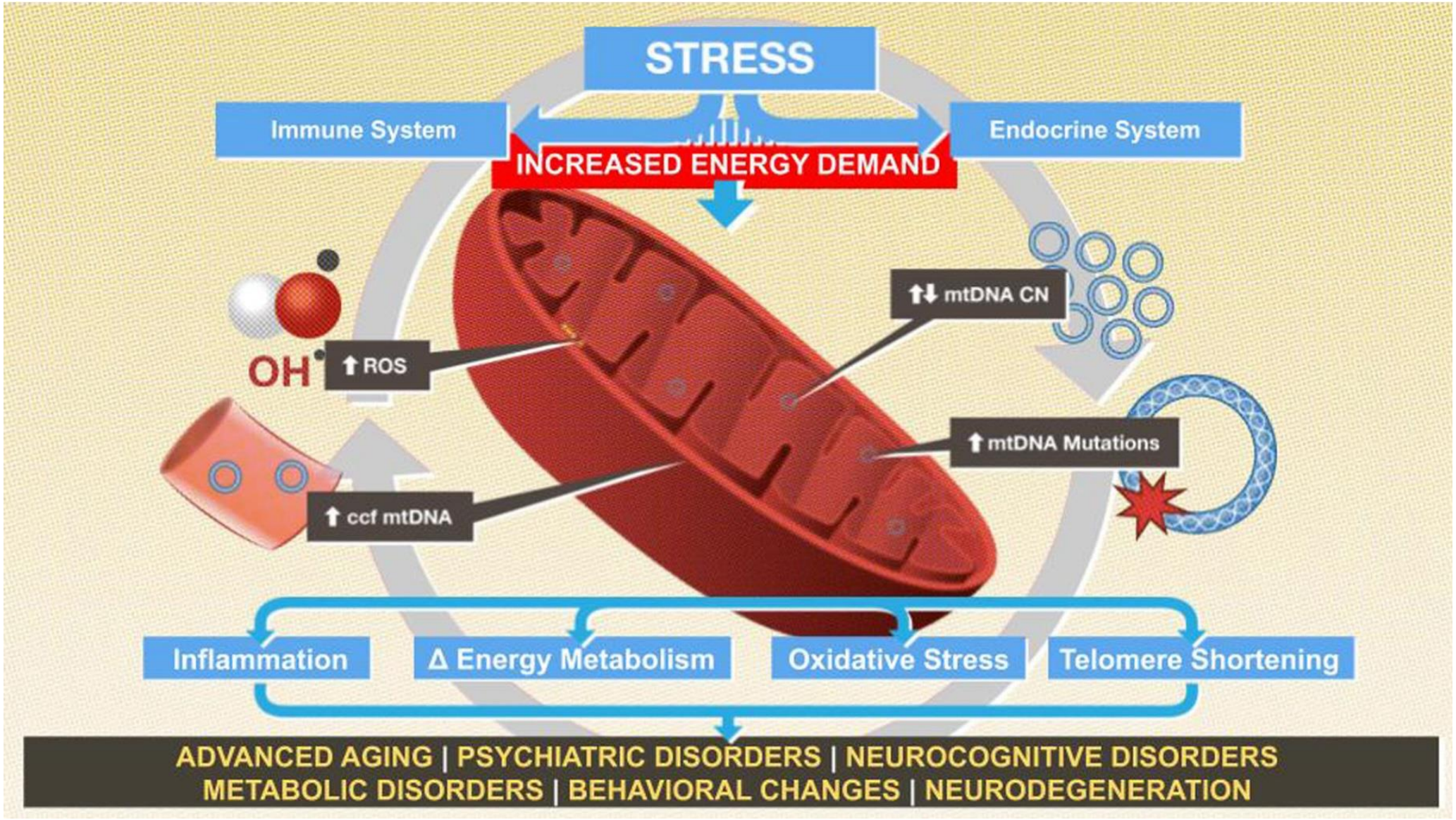


Teresa Daniels et al. Stress and Psychiatric Disorders: The Role of Mitochondria. Annu Rev Clin Psychol . 2020 May 07; 16: 165–186. doi:10.1146/annurev-clinpsy-082719-104030.

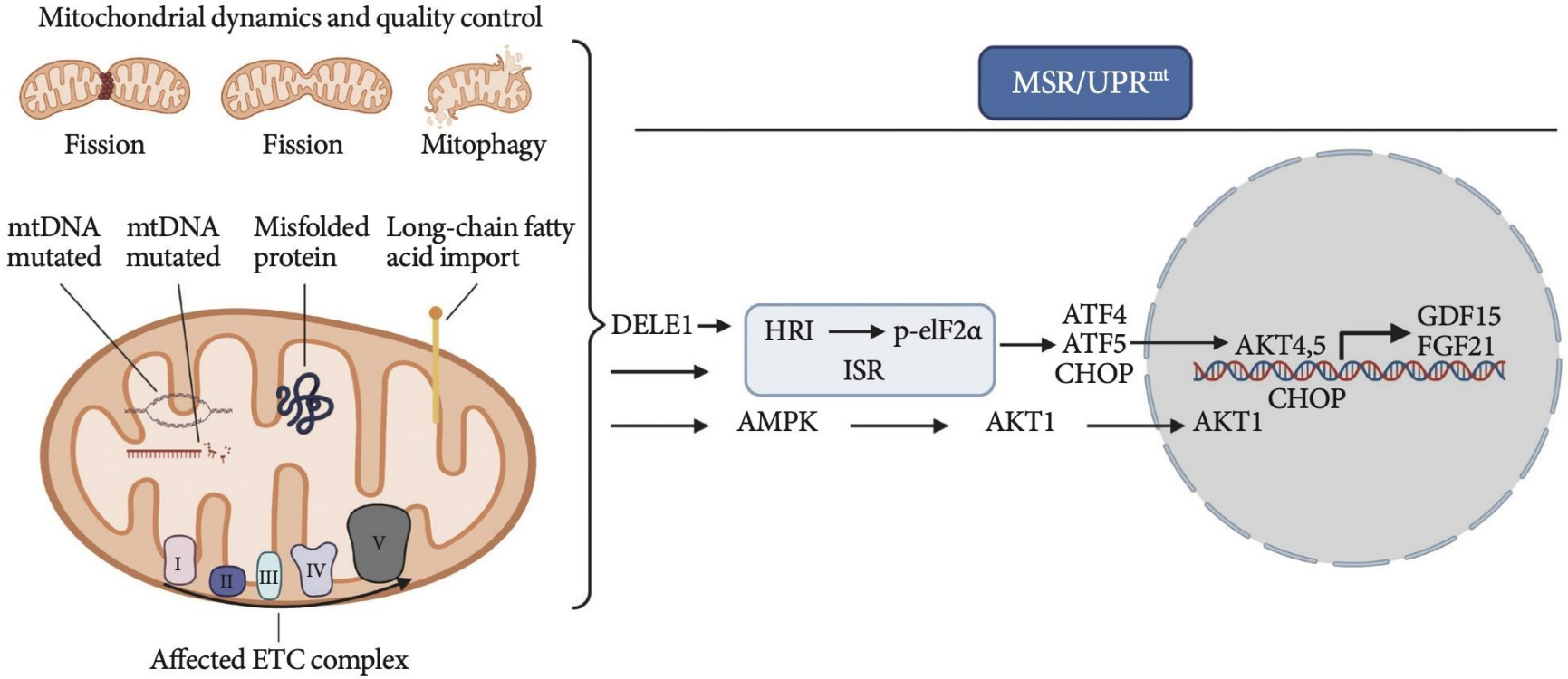


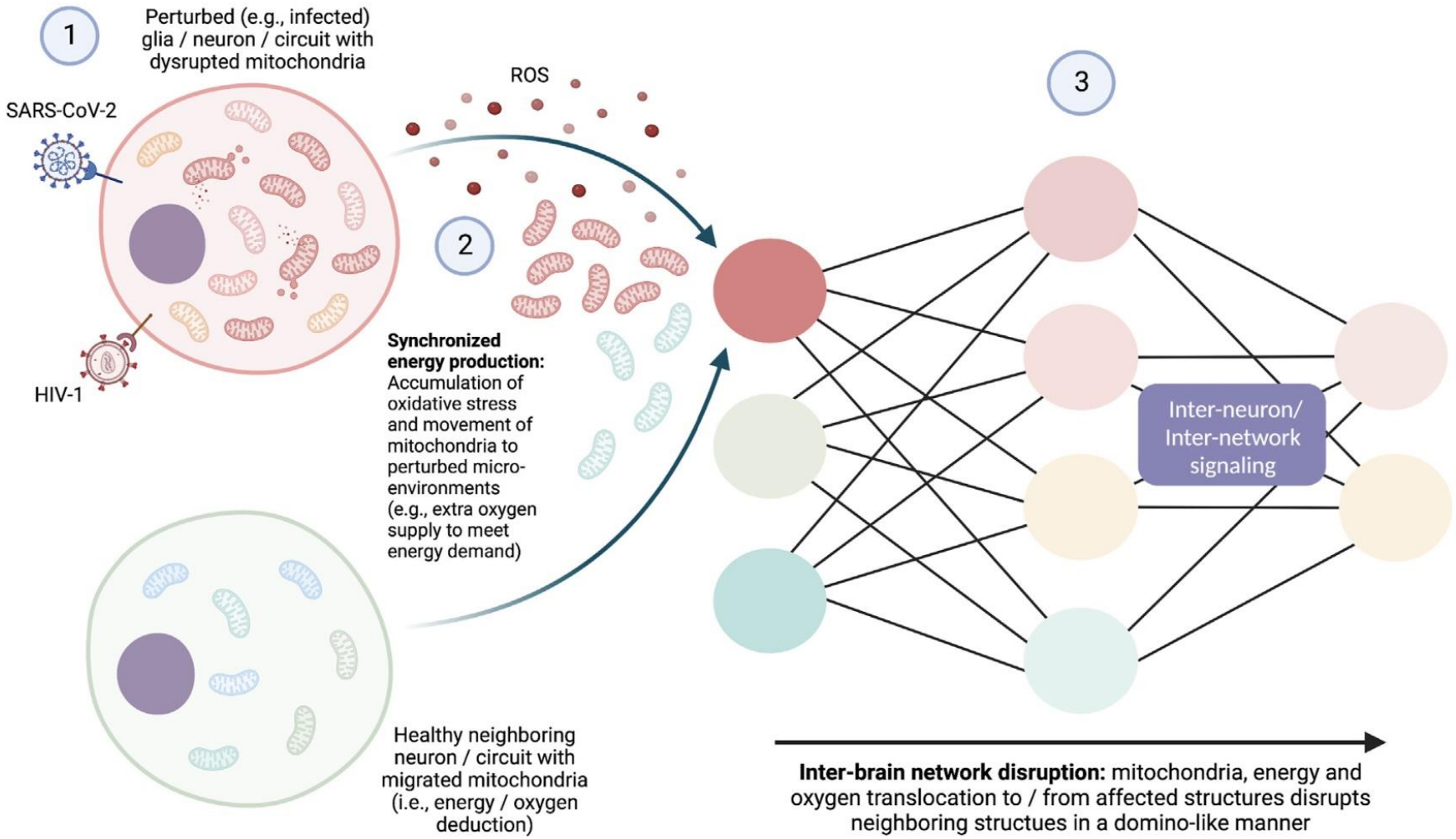
Fig. 1. Regulation of fibroblast growth factor 21 (FGF21) and growth differentiation factor 15 (GDF15) expression by mitochondrial stress response (MSR) and mitochondrial unfolded protein response (UPR^{mt}). The integrated stress response (ISR) is a cellular pathway activated in response to mitochondrial defects. In this pathway, a molecule called DAP3 binding cell death enhancer (DELE) plays a crucial role. DELE activates the heme-regulated inhibitor (HRI), which leads to the phosphorylation of eukaryotic initiation factor 2α (p-eIF2α) or triggers the ISR directly. This activation of the ISR facilitates the expression of key regulatory factors, such as activating transcription factors 4 (ATF4), ATF5, and C/EBP homologous protein (CHOP), which act as crucial regulators for the expression of FGF21 and GDF15. Additionally, an elevated ratio of adenosine monophosphate (AMP)/adenosine triphosphate (ATP), signaling energy stress, can induce the activation of AMP-activated protein kinase (AMPK). This activation occurs through a potential AKT serine/threonine kinase 1 (AKT1)-mediated mechanism. Ultimately, the activation of AMPK stimulates the expression of FGF21 or GDF15, further contributing to the regulatory processes involved in MSR and UPR^{mt}. ETC, electron transport chain.

Benyuan Zhang et al. Mitochondrial Stress and Mitokines: Therapeutic Perspectives for the Treatment of Metabolic Diseases. Diabetes Metab J 2024;48:1-18. https://doi.org/10.4093/dmj.2023.0115

1. Perturbed cellular function:
- Pathogens, aging, disorders, etc.
- Ca2+ imbalance
- Hypoxia / Inflammation
- Glial activation

2. Neuronal energy perturbation:
- Mitochondrial sensory response
- Mitoch. dysfunction / movement
- Altered ATP production
- Oxidative stress (e.g., ROS)

3. Energy dips affect cogntive processing:
- Knowledge / Intellect / Language
- Memory / Learning / Recall
- Decision-making / Executive functions
- Perception / Consciousness / Psyche



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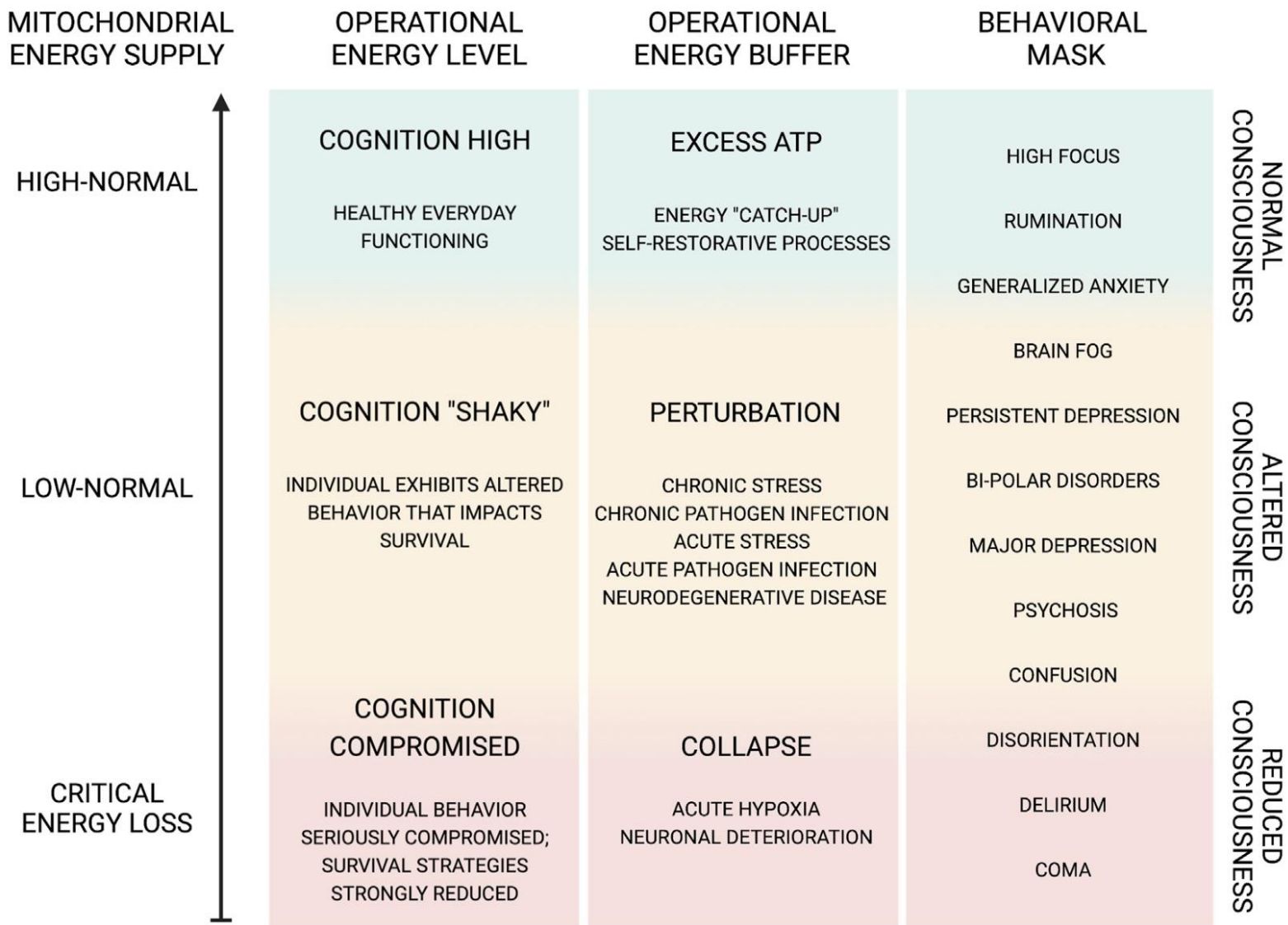

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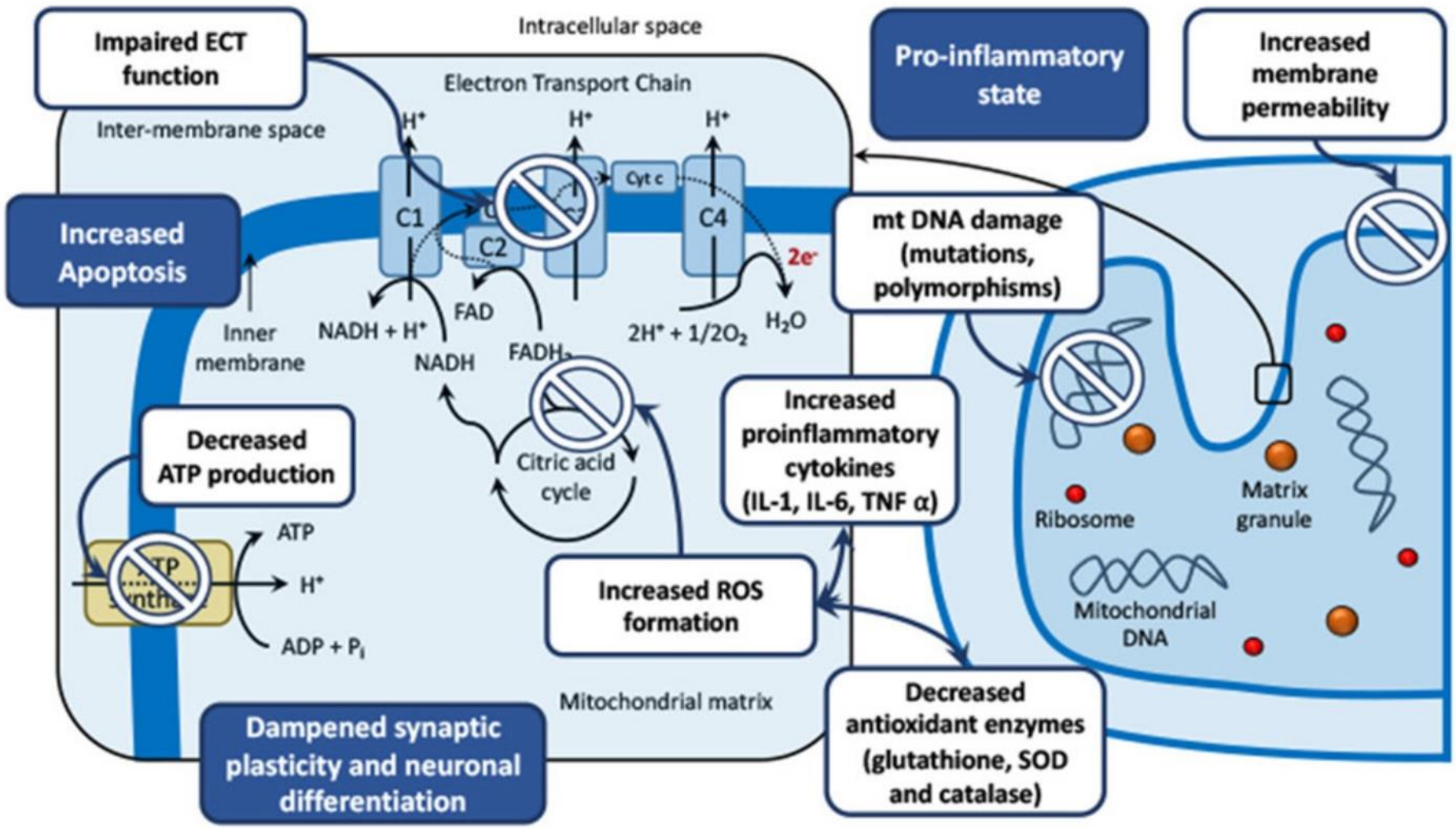

Giménez-Palomo A, Dodd S, Anmella G, Carvalho AF, Scaini G, Quevedo J, Pacchiarotti I, Vieta E and Berk M (2021) The Role of Mitochondria in Mood Disorders: From Physiology to Pathophysiology and to Treatment. Front. Psychiatry 12:546801. doi: 10.3389/fpsyt.2021.546801

Depression

Mitochondrial Genetics

- mtDNA deletions, lower mtDNA copy numbers
  - oxidative damage, inflammation
- variation in the mtDNA copy numbers
  - cognitive impairments
- Downregulation of DNA repair enzymes
  - DNA polymerase gamma (POLγ)
  - 8-oxoguanine-DNA glycosylase 1 (OGG1)

Khan, M.; Baussan, Y.; Hebert-Chatelain, E. Connecting Dots between Mitochondrial Dysfunction and Depression. Biomolecules 2023, 13, 695. https://doi.org/10.3390/ biom13040695

Mitochondrial Proteome

- Altered levels of proteins
  - OXPHOS, pyruvate metabolism and the tricarboxylic acid cycle, etc
- 21% of mitochondrial proteins have altered levels
- 20 subunits of the ETC complexes were increased
- Increased levels of ETC complex I and IV, cytochrome c and ATP synthase
  - dorsolateral prefrontal, anterior cingulate and parieto-occipital cortices
- Carbonic anhydrase and aldolase c
  - increased in the frontal cortex and the anterior cingulate cortex

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OXPHOS and ATP Production

- Decreased mitochondrial ATP production
- A decreased activity of ETC complexes I+III and II+III

Oxidative Stress in Depression

- Excess ROS - damage to proteins, lipids and DNA, including mtDNA
- Alterations of the complex I subunits NDUFV1, NDUFV2 and NDUFS1 and increased oxidative damage in the cerebellum
- Decreased level of antioxidant enzymes – eg. manganese superoxide dismutase

Khan, M.; Baussan, Y.; Hebert-Chatelain, E. Connecting Dots between Mitochondrial Dysfunction and Depression. Biomolecules 2023, 13, 695. https://doi.org/10.3390/ biom13040695

Calcium Homeostasis

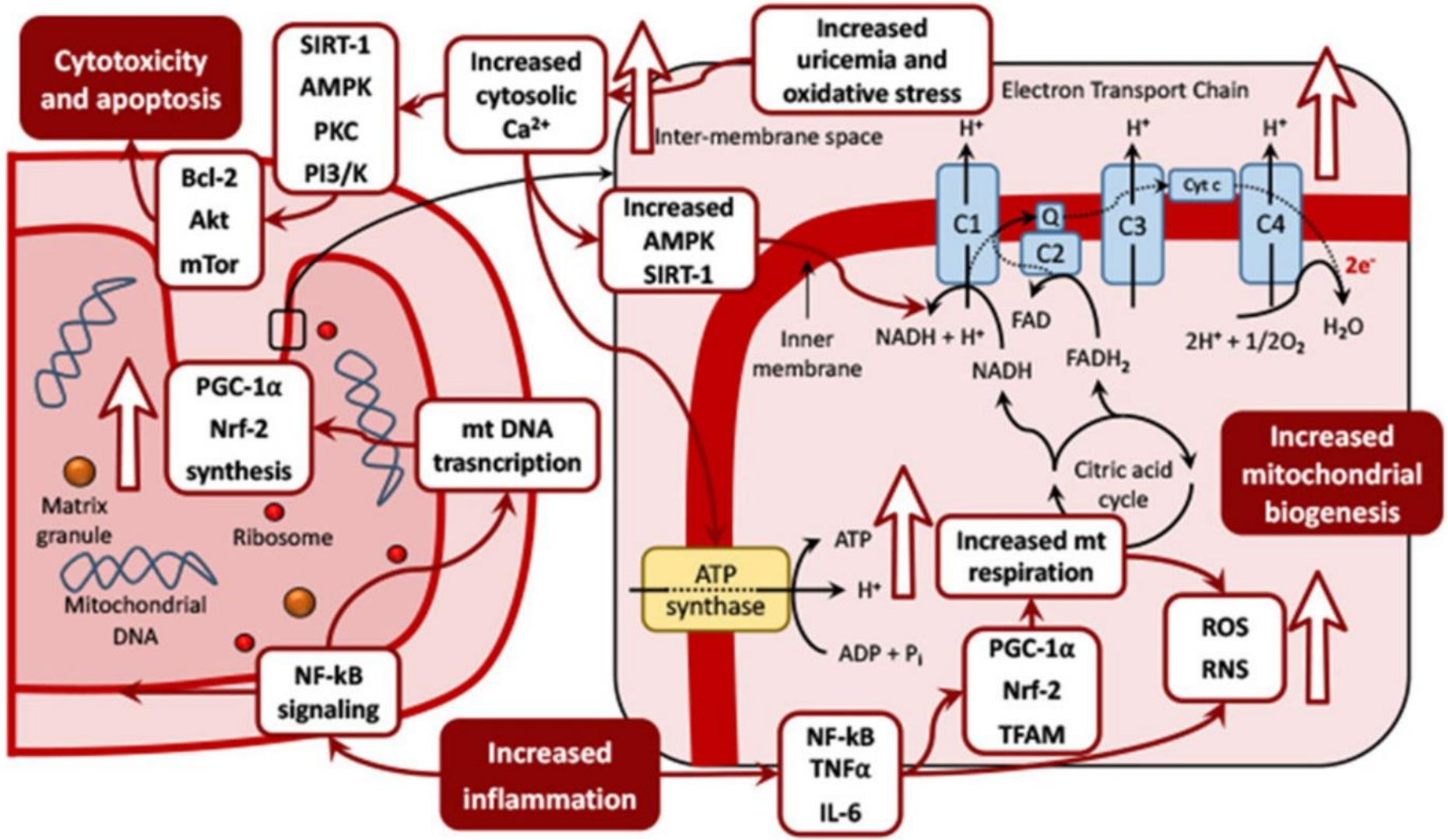
- Dysregulation of mitochondrial Ca2+ homeostasis
  - *Cacna1c* as a candidate risk gene for multiple neuropsychiatric disorders, including bipolar disorder, schizophrenia and depression
  - *Cacna1c* encodes the pore-forming α1C subunit of the L-type Ca^{2+} channel CaV1.2
  - CaV1.2 channels are critical modulators

Khan, M.; Baussan, Y.; Hebert-Chatelain, E. Connecting Dots between Mitochondrial Dysfunction and Depression. Biomolecules 2023, 13, 695. https://doi.org/10.3390/ biom13040695

Inflammation

- Dysregulation of both the innate and adaptive immune system
- Higher levels of circulating pro-inflammatory cytokines
  - Activation of the proinflammatory cytokines interferon-γ, interleukin (IL)-2, 1β, IL-6 and tumor necrosis factor- α (TNF-α)
- Lower levels of anti-inflammatory cytokines
  - Reduction in the anti-inflammatory cytokines IL-4 and IL-10

Khan, M.; Baussan, Y.; Hebert-Chatelain, E. Connecting Dots between Mitochondrial Dysfunction and Depression. Biomolecules 2023, 13, 695. https://doi.org/10.3390/ biom13040695



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Mania

- Increased mitochondrial biogenesis
- Increased inflammation and elevated production of ROS and RNS, driven by increased activity of the NF-kB signaling pathway
  - Upregulation of PGC-1α, Nrf-2, and TFAM
  - PGC-1α and Nrf-2 stimulate mitochondrial respiration
- Increased oxidative stress – increase Ca2+ ions seen in mania

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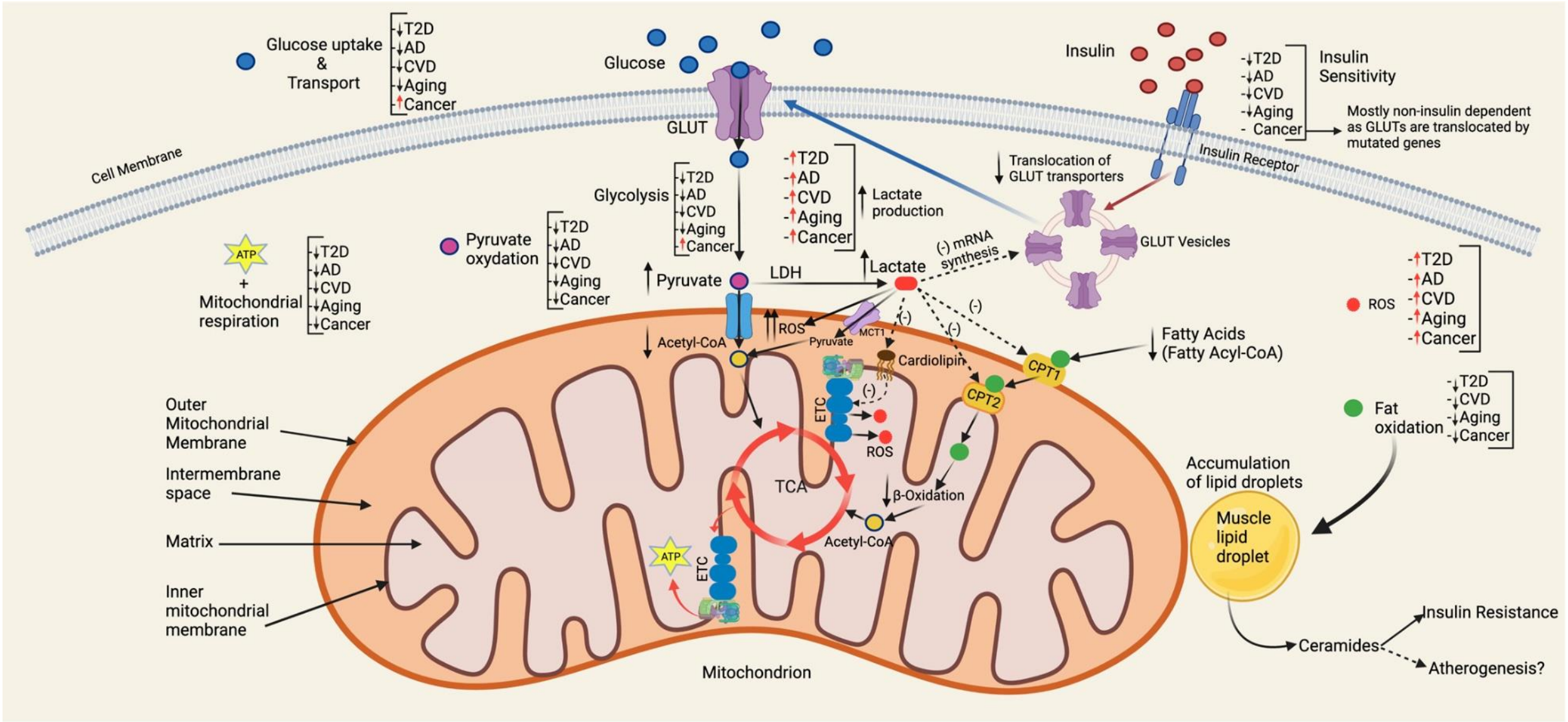
- Elevated Ca2+ - activation of AMPK and SIRT1
  - increase the activity of NAD+
- Increased activity of SIRT1, AMPK, PKC PI3/K
- Activation of proapoptotic pathway cascades
  - Bcl-2, Akt and mTor
- Increased uric acid levels
  - increase the uptake of Ca2+ ions by mitochondria
  - increase the mitochondrial membrane potential
  - enhance ATP production

Giménez-Palomo A, Dodd S, Anmella G, Carvalho AF, Scaini G, Quevedo J, Pacchiarotti I, Vieta E and Berk M (2021) The Role of Mitochondria in Mood Disorders: From Physiology to Pathophysiology and to Treatment. Front. Psychiatry 12:546801. doi: 10.3389/fpsyt.2021.546801

Psychiatric Diseases	Preclinical Models		Mitochondrial Involvement		Findings in Kynurenines
Major depressive disorder	CMS	-	decreased ATP, ATPase activity		
	TST	-	altered membrane potential		
				-	decreased Trp, KYN, KYNA
	FST		-	-	increased QUIN
	$Tph1^{-/-}$		-		
	$Tph2^{-/-}$		-		
	$Tph1/Tph2^{-/-}$		-		
	TPH2 variant (R439H) KI		-		
Generalized anxiety disorder	outbred Wistar rats	-	reduced mitochondrial GTPase expression		
		-	altered mitochondrial morphology and functions		
				-	decresed KYN
	social hierarchy	-	NAc mitochondrial bioenergetic profiles		

Tanaka, M.; Szabó, Á.; Spekker, E.; Polyák, H.; Tóth, F.; Vécsei, L. Mitochondrial Impairment: A Common Motif in Neuropsychiatric Presentation? The Link to the Tryptophan-Kynurenine Metabolic System. Cells 2022, 11, 2607. https:// doi.org/10.3390/cells11162607

Psychiatric Diseases	Preclinical Models		Mitochondrial Involvement		Findings in Kynurenines
Post-traumatic stress disorder	$FKBP5^{-/-}$ $PAC1R^{-/-}$ $5\text{-}HT1AR^{-/-}$ $COMT^{-/-}$ $GAD6^{-/-}$ $GABAB1a^{-/-}$ $CB1R^{-/-}$ single prolonged stress model	- - - - - - - -	- - - - - - - abnormal apoptosis		-
Bipolar disorder	ClockΔ19 dominant negative mutant of mtDNA Polg1 -	- - -	- - complex I expression abnormality	- - -	reduced KYNA increased 3-HK/KYN, 3-HK/KYNA ratio increased KYNA in CSF
Substance use disorder	-	-	reduced mitochondrial copy numbers	- -	higher 5-HT lower KYN/5-HT ratio
Schizophrenia	DISC1 hypertensive rats	- -	affect mitochondrial transport, fission, and fusion -	- - -	higher KYN and KYN/TRP ratio increased KYN, KYNA decreased KYNA/KYN ratio
Autism spectrum disorder	$ND6^{P25L}KI$ $Shank3^{\Delta c/\Delta c}$ Cntnap2 KO $ADGRL3^{-/-}$ valproate polyinosinic–polycytidylic acid	- - - - - -	- - - - - mitochondrial dysfunction	- - -	lowered KYNA higher KYN/KYNA ratio higher KYN/Trp ration, KYN, QUIN
Attention-deficit hyperactivity disorder	$Ptchd1^{-/-}$ -	- -	- higher mtDNA copy number	- -	lowered Trp, KYNA, XA, 3-HAA higher Trp, KYN



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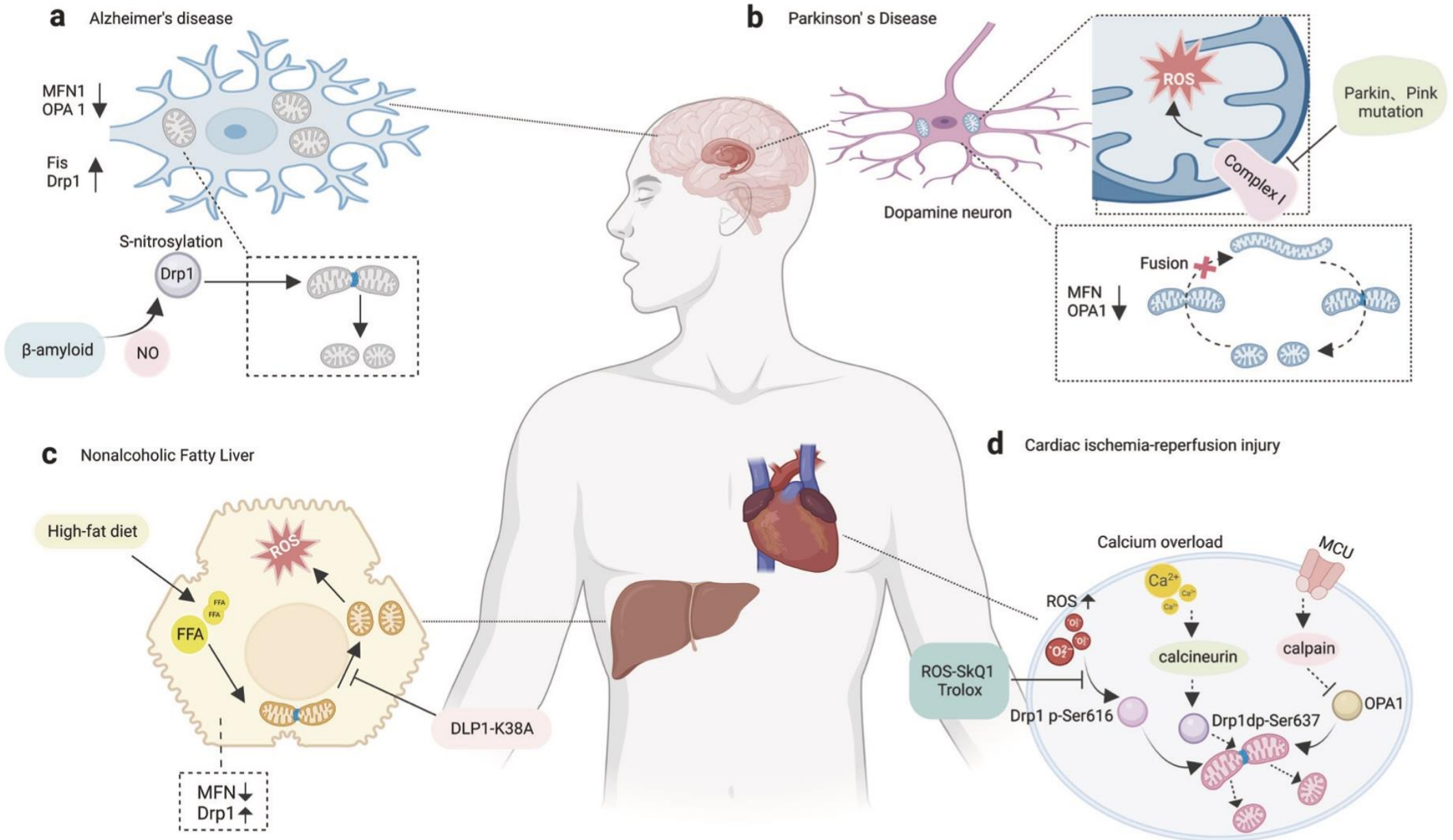

Wen Chen et al. Mitochondrial dynamics in health and disease: mechanisms and potential targets. Signal Transduction and Targeted Therapy (2023)8:333 ; https://doi.org/10.1038/s41392-023-01547-9

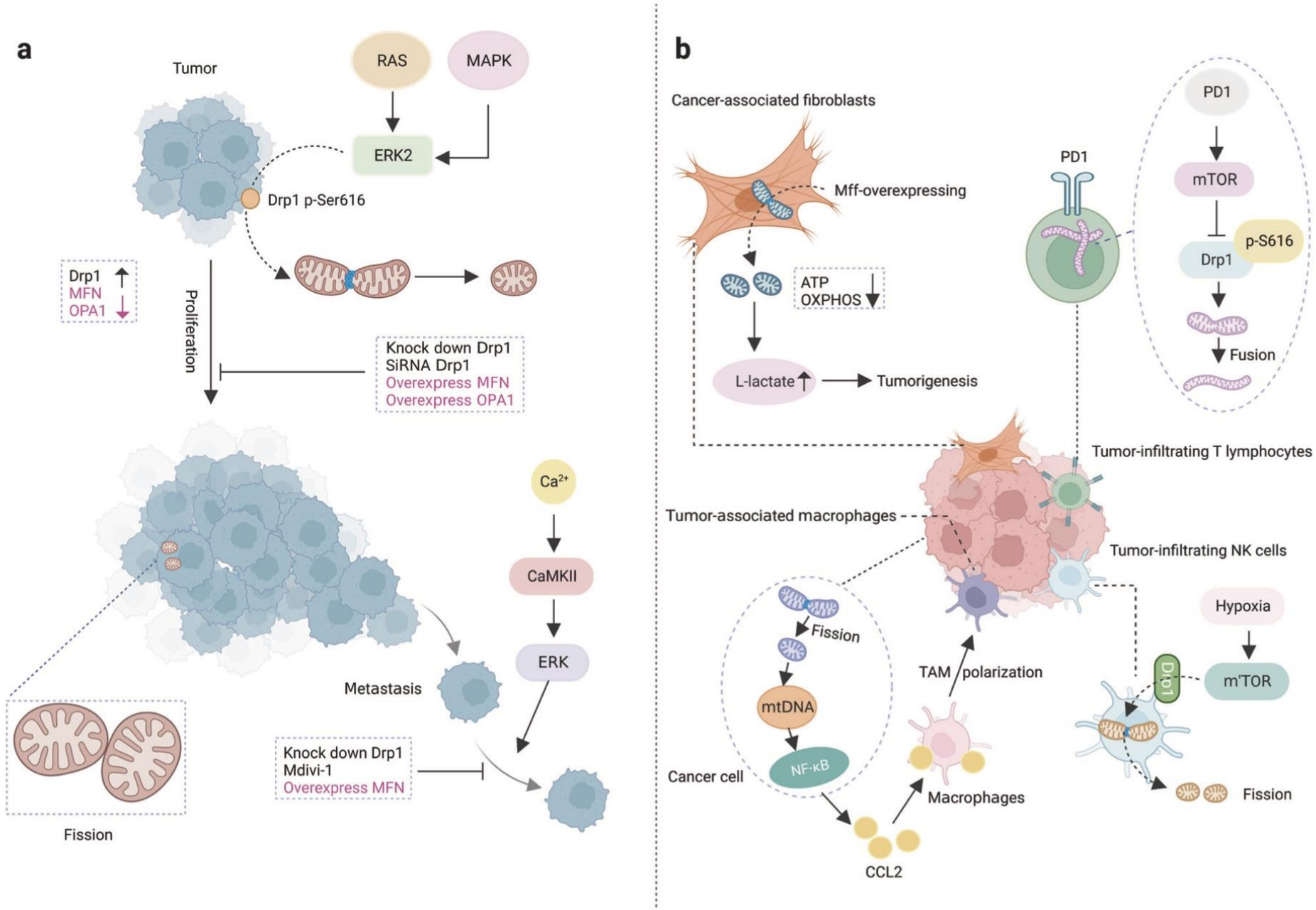

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Table 1. Highly variable nervous system manifestations of mitochondrial diseases

Condition	Leigh syndrome	Alpers-Huttenlocher	MELAS	Mitochondrial ataxia w/o epilepsy	Parkinsonism	Sensory organ defects
most common defect	subunits and assembly factors of OXPHOS complexes	mtDNA replisome POLG1, Twinkle	mitochondrial translation tRNALeu(UUR)	mtDNA replisome frataxin	mtDNA replisome Pink1, Park2	OXPHOS subunits, mt-translation, mt-replisome
potential molecular mechanisms	hypoxia/ hyperoxia, energy crisis, lactacidosis, oxidative stress, microglial activation, macrophage, or lymphocyte invasion to CNS	toxic astrocyte reactivation, microgliosis, inflammation	lactic acidosis, one-carbon metabolic remodeling, redox imbalance, nitric oxide metabolism, L-arginine deficiency	poor antiviral defense, inflammation, astrocyte reactivation, stalled autophagy	mt-antigen presentation, organellar turnover, metabolic remodeling, oxidative stress	ionic imbalance, lack of inhibition of sensory signals, glutamate toxicity, metabolic remodeling, energy crisis protein/organellar turnover
typical models for mechanistic studies	NDUFS4-knockout mice	Twinkle-cKO mice, GFAP promoter	patient findings, human samples, cell lines	MIRAS knock-in mice, Fxn-cKO-prion protein promoter; human samples, cell cultures	parkin S65A knockin mouse	OPA1 mutations expressed in retinal pigment cells
main affected brain area, patients	symmetric hypervascularized necrotic lesions in the brain stem	laminar necrosis, spongiotic lesions of cerebral cortex	metabolic strokes in the cerebral cortex, often occipital	Symmetric lesions in the cerebellum, thalamus	loss of neurons in substantia nigra, autonomous nervous system dysfunction	atrophy of retina, optic nerve, ocular muscles, inner ear, or sensory nerves
typical life stage of manifestation	before 2 years	2–4 years	before age 20, but may occur any age	FRDA: 5–15; MIRAS: 10–45	after 30 years	all ages

Anu Suomalainen and Jodi Nunnari. Mitochondria at the crossroads of health and disease. Cell 187,May 23,2024

Neurological Diseases	Preclinical Models	Mitochondrial Involvement	Findings in Kynurenines
Alzheimer's disease	>170 genetic models (APP, PSEN-1, PSEN-2)	-	
	3xTg-AD	- decreased mitochondrial respiration - decreased pyruvate dehydrogenase protein - increased mitochondrial Aβ level	- increased ratio of KYN/Trp - decreased KYNA - 3-HK/KYN positively correlated with t-tau and p-tau peptides
	TgAPParc	- decreased mitochondrial membrane potential - increased reactive oxygen species - increased oxidative DNA damage - mitochondria impairments	- KYN and PIC negatively correlated with t-tau and p-tau peptides
	APP_{SWE}	-	
	$PSEN1_{dE9}$	-	
	$SVCT2^{+/-}$	-	
	human Aβ-KI	-	
Parkinson's disease	PINK1	-	
	Parkin	-	
	Parkinson disease protein 7	-	
	CHCHD2	- fragmented mitochondria	- lower activities of KAT I and KAT II - decreased KYNA - increased 3-HK - lower KYNA/KYN ratio - increased QUIN - higher QUIN/KYNA ratio
	complex I Park model	- neurodegeneration	
	methyl-4-phenyl-1,2,3,6-tetrahydropyridine	-	
	Rotenone	-	
	6-hydroxydopamine	-	

Neurological Diseases	Preclinical Models	Mitochondrial Involvement	Findings in Kynurenines
Multiple sclerosis	experimental autoimmune/allergic encephalomyelitis (EAE)	- depolarized fragmented mitochondria - trafficking-impaired	- increased KYN/TRP ratio - decreased NADH - higher 3-HK - higher QUIN/KYNA ratio
	Theiler's murine encephalomyelitis virus-induced chronic demyelination	-	- Trp, QUIN, KYNA depending on subtypes - higher QUIN
	cuprizone-induced demyelination	- megamitochondria	- higher QUIN/KYN ratio
Huntington's disease	R6/1	-	- lower Trp
	R6/2	-	- higher KYN
	HTT+97CAG-CAA repeats	-	- higher KYN/Trp ratio
	KI (endogenous Hdh promoter)	-	- higher 3-HK - higher HAO activity - lower KYNA - lower KAT activity
	HdhQ111KI	- multiple mitochondria abnormality	- AA levels correlated with the number of CAG repeats

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Neurological Diseases	Preclinical Models	Mitochondrial Involvement	Findings in Kynurenines
Amyotrophic lateral sclerosis	FVB-C9orf72 BAC	-	
	Cu/Zn SOD1-G93A	-	
	TDP43-Q331K	-	
	iPSC model of C9orf72-associated ALS	- swollen mitochondria - cluster formation of mitochondria - elongated spherical mitochondria - mitochondrial fission and apoptosis	- increased TRP, KYN, QUIN - decreased PIC - KYNA inconclusive
	SOD1 G93A	-	
	BPA	- Drp1 translocation - mitochondrial RCS	
	BSSG	-	
Migraine	inflammatory soup	- small, fragmented mitochondria - reduced mt DNA - increased Drp1 fission protein - decreased Mfn1 fusion protein - valproic acid stabilized mitochondria	- decreased L-KYN, KYNA, 3-HK, 3-HAA, 5-HIAA, QUIN - increased L-Trp, AA, XA
	nitroglycerin-induced trigeminovascular activation	-	

treament targets

Effect of traditional drugs

- Electron Transport Chain (ETC) – Li, Val
- Oxidative stress – Li , Val, Ltg
- Anti-apoptotic protein Bcl-2 – Li, Val, ECT increase
- Hyperexcitability - Li
- Ca^{2+} & BDNF - Li
- Lactate – Li, Val, Quet decrease

Maya Kuperberg et al. Targeting Mitochondrial Dysfunction for Bipolar Disorder. Curr Topics Behav Neurosci (2021) 48: 61–100. https://doi.org/10.1007/7854_2020_152

TABLE 1 | Effects of conventional pharmacotherapy on mitochondrial functions.

	Molecular mitochondrial properties	**Clinical properties**	
	Neuronal survival	**Inflammation and oxidative/nitrosative stress**	
Mood stabilizers			
Lithium (174–177)	Reduces apoptosis*	Prevents excessive mitochondrial calcium influx*	Mood-stabilizing properties in BD and antidepressant properties in MDD
	Enhanced neuroprotection and neurotrophism	Reduces oxidative stress*	
	Reduced cortical atrophy in BD	Antioxidant effect*	
Valproic acid (178, 179)	Reduces apoptosis*	Reduces oxidative stress in mitochondria*	Mood-stabilizing properties in BD
		Antioxidant effect*	
Antidepressants (99, 180, 181)	Reduce apoptosis*	Increase mitochondrial biogenesis*	Antidepressant properties in BD
	Enhanced neurotrophism	Reduce oxidative stress (mitochondrial and peripheral)*	Risk of manic switch
Antipsychotics (182–185)		Reduce oxidative stress in brain mitochondria*	Antimanic and mood-stabilizing properties in BD

TABLE 2 | Effects of novel therapies on mitochondrial function.

Novel therapies	Molecular mitochondrial properties		Clinical properties
	Neuronal survival	**Inflammation and oxidative/nitrosative stress**	
Pramipexole (186, 187)	Upregulates Bcl- 2		Antidepressant efficacy in treatment-resistant BD
Nutraceuticals		Reduces oxidative stress (in brain and periphery)*	Improves depressive and reduces manic symptoms
N-acetylcysteine (188–190)			
Omega-3 fatty acids (191, 192)		Reduce oxidative stress	Better functioning in BD
		Increase antioxidants	Improve depressive symptoms
Alpha-lipoic acid (193–196)	Reduces apoptosis*	Reduces oxidative stress*	Reverses and prevents amphetamine-induced behavioral and neurochemical alterations*
	Enhanced neuroprotection*		
Acetyl-L-carnitine (194–196)	Reduces apoptosis*		Improvements in depressive disorders
	Enhanced neuroprotection*		
S-Adenosylmethionine (197–199)		Reduces oxidative stress*	Improvements if supplemented in depressive disorders
			Potential risk of manic switch in BD (one study)

Novel therapies	Molecular mitochondrial properties		Clinical properties
	Neuronal survival	Inflammation and oxidative/nitrosative stress	
Creatine monohydrate (200)			Improvements in depressive symptoms
			Potential risk of manic switch in BD (one study)
Leucine, isoleucine, and valine (201)			Reduction in manic severity (one study)
L-tryptophan (202)			Reduction of manic symptoms
			Potential risk of depressive switch in BD (one study)
Carnosine (203, 204)		Reduces oxidative stress*	Improvement of behavior, cognition, and overall well-being
Inositol (205, 206)			Improvements in depressive symptoms in BD
Coenzyme Q10 (207)		Reduces oxidative stress	Improvements in depressive symptoms and functioning in BD
Melatonin (208–210)		Increases BDNF and ERK1/2*	Improvements in depressive symptoms. Scarce effects proven in BD.
		Reduces peripheral oxidative stress*	
Vitamin C and E (211)			Improve severity in depression
Vitamin B3 (211)		Reduces oxidative stress*	Enhances social behavior*
Folic acid (212)		Reduces oxidative stress*	Reduction in manic symptoms
Ketogenic diet (213)			Reports on mood stabilization

	ATP production	Mitochondrial biogenesis	Oxidative stress	Clinical evidence in mood disorder
Bezafibrate (Ioannou et al. 2010; Huang et al. 2017)	Increase	Increase	Decrease	Evidence in depression. Studies on BD underway
Minocycline	–	–	Decrease	Inconsistent. Studies underway
N-Acetyl-cysteine (NAC) (Tardiolo et al. 2018)	–	–	Decrease	Inconsistent, but positive evidence in bipolar depression. Effects take a long time to become apparent
Co-enzyme Q10	Increase	?	Decrease	Evidence in bipolar depression. Effects take a long time to become apparent
Melatonin	Increase	Increase	Decrease	Evidence in unipolar and bipolar depression
Ebselen	–	–	Decrease	Studies currently underway
Mangosteen	Increase	–	Decrease	Improvement in psychotic and affective symptoms of schizophrenia
Ketogenic diet	Increase	Increase	Decrease	Animal models and human case reports
Resveratrol and pterostilbene	Increase	Increase	Decrease	Animal models show effectiveness. Human studies underway for resveratrol
Taurine	Increase	?	Decrease	Animal models only

Maya Kuperberg et al. Targeting Mitochondrial Dysfunction for Bipolar Disorder. Curr Topics Behav Neurosci (2021) 48: 61–100. https://doi.org/10.1007/7854_2020_152

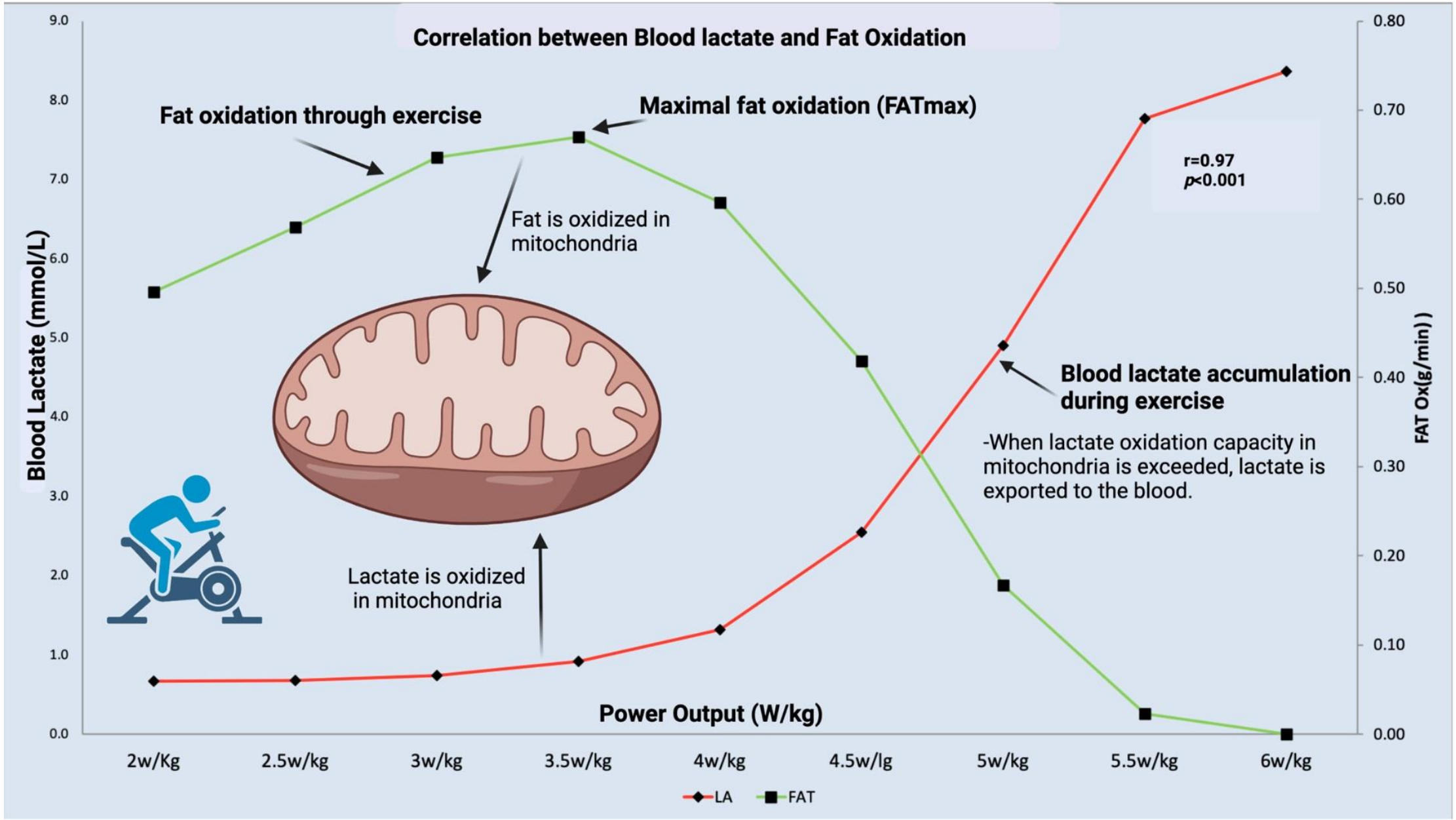
PPARg agonists in Alzheimer's disease

- Rosiglitazone activates neuronal PPARg
- Increases neuronal mitochondrial biogenesis and bioenergetics
- Decreases the probability that mitochondrial function will fall below cortical bioenergetic threshold

Liming Pei and Douglas C. Wallace. Mitochondrial Etiology of Neuropsychiatric Disorders. https://doi.org/10.1016/j.biopsych.2017.11.018

Table 2. Compounds and gene Intervention regulate mitochondrial dynamics for diseases

Compounds	Mechanism	Diseases
Mitochondrial Fission		
Mdivi-1	Inhibited Drp1	AD、PD、IRI
P110	Inhibited GTPase activity of Drp1 and its interaction with Fis1	PD、HD
Dynasore	Inhibited GTPase activity of Dynamin 1, Dynamin 2, Drp1	AD、CVD
1H-pyrrole-2-carboxamide compounds	Inhibited GTPase activity of Drp1	AD
Exenatide	Inhibited the mitochondrial localization of Drp1	HF
Mitochondrial Fusion		
M1	Stimulated Mitofusins	IRI
Enzyme (HO-1)	Upregulated MFN1/2 expression	Cardiomyopathy
Melatonin	Activated the Notch1/MFN2 signaling pathway, upregulated MFN2 expression	IRI
15-Oxospiramilactone (S3)	Deubiquitinated MFN1/2, augmented the activity of MFN1/2	IRI
Punicalagin	Stimulated OPA1	Diabetes
κ-opioid receptor	Stimulated OPA1	IRI
Paeonol	Stimulated OPA1	Diabetes
Gene Intervention		
Overexpression of OPA1	Promoted mitochondrial fusion by increasing expression of OPA1	AD、CVD
Overexpression of MFN2	Promoted fusion by increasing expression of MFN2	Cancer、Diabetes
Knockdown or siRNA of Drp1	Inhibited Drp1 and promotes mitochondrial fusion	Cancer



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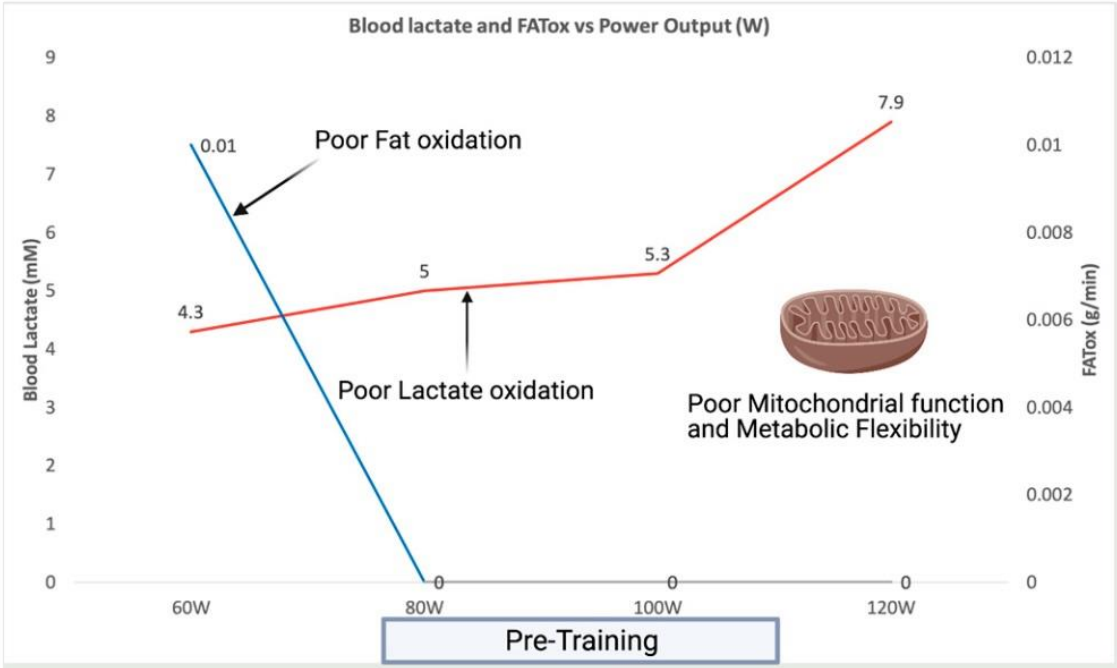

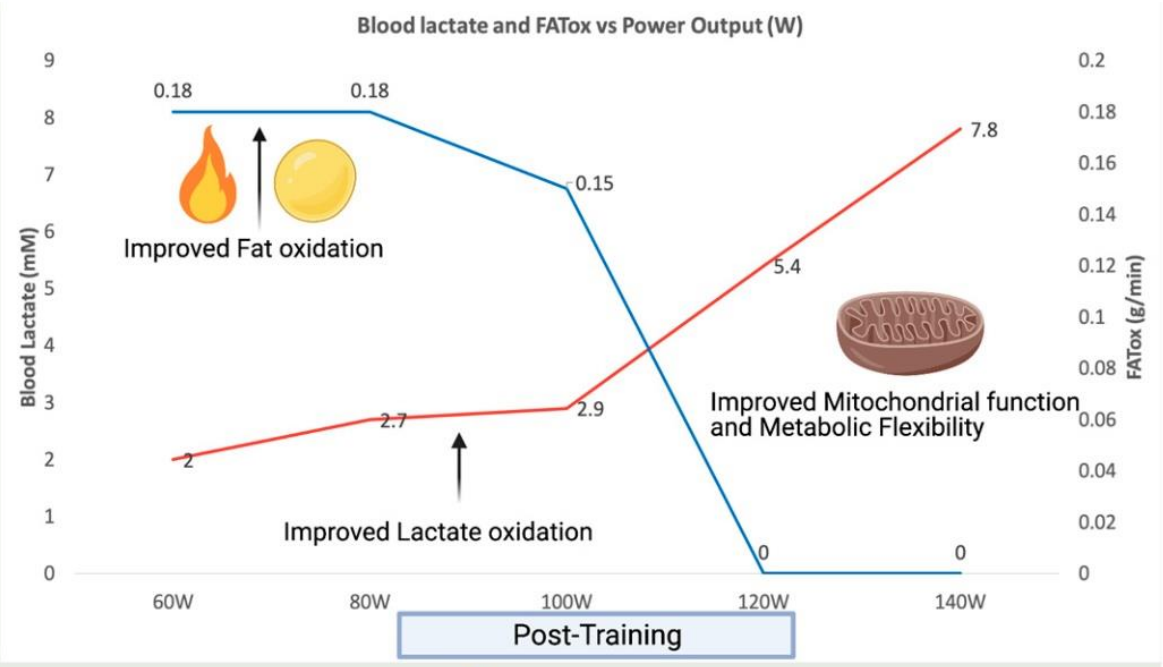

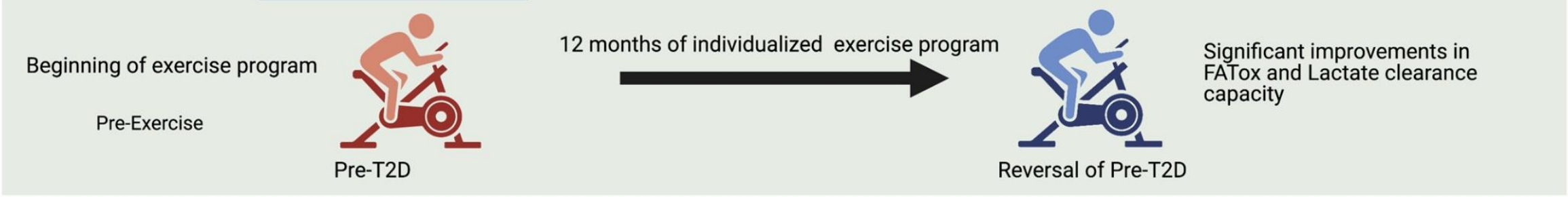

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Thank You