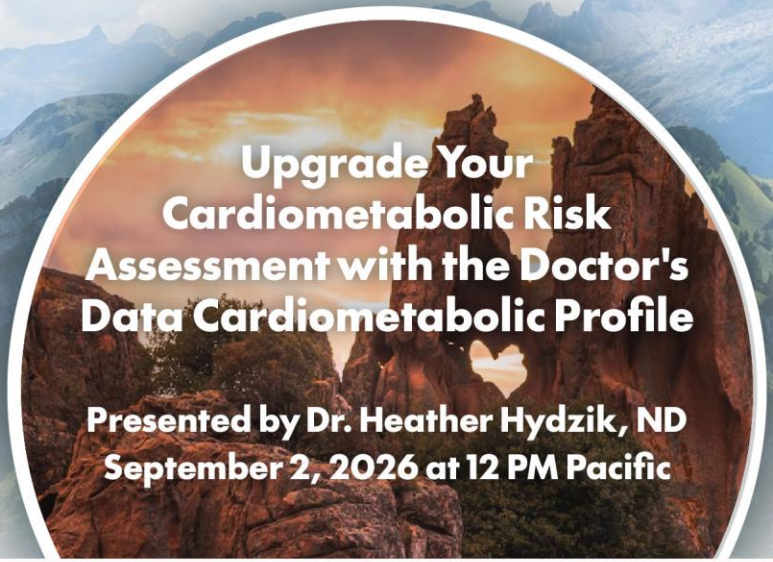
UPCOMING EVENTS



Visit doctorsdata.com/Register-for-Webinars

Wellness Wednesday

WILL BEGIN SHORTLY

MORE WEB EVENTS

The Hormone–Mitochondria Axis

Linking Endocrinology to Cellular Bioenergetics

By Laura Neville, ND

Wellness Wednesday

DOCTOR'S DATA INC.

Mitochondrial Basics

Hormone Connection

Mitochondrial Life Cycle and Cellular Respiration

Associated Pathologies

Mitochondrial Health Assessment

Treatments

Mitochondrial-Hormone Roadmap

Mitochondrial Basics

Mitochondria

- The word "mitochondria" is derived from Greek roots. It combines two terms: "mitos", meaning "thread," and "chondrion", meaning "granule" or "grain."
- This nomenclature reflects the organelle's thread-like appearance under a microscope. The term was first coined by Carl Benda in 1898.

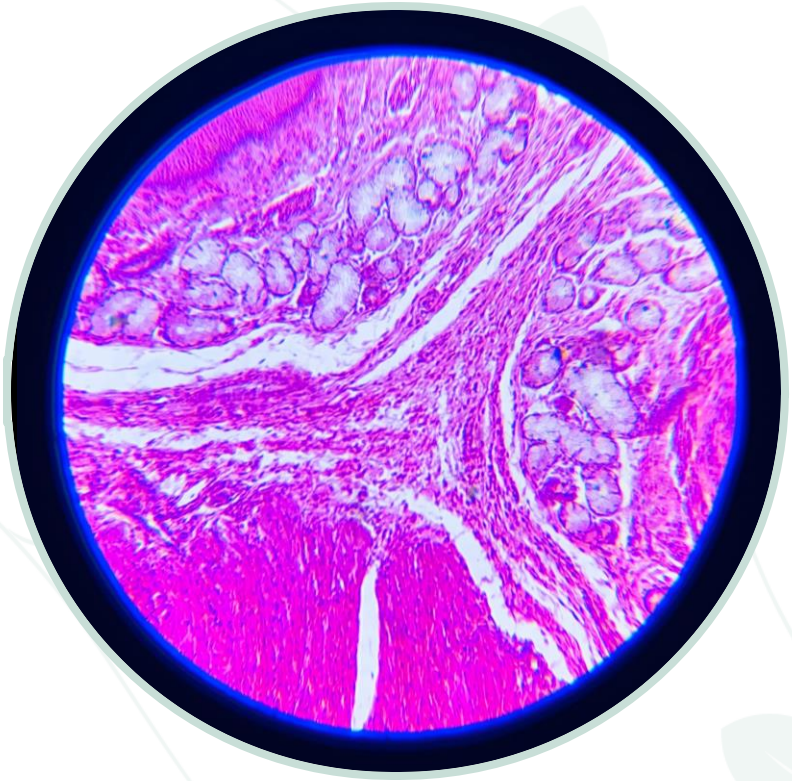
Wellness Wednesday

Allen, Carol & van der Giezen, Mark & Allen, John. (2007). Origin, Function, and Transmission of Mitochondria. 10.1007/978-3-540-38502-8_3.

DOCTOR'S DATA INC

Powerhouse

- Mitochondria are often referred to as the "powerhouse of the cell" due to their role in energy production.
- They are essential for various metabolic processes and are found in most eukaryotic cells
- Found in every cell of the body other than mature red blood cells



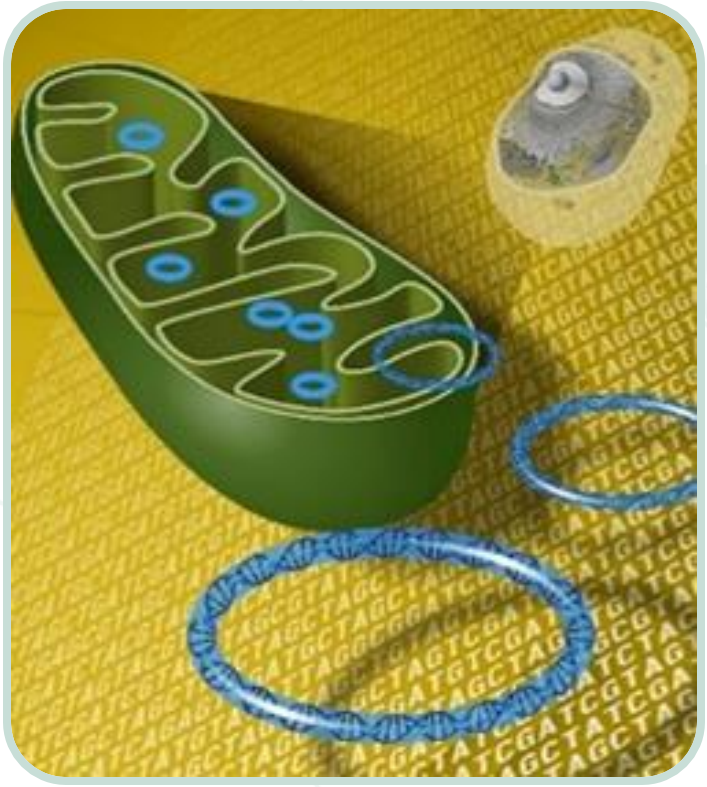
Allen, Carol & van der Giezen, Mark & Allen, John. (2007). Origin, Function, and Transmission of Mitochondria. 10.1007/978-3-540-38502-8_3.

Origins

- We still do not know exactly how these little powerhouses evolved to be found inside of cells.
- The most commonly accepted hypothesis is that they were bacteria-like organisms which were swallowed up by ancestral cells nearly two billion years ago.
- These little bugs were able to produce energy for the larger cell, and the two found themselves in a symbiotic relationship with each other.

https://www.mcgill.ca/oss/article/general-science/mitochondria-story-mothers-teenagers-and-energy

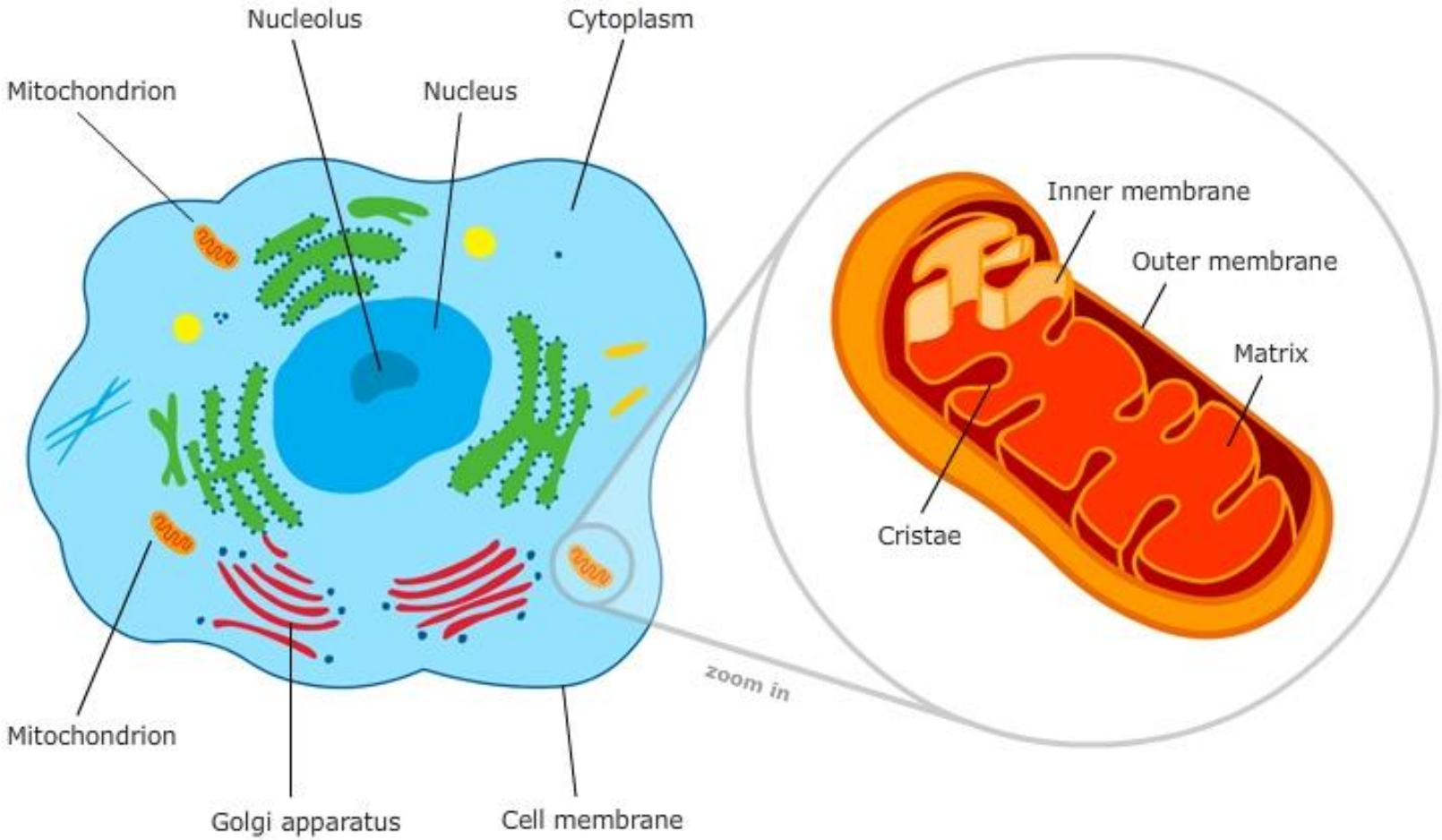
Unique DNA

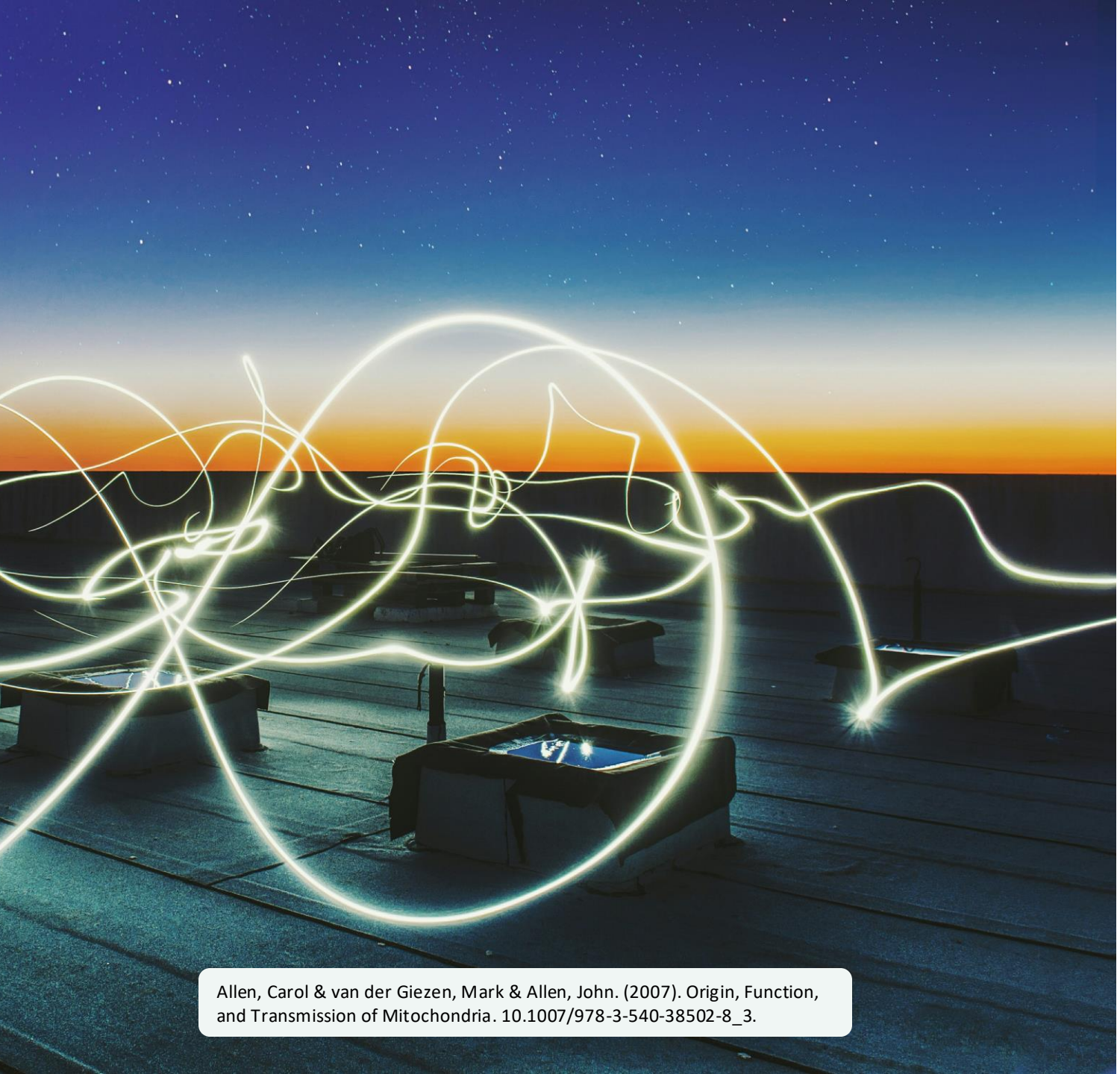


Credit: National Human Genome Research Institute

- Mitochondria are also the only structure in cells with their own unique DNA.
- Unlike nuclear DNA, which is inherited from both parents, mitochondrial DNA is usually inherited only from mothers. Both egg and sperm cells contain mitochondria with mitochondrial DNA, but after fertilization the mitochondria from the sperm are almost always destroyed.
- Mitochondrial DNA forms a circle and contains 37 genes. This makes it tiny compared to our nuclear DNA, which contains about 20,000 genes.

https://nigms.nih.gov/biobeat/2020/05/the-maternal-magic-of-mitochondria





Allen, Carol & van der Giezen, Mark & Allen, John. (2007). Origin, Function, and Transmission of Mitochondria. 10.1007/978-3-540-38502-8_3.

Energy Production

- Mitochondria are best known as the cell's **energy-producing organelles**, but their role goes well beyond making ATP.
- At the most basic level, they convert nutrients from food—carbohydrates, fats, and proteins—into usable cellular energy through a process called **oxidative phosphorylation**. This is where most ATP (the cell's energy "currency") is generated.

ATP – Adenosine Triphosphate

- The key to understanding the role that ATP plays is in the word “triphosphate.”
- The molecule **adenosine** is attached to **three phosphate groups**, where each phosphate is an atom of phosphorus bound to four atoms of oxygen.
- The movement of these phosphate groups from one molecule to another is how energy is transferred.
- These phosphate groups are like dollars being exchanged from one molecule to another, and most of the ATP is made by the currency mint of the cell, the mitochondrion.

"Mitochondria: A Story of Mothers, Teenagers, and Energy"
September 30, 2022, by the McGill Office for Science and Society.

Beyond Energy Production . . .

- They help regulate **metabolism**, deciding whether fuels are burned for energy or stored.
- They play a central role in **cell signaling**, helping cells respond to stress, hormones, and changes in energy demand.
- Mitochondria are also involved in **apoptosis**, the programmed removal of damaged or unneeded cells, which is essential for healthy tissue turnover and cancer prevention.
- They are major regulators of **oxidative stress**, producing reactive oxygen species (ROS) as a byproduct of energy production, while also housing antioxidant systems to keep that in balance.

Wellness Wednesday

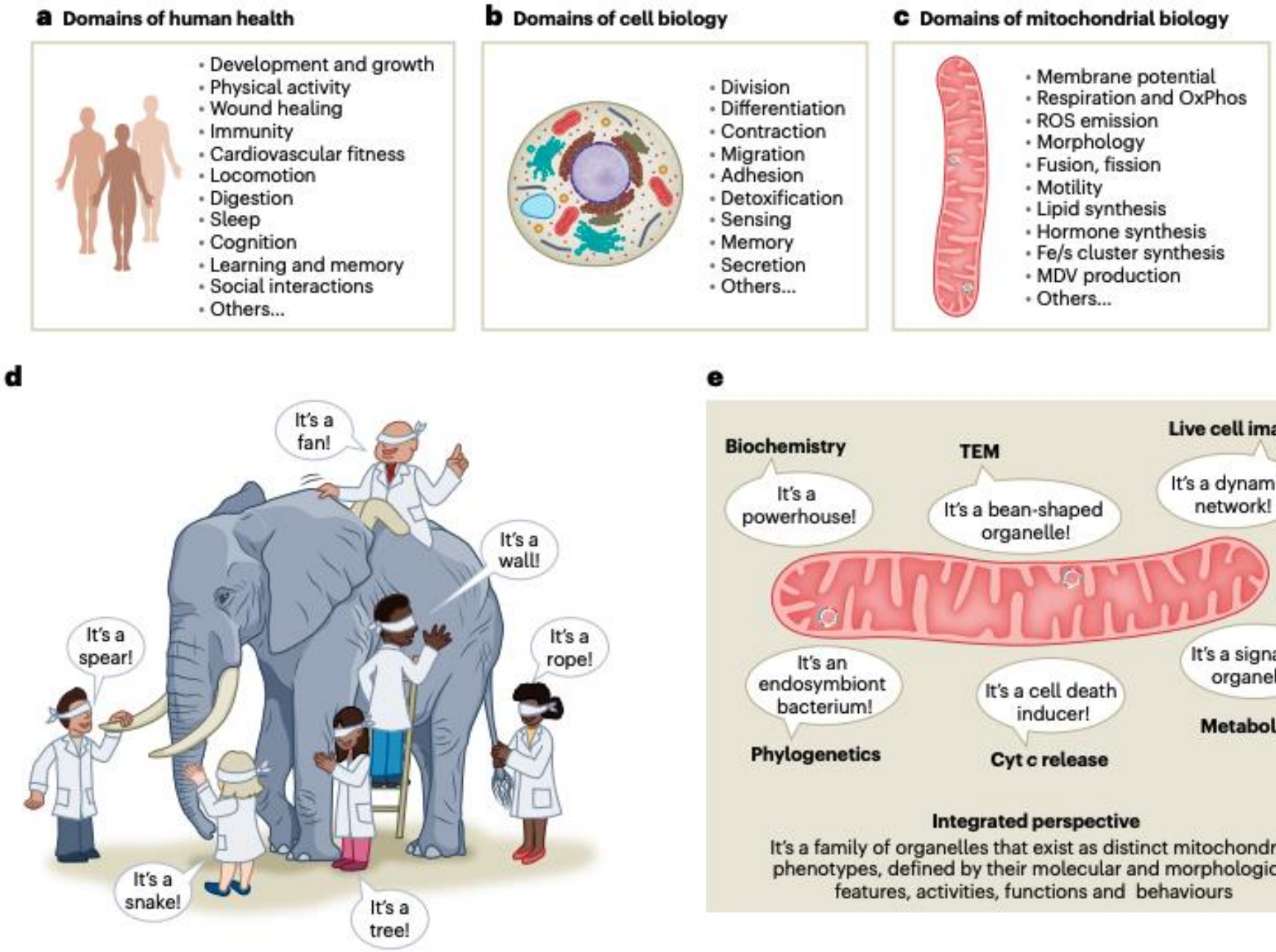
"Mitochondria: A Story of Mothers, Teenagers, and Energy"
September 30, 2022, by the McGill Office for Science and Society.

DOCTOR'S DATA INC.

Cellular Control Centers

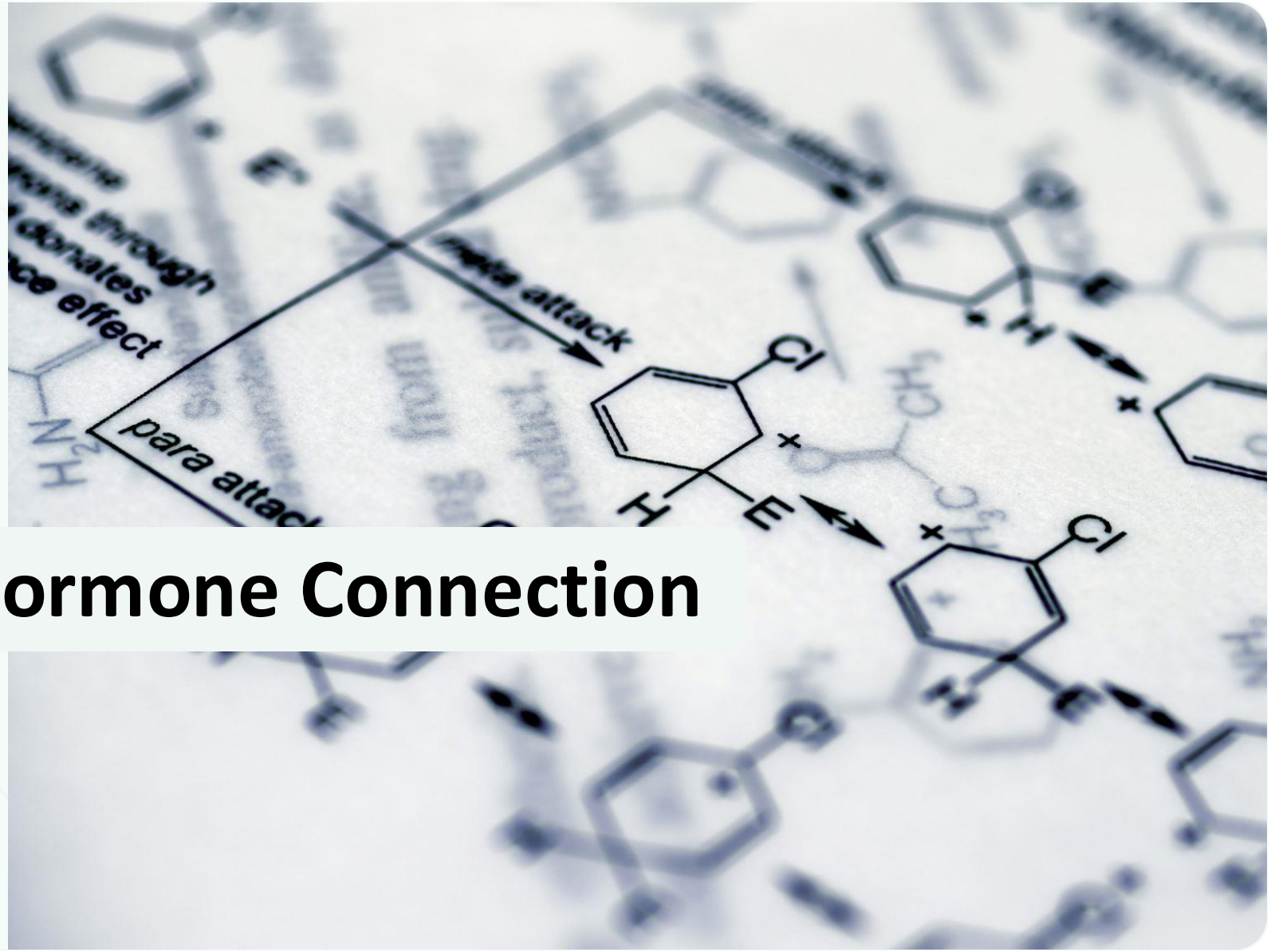
- In addition, they contribute to:
  - **calcium balance**
  - immune signaling
  - Aspects of **steroid hormone synthesis**, particularly in tissues like the adrenal glands and ovaries.
- Because of these combined roles, mitochondria are often described as metabolic “control centers” of the cell, integrating energy production with cellular health, signaling, and survival decisions.

Shaw GA. Mitochondria as the target for disease related hormonal dysregulation. Brain Behav Immun Health. 2021 Sep 21;18:100350. doi: 10.1016/j.bbih.2021.100350. PMID: 34746877; PMCID: PMC8554460.



Monzel AS, Enríquez JA, Picard M. Multifaceted mitochondria: moving mitochondrial science beyond function and dysfunction. Nat Metab. 2023 Apr;5(4):546-562. doi: 10.1038/s42255-023-00783-1. Epub 2023 Apr 26. PMID: 37100996; PMCID: PMC10427836.

Mitochondrial-Hormone Connection



Wellness Wednesday

DOCTOR'S DATA INC.

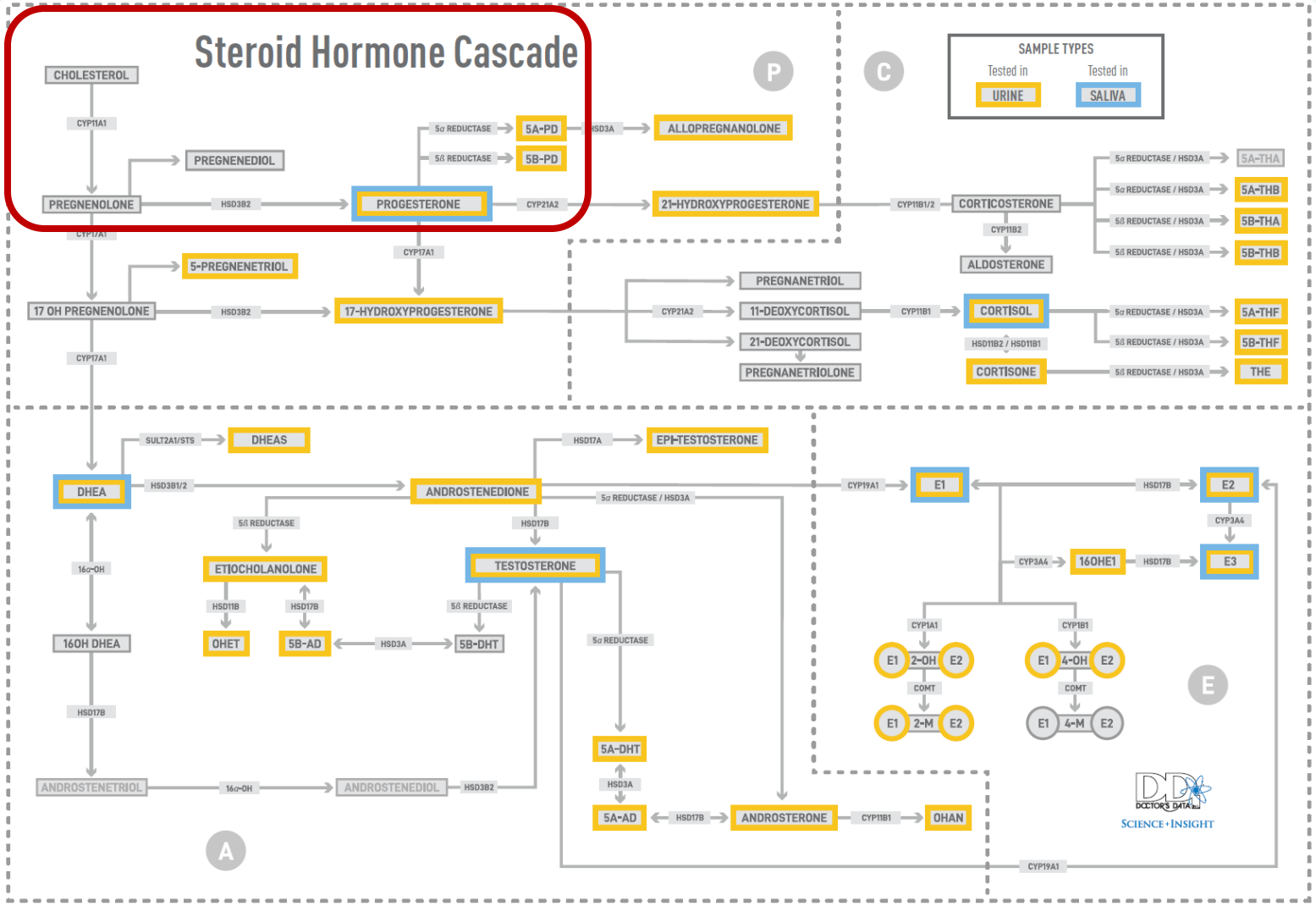
Hormones and Mitochondria

- The interaction between mitochondria and hormones is reciprocal.
- Sex hormones are synthesized mainly in the adrenal glands, gonads and placenta, and *the initial step in their formation occurs within the mitochondria,* where cholesterol is converted into pregnenolone.
- Pregnenolone exits the mitochondria and undergoes conversion into progesterone in the endoplasmic reticulum, eventually giving rise to tissue and cell-specific steroid hormones downstream.

Wellness Wednesday

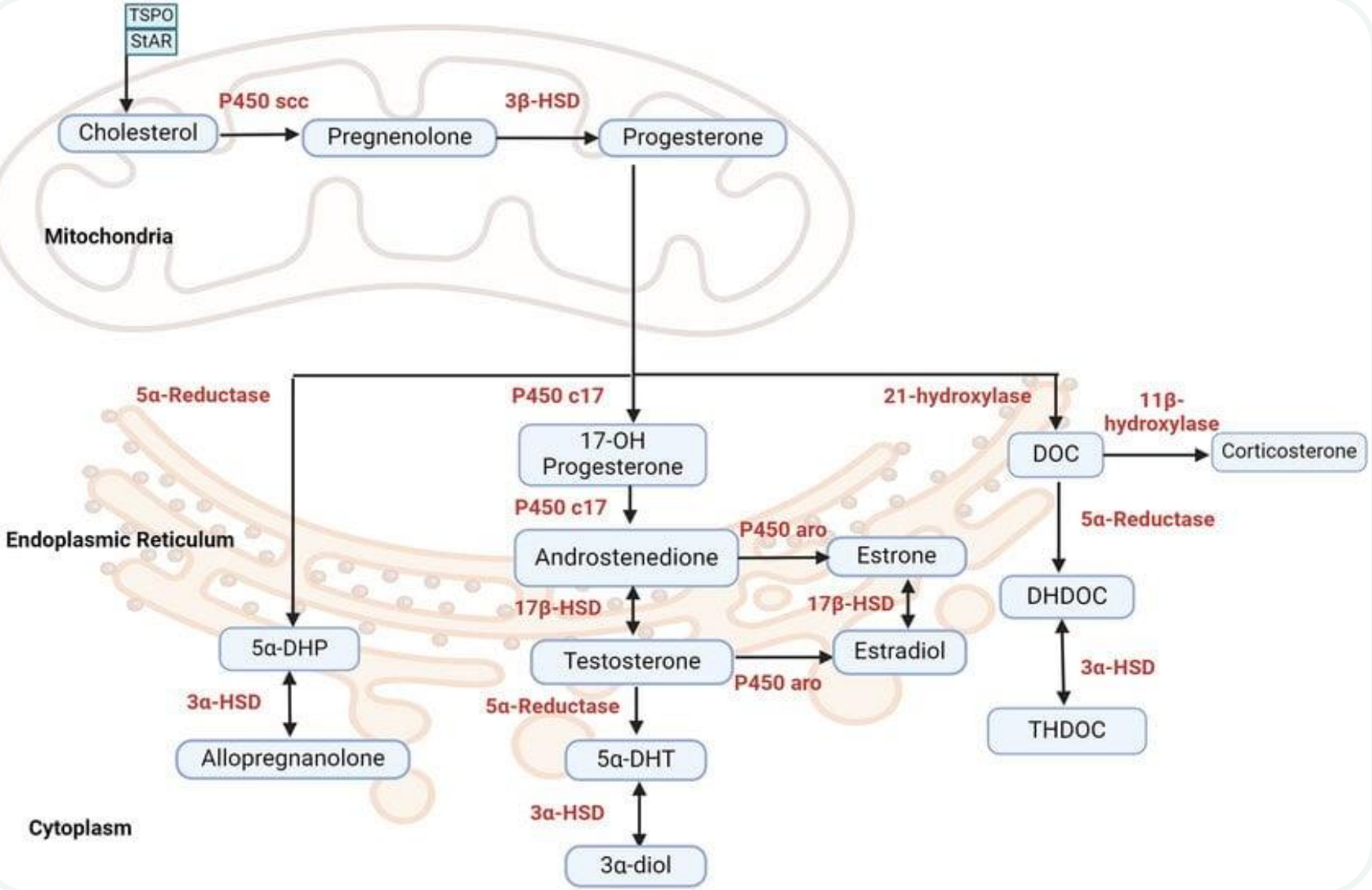
Ma Y, Zheng Y, Zhou Y, Weng N, Zhu Q. Mitophagy involved the biological processes of hormones. *Biomed Pharmacother*. 2023;167:115468. doi:10.1016/j.biopha.2023.115468

DOCTOR'S DATA INC



Wellness Wednesday

DOCTOR'S DATA INC.



Gore IR, Gould E. Developmental and adult stress: effects of steroids and neurosteroids. *Stress*. 2024;27(1):2317856. doi:10.1080/10253890.2024.2317856

Hormones & Mitochondria

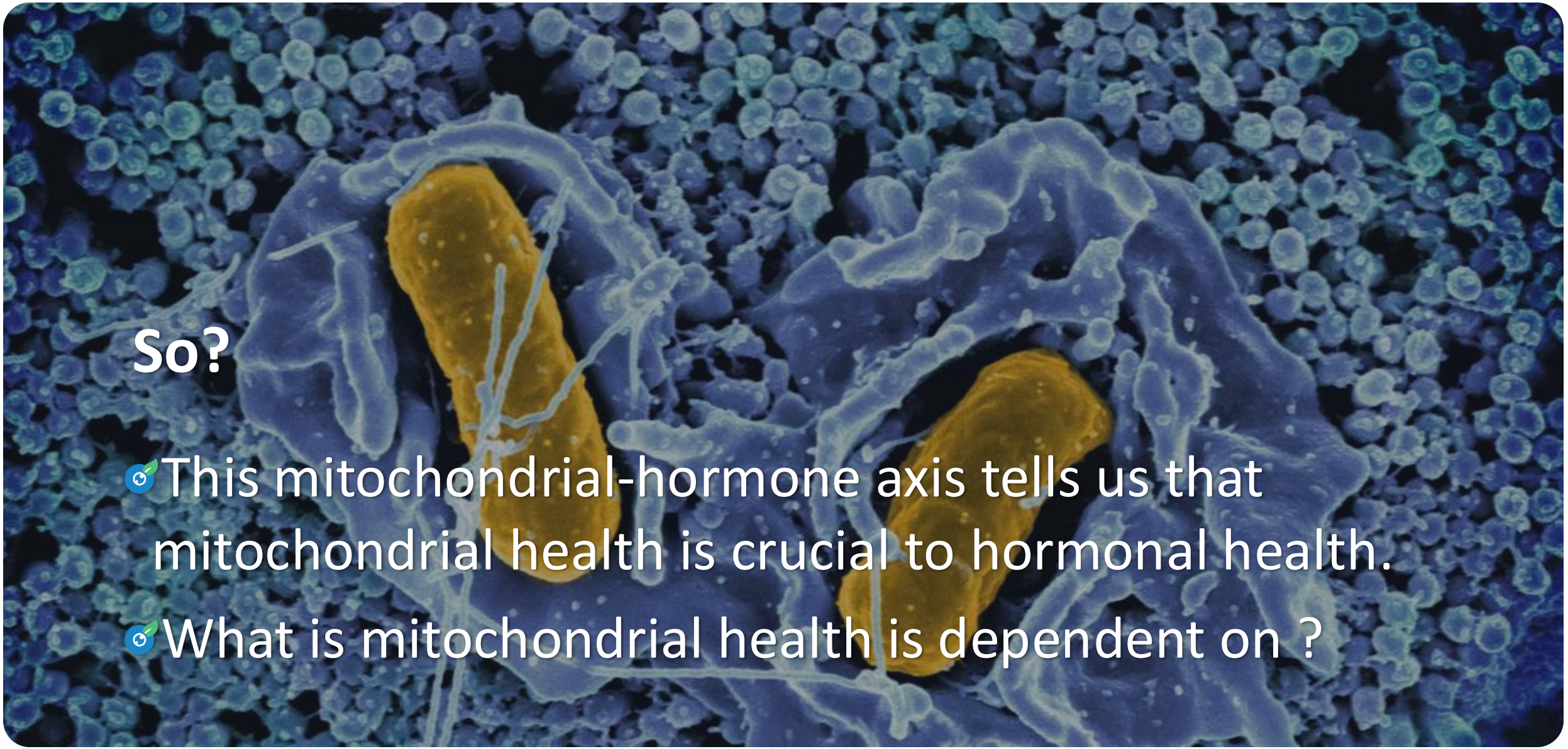
- Mitochondria supply the energy required for hormones to perform their normal biological functions.
- Steroid hormones and thyroid hormones often participate in energy-related aspects of metabolism, growth, and development. It has been found that steroids and thyroid hormones can stimulate upregulation of nuclear and mitochondrial OXPHOS genes, which implies that *hormones can, in turn, regulate mitochondria.*
- The gradual discovery of hormone receptors on the mitochondrial membrane underscores their significance in maintaining mitochondrial ”balance” (including mitochondrial formation, fission, and mitophagy).

Ma Y, Zheng Y, Zhou Y, Weng N, Zhu Q. Mitophagy involved the biological processes of hormones. *Biomed Pharmacother*. 2023;167:115468. doi:10.1016/j.biopha.2023.115468

Hormones & Mitochondria

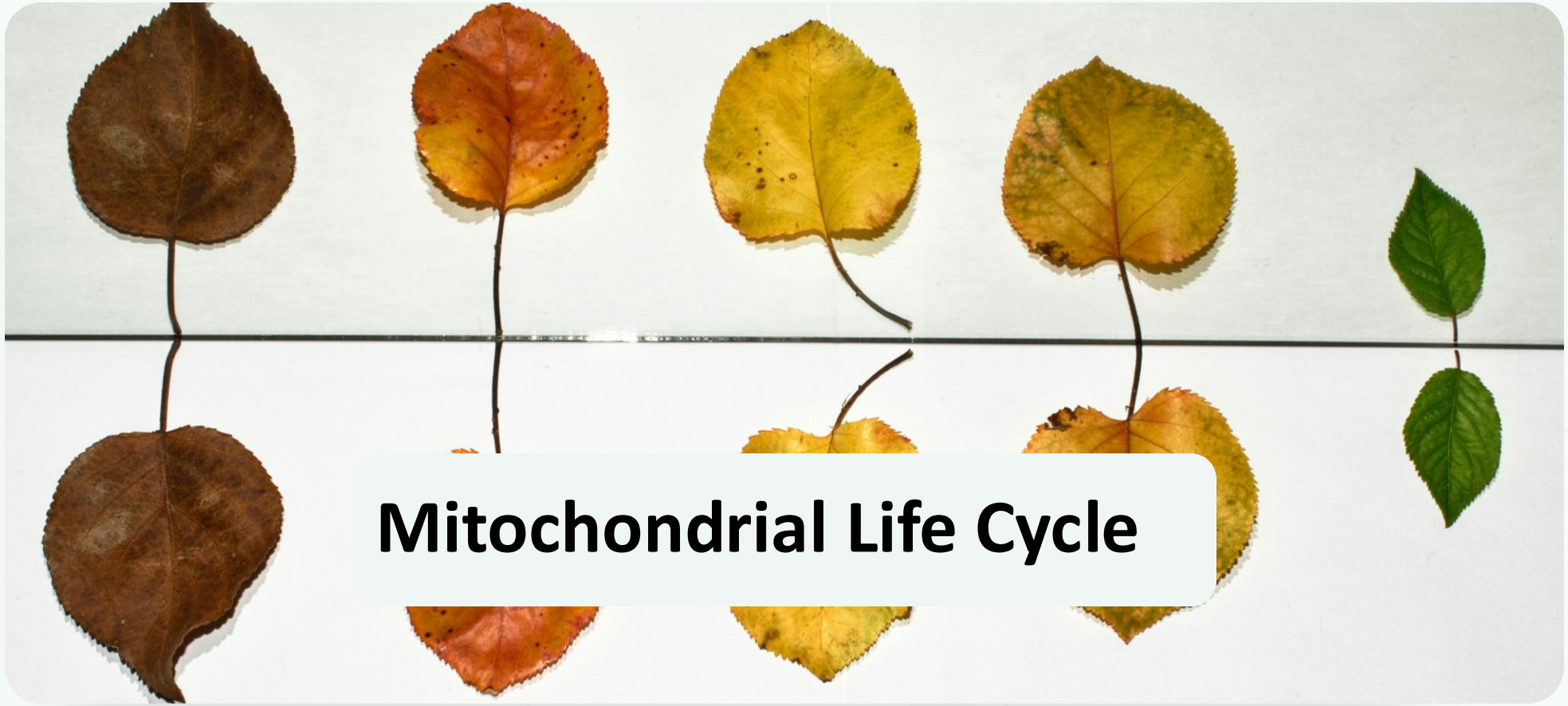
- Mitochondria are not only the initial site of steroidogenesis, but also use sex steroid hormones as modulatory factors for its own function and gene transcription
- Sex steroid hormone production is both a regulator and is regulated by mitochondrial activity and functionality.
- Receptors for these hormones have been found at varying levels in the mitochondria of both males and females

Miller W.L. Steroid hormone synthesis in mitochondria. Mol. Cell. Endocrinol. 2013;379:62–73. doi: 10.1016/j.mce.2013.04.014.



So?

- This mitochondrial-hormone axis tells us that mitochondrial health is crucial to hormonal health.
- What is mitochondrial health is dependent on ?



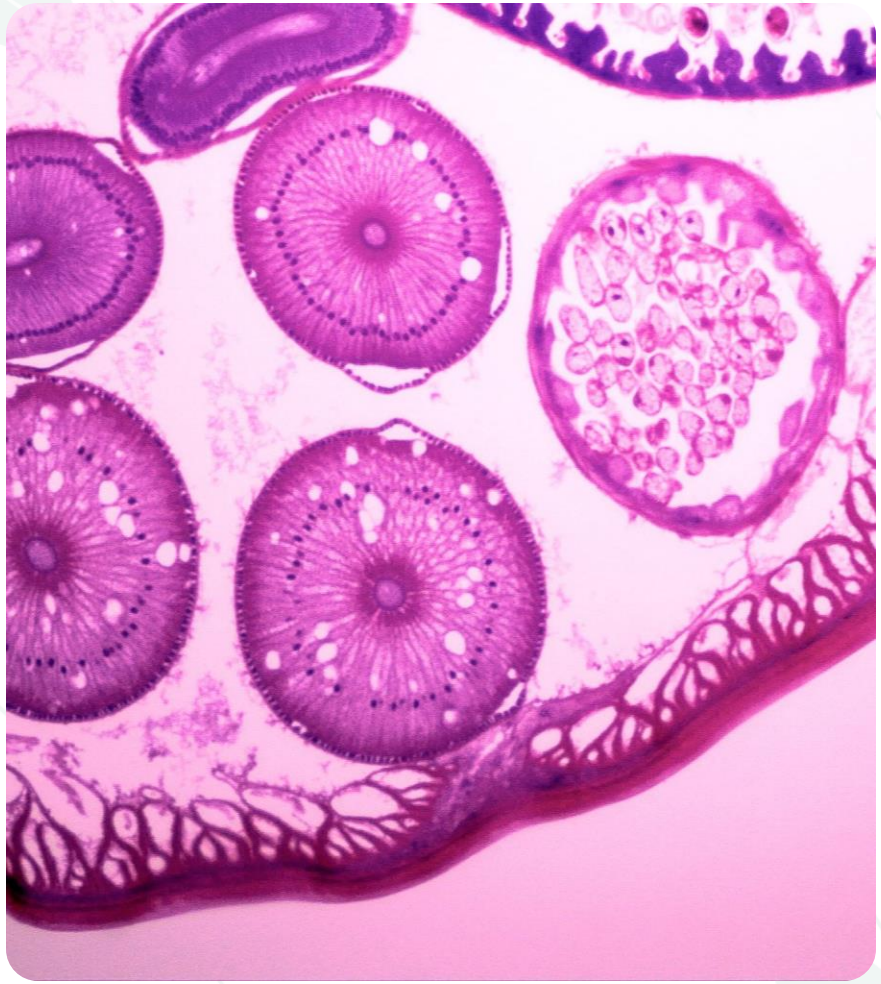
Mitochondrial Life Cycle

Mitochondrial Life Cycle

Mitochondria are dynamic structures—they are constantly being **made, divided, and removed** in response to a cell's energy needs and stress levels.

This ongoing cycle is called **mitochondrial turnover**, and it includes three key processes:

- **biogenesis (formation)**
- **fission/fusion**
- **mitophagy**



Diaz F, Moraes CT. Mitochondrial biogenesis and turnover. Cell Calcium. 2008 Jul;44(1):24-35. doi: 10.1016/j.ceca.2007.12.004. Epub 2008 Apr 18. PMID: 18395251; PMCID: PMC3175594.

Mitochondrial Formation (Biogenesis)

Mitochondrial biogenesis is the process of creating new mitochondria and expanding the existing mitochondrial network. It is not a simple "copy and paste" process. Instead, it requires coordinated activity between:

- Nuclear DNA (which encodes most mitochondrial proteins)
- Mitochondrial DNA (mtDNA) (which encodes a small but essential set of proteins)

Key regulators:

- PGC-1α (peroxisome proliferator-activated receptor gamma coactivator 1-alpha) → master regulator
- NRF1/NRF2 → activate genes for mitochondrial proteins
- TFAM (mitochondrial transcription factor A) → helps replicate and maintain mtDNA

What stimulates biogenesis?

- Exercise (especially endurance training)
- Cold exposure
- Caloric restriction (mild stress)
- Increased energy demand (e.g., muscle use)
- Hormonal signals (thyroid hormone, estrogen, insulin signaling balance)

Outcome:

More mitochondria → improved ATP capacity and metabolic flexibility.

Wellness Wednesday

Popov LD. Mitochondrial biogenesis: An update. J Cell Mol Med. 2020 May;24(9):4892-4899. doi: 10.1111/jcmm.15194. Epub 2020 Apr 12. PMID: 32279443; PMCID: PMC7205802.

DOCTOR'S DATA INC

Mitochondrial Fission

The process where one mitochondrion splits into two.

This is not random—it is tightly regulated and serves several purposes:

- Allows **mitochondria to distribute evenly during cell division**
- Helps isolate damaged regions of mitochondria
- Supports rapid adaptation to energy demands

Key proteins involved:

- Drp1 (dynamin-related protein 1) → primary "cutting" protein
- Fis1, Mff, MiD49/51 → help recruit Drp1 to mitochondria

Why fission matters:

- Small mitochondria are easier to move and distribute
- Damaged sections can be separated for removal
- Helps prevent dysfunctional mitochondria from spreading damage

However, excessive fission is often associated with:

- Oxidative stress
- Inflammation
- Metabolic dysfunction

Wai, T., & Langer, T. (2016). "Mitochondrial Dynamics and Quality Control." * llega. Cell* 26 (1): 28–37

Mitochondrial Fusion

(Fusion is the opposite of fission and is essential to understand the balance.)
Fusion allows mitochondria to merge into interconnected networks.

Key proteins:

- Mitofusin 1 (Mfn1)
- Mitofusin 2 (Mfn2) (also important for ER-mitochondria communication)
- OPA1 (inner membrane fusion)

Why fusion matters:

- Mixes mitochondrial contents (including mtDNA, proteins, metabolites)
- Dilutes damage
- Improves efficiency of ATP production
- Supports cellular resilience under stress

Wellness Wednesday

Archer SL. Mitochondrial dynamics--mitochondrial fission and fusion in human diseases. N Engl J Med. 2013 Dec 5;369(23):2236-51. doi: 10.1056/NEJMra1215233. PMID: 24304053.

DOCTOR'S DATA INC

Mitophagy (Mitochondrial Quality Control)

The selective removal of damaged or dysfunctional mitochondria via autophagy.
Think of it as a cellular recycling and quality-control system.

Key pathway:

- PINK1 (PTEN-induced kinase 1)
- Parkin (an E3 ubiquitin ligase)

How it works:

1. Damaged mitochondria lose membrane potential
2. PINK1 accumulates on the outer mitochondrial membrane
3. Parkin is recruited and tags the mitochondrion for destruction
4. The mitochondrion is engulfed by an autophagosome
5. It is broken down in the lysosome and recycled

Why mitophagy is essential:

- Prevents accumulation of damaged mitochondria
- Reduces reactive oxygen species (ROS)
- Maintains metabolic efficiency
- Protects against inflammation and cellular aging

Wellness Wednesday

Narendra, D. P., et al. (2010). "PINK1 is selectively stabilized on impaired mitochondria to activate Parkin and promote mitophagy." *PLoS Biology*, 8(1), e1000298.

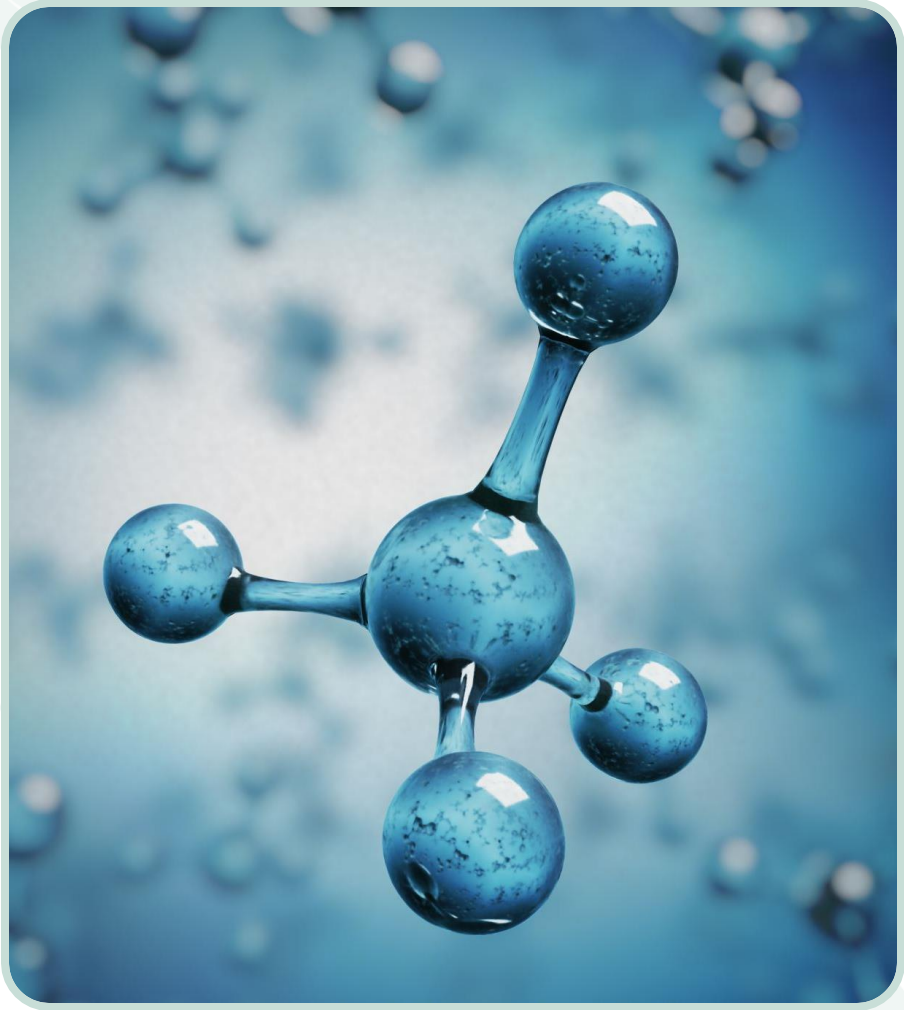
DOCTOR'S DATA INC

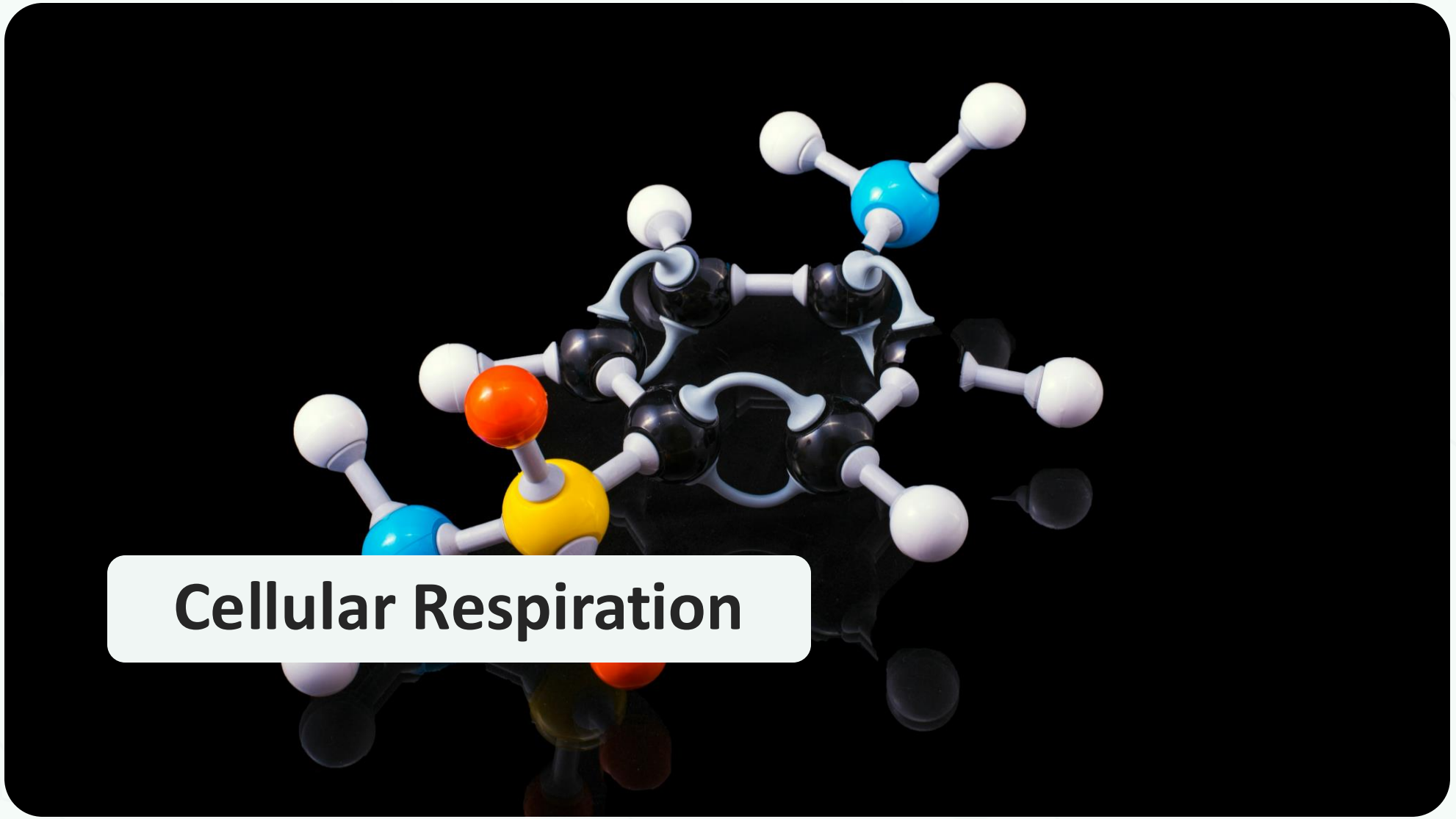
Big picture takeaway

Healthy cells maintain a dynamic balance:

- Too little biogenesis → low energy capacity
- Too much fission → fragmented, stressed mitochondria
- Too little fusion → reduced resilience
- Impaired mitophagy → accumulation of dysfunctional mitochondria

Together, these processes determine cellular energy production, metabolic health, and resilience to stress.

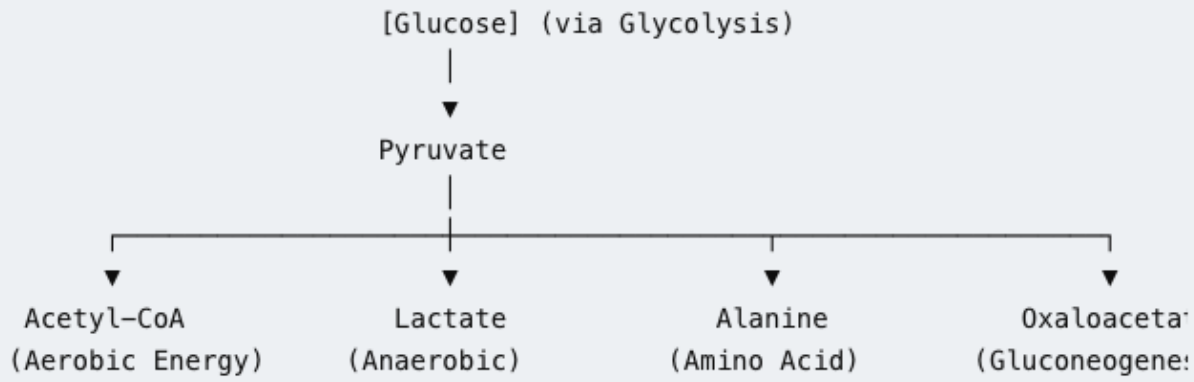



Cellular Respiration

Cellular Respiration

- Mitochondria require an adequate supply of **vitamins, minerals, amino acids, fatty acids, antioxidants, and metabolic cofactors** to efficiently produce ATP, regulate cellular signaling, manage oxidative stress, and maintain overall cellular health.
- These nutrients support the major mitochondrial pathways including:
  - mitochondrial biogenesis
  - **glycolysis**
  - **pyruvate metabolism**
  - **the tricarboxylic acid (TCA/Krebs) cycle**
  - **fatty acid oxidation**
  - **electron transport chain activity**
  - **oxidative phosphorylation**
  - **antioxidant defense**
  - mitophagy

Spinelli JB, Haigis MC. The multifaceted contributions of mitochondria to cellular metabolism. Nat Cell Biol. 2018 Jul;20(7):745-754. doi: 10.1038/s41556-018-0124-1. Epub 2018 Jun 27. PMID: 29950572; PMCID: PMC6541229.



- **Glycolysis-** the ancient, universal metabolic pathway that breaks down a six-carbon sugar (glucose) into two molecules of three-carbon pyruvic acid (pyruvate). It's the first step in carbohydrate metabolism. Taking place in the cytoplasm, it extracts chemical energy and stores it in the form of ATP and NADH.
- **Pyruvate metabolism (4 fates) -** Because pyruvate is positioned at the intersection of aerobic respiration, anaerobic fermentation, amino acid synthesis, and glucose production, it is often called the "metabolic crossroads" or a "jack of all trades" molecule

- Pyruvate metabolism is the comprehensive set of cellular choices that dictate whether a cell uses pyruvate to **make immediate energy** (Acetyl-CoA), **sustain glycolysis without oxygen** (Lactate), **synthesize new glucose** (Oxaloacetate), or **interchange with proteins** (Alanine).

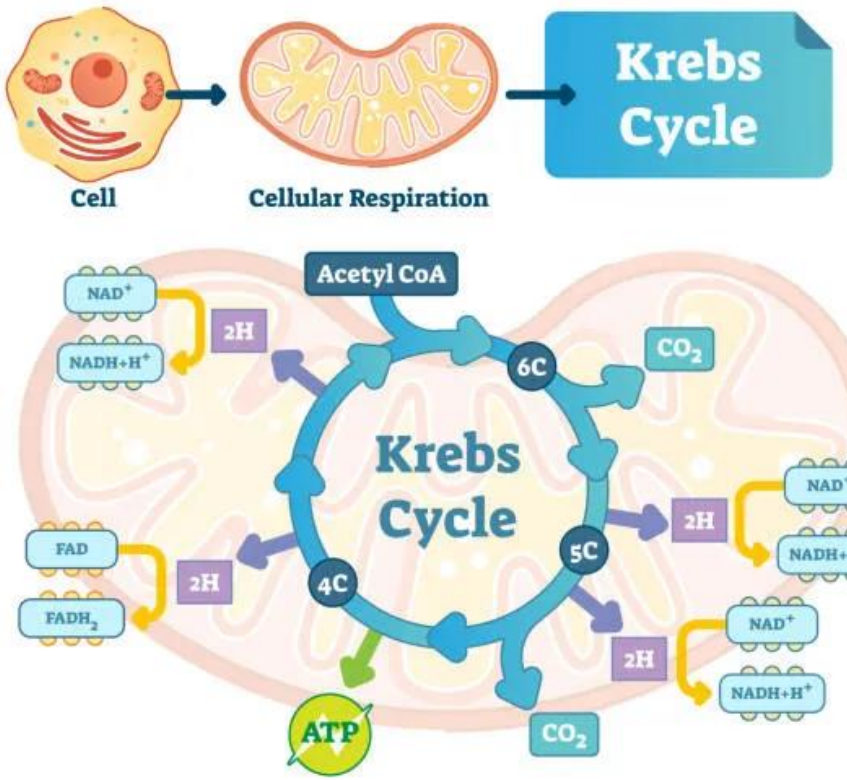
Wellness Wednesday

Spinelli JB, Haigis MC. The multifaceted contributions of mitochondria to cellular metabolism. Nat Cell Biol. 2018 Jul;20(7):745-754. doi: 10.1038/s41556-018-0124-1. Epub 2018 Jun 27. PMID: 29950572; PMCID: PMC6541229.

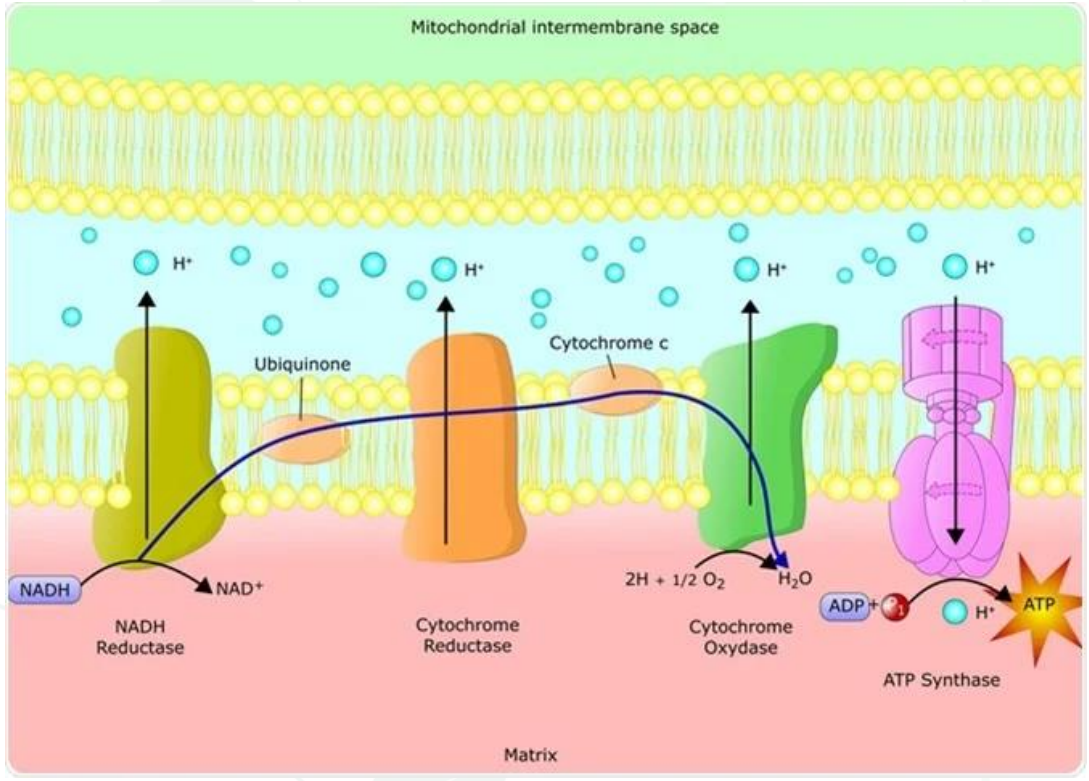
DOCTOR'S DATA INC

TCA Cycle

- **Location:** The cycle takes place in the mitochondrial matrix of eukaryotic cells.
- **Purpose:** It harvests high-energy electrons from carbon-based molecules.
- **Next Step:** The NADH and FADH2 move on to the **Electron Transport Chain** to generate a significantly larger amount of ATP.
- Requires macronutrients (carbs, fats, proteins) and B vitamin coenzymes, along with minerals and micronutrients:
  - B1 (thiamine) – feeds enzyme a-ketoglutarate dehydrogenase
  - B2 Riboflavin – forms FAD
  - B3 (niacin)- forms NAD+
  - B5 (pantothenic Acid) forms CoA
  - B7 (Biotin)- required by helper enzyme to regenerate oxaloacetate
  - Magnesium – mandatory cofactor
  - Iron
  - Alpha Lipoic Acid



Spinelli JB, Haigis MC. The multifaceted contributions of mitochondria to cellular metabolism. Nat Cell Biol. 2018 Jul;20(7):745-754. doi: 10.1038/s41556-018-0124-1. Epub 2018 Jun 27. PMID: 29950572; PMCID: PMC6541229.



Electron Transport Chain

The **Electron Transport Chain (ETC)** is the final, high-payout stage of cellular respiration, serving as the literal primary driver of **mitochondrial health and cellular aging**. While your previous diagram of the Krebs Cycle showed how the cell harvests electrons into carrier bags NADH and FADH2), the ETC is where those bags are unzipped to create massive amounts of energy.

- Takes place in the inner mitochondrial membrane
- The ETC is the core indicator of overall mitochondrial vitality. Its efficiency dictates the balance between cell survival and cellular damage.
- Healthy mitochondria = maximum ATP output, minimal free radical damage, low oxidative stress = longevity and healthy metabolism

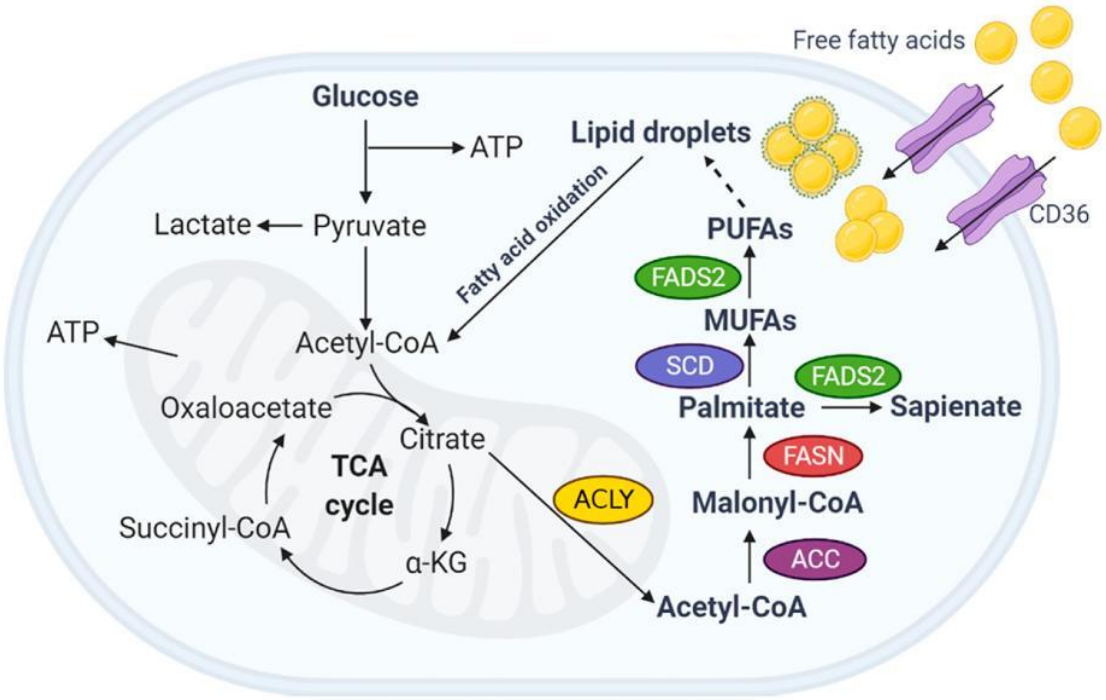
Wellness Wednesday

DOCTOR'S DATA INC

Spinelli JB, Haigis MC. The multifaceted contributions of mitochondria to cellular metabolism. Nat Cell Biol. 2018 Jul;20(7):745-754. doi: 10.1038/s41556-018-0124-1. Epub 2018 Jun 27. PMID: 29950572; PMCID: PMC6541229.

Fatty Acid Oxidation

- **Beta-oxidation/fatty acid oxidation** is the multi-step metabolic process by which the cell breaks down **fatty acid molecules** within the mitochondrial matrix to generate massive amounts of cellular energy.

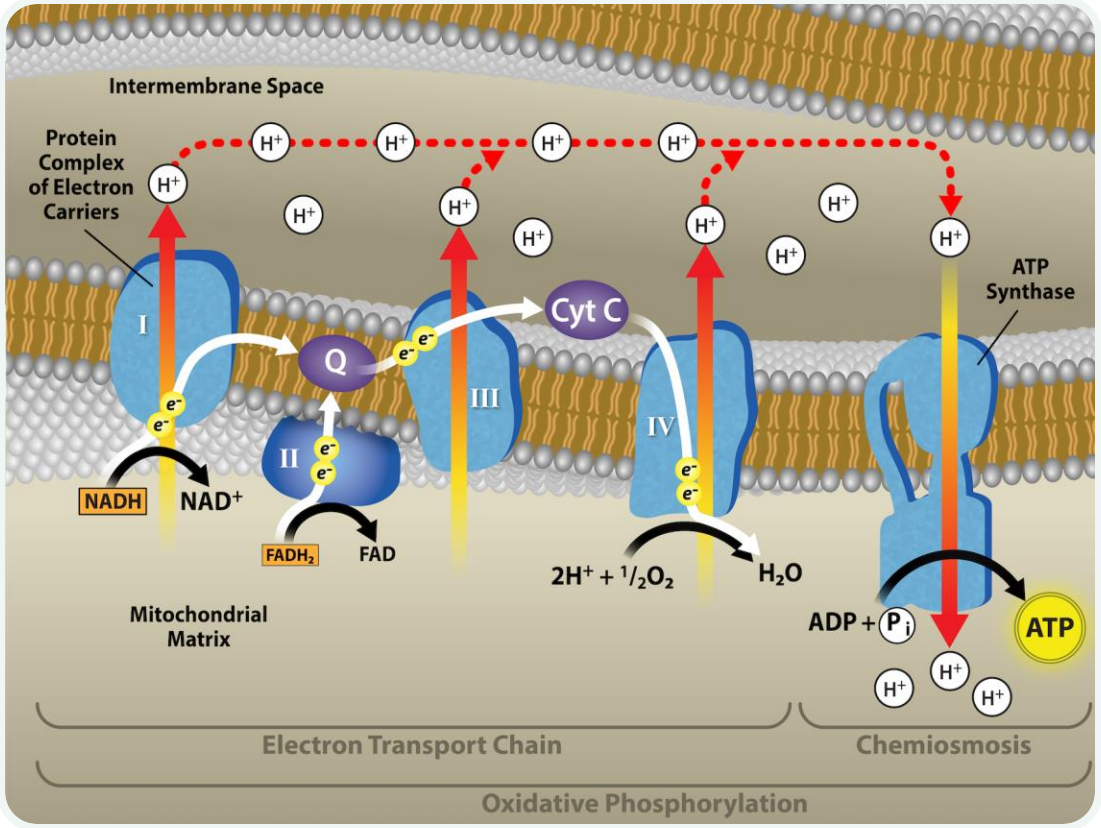


- While glucose (from carbohydrates) provides quick fuel, beta-oxidation is the pathway that allows your mitochondria to tap into stored fat for sustained, highly dense energy production.

Spinelli JB, Haigis MC. The multifaceted contributions of mitochondria to cellular metabolism. Nat Cell Biol. 2018 Jul;20(7):745-754. doi: 10.1038/s41556-018-0124-1. Epub 2018 Jun 27. PMID: 29950572; PMCID: PMC6541229.

Oxidative Phosphorylation

- Oxidative phosphorylation is the final, most efficient stage of cellular respiration. Occurring in the mitochondria, it generates ATP by harnessing energy from electrons released during the breakdown of nutrients. It combines two key events: the **Electron Transport Chain** and **Chemiosmosis**



Spinelli JB, Haigis MC. The multifaceted contributions of mitochondria to cellular metabolism. Nat Cell Biol. 2018 Jul;20(7):745-754. doi: 10.1038/s41556-018-0124-1. Epub 2018 Jun 27. PMID: 29950572; PMCID: PMC6541229.

Mitochondrial Associated Pathologies

Wellness Wednesday

Associated Pathologies – Overview

- Mitochondrial function and endocrine signaling are tightly interconnected—hormones regulate mitochondrial biogenesis, energy production, and oxidative stress handling, while mitochondria are required for hormone synthesis and metabolism.

- When this “hormone–mitochondria axis” is disrupted, it is associated with a broad range of clinical conditions.

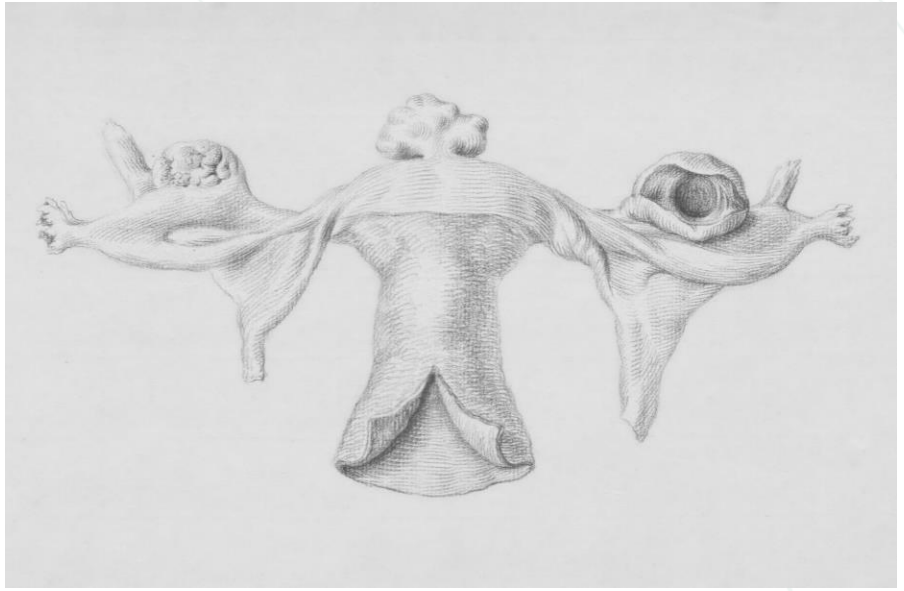
- Hormonal and mitochondrial dysfunction rarely present as a single disease. Instead, they form a **cross-system metabolic phenotype** that can manifest as reproductive, metabolic, neurologic, cardiovascular, or inflammatory disease depending on tissue vulnerability and genetic/environmental context.

Bynum H, Edwards KS. Sex Differences in Mitochondrial Function: Endocrine Regulation, Immunometabolic Signaling, and Implications for Health and Disease. Int J Mol Sci. 2026 May 30;27(11):4966. doi: 10.3390/ijms27114966. PMID: 42278492; PMCID: PMC1325656

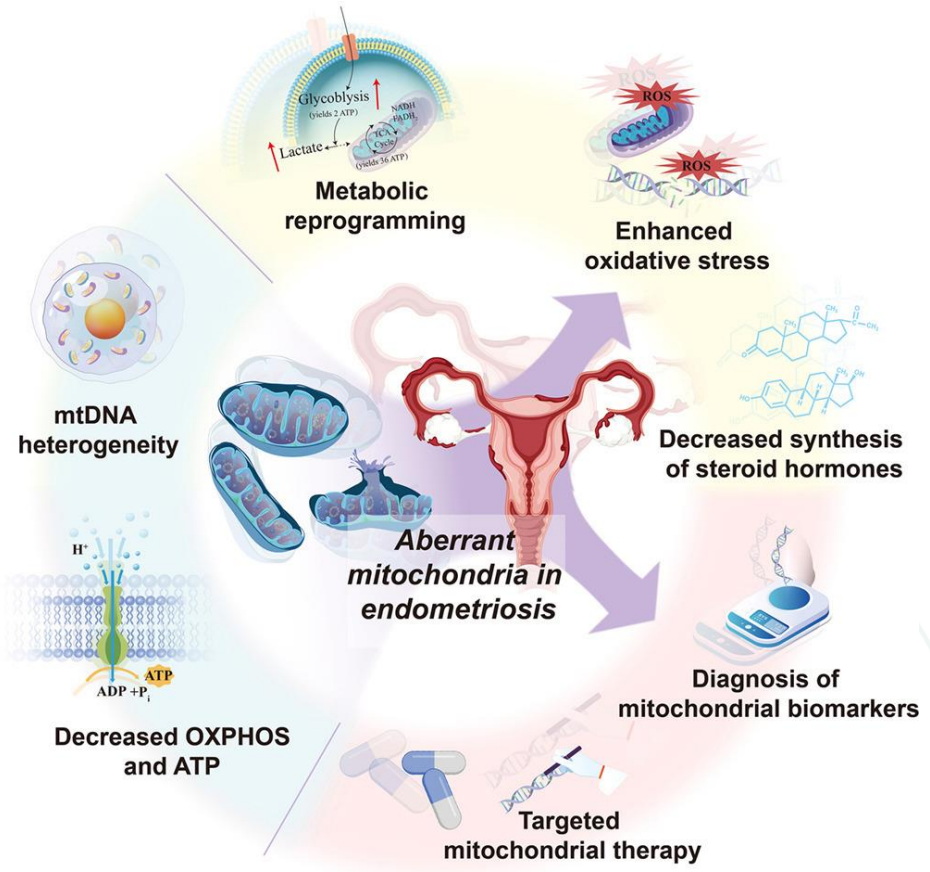
Reproductive & Endocrine Disorders

Strongly linked to ovarian, adrenal, and hypothalamic mitochondrial dysfunction.

- Polyendocrine Metabolic Ovarian Syndrome (PMOS / PCOS spectrum)
- Infertility (ovulatory dysfunction)
- Hypogonadism (male and female)
- Luteal phase dysfunction
- Premature ovarian insufficiency (POI)
- Endometriosis (associated mitochondrial and oxidative stress dysfunction)
- Functional hypothalamic amenorrhea (energy deficiency-linked endocrine suppression)



- Zhang J, Bao Y, Zhou X, Zheng L. Polycystic ovary syndrome and mitochondrial dysfunction. Reprod Biol Endocrinol. 2019 Aug 16;17(1):67. doi: 10.1186/s12958-019-0509-4. PMID: 31420039; PMCID: PMC6698037.
- Shen D, Qi C, Hu P, Li J, Shen Y. Mitochondrial Involvement in the Pathogenesis of Endometriosis and its Potential as Therapeutic Targets. Reprod Sci. 2025 Apr;32(4):935-949. doi: 10.1007/s43032-025-01827-5. Epub 2025 Mar 10. PMID: 40064837.



- Shen D, Qi C, Hu P, Li J, Shen Y. Mitochondrial Involvement in the Pathogenesis of Endometriosis and its Potential as Therapeutic Targets. Reprod Sci. 2025 Apr;32(4):935-949. doi: 10.1007/s43032-025-01827-5. Epub 2025 Mar 10. PMID: 40064837.
- Rong Y, Zhu J, Wang C ... Aberrant mitochondria in endometriosis: From pathogenic mechanisms to therapeutic opportunities iScience, 2026; 29

Clinical Spotlight

Endometriosis

- Mitochondrial dysfunction drives endometriosis through metabolic reprogramming (a shift to glycolysis similar to the Warburg effect), oxidative stress, and mtDNA damage. ERβ translocates INTO mitochondria in endometriotic cells, protecting them from apoptosis — meaning estrogen's normally protective role is co-opted to sustain ectopic lesions.
- *Clinical implication: targeting mitochondrial oxidative stress (antioxidants, especially glutathione, vitamin C and E) may improve outcomes beyond hormonal therapy alone.*

Clinical Spotlights — Conditions of Focus

Neurodegeneration & The Menopausal Brain

- The brain uses ~20% of the body's ATP despite being only 2% of body weight. When mitochondrial function declines in neural tissue, it drives depression, cognitive decline, and neurodegenerative risk. Sex hormone loss at menopause measurably accelerates this — Parkinson's and Alzheimer's rates in women rise sharply post-menopause. PINK1 and Parkin — mitophagy genes — are among the most well-known Parkinson's genes.
- *Clinical implication: mitochondrial support and timely sex hormone therapy may together protect long-term brain health.*

ME/CFS, Long COVID & Post-Exertional Conditions

- Chronic fatigue syndrome, Long COVID, fibromyalgia, and post-exertional malaise represent measurable bioenergetic failure — not psychosomatic symptoms. Mitochondrial ATP production is demonstrably impaired. NAD+ depletion is common. These patients need mitochondrial restoration, not reassurance or graded exercise.
- *Clinical implication: NAD+ precursors, L-carnitine, B vitamins, and mitochondrial antioxidants may offer meaningful benefit in these populations.*

- Henderson VW, Brinton RD. Menopause and mitochondria: windows into estrogen effects on Alzheimer's disease risk and therapy. Prog Brain Res. 2010;182:77-96. doi: 10.1016/S0079-6123(10)82003-5. PMID: 20541661; PMCID: PMC5776041.
- Molnar T, Lehoczki A, Fekete M, Varnai R, Zavori L, Erdo-Bonyar S, Simon D, Berki T, Csecsei P, Ezer E. Mitochondrial dysfunction in long COVID: mechanisms, consequences, and potential therapeutic approaches. Geroscience. 2024 Oct;46(5):5267-5286. doi: 10.1007/s11357-024-01165-5. Epub 2024 Apr 26. PMID: 38668888; PMCID: PMC11336094.

Associated Pathologies — The Shared Biology

- When the hormone-mitochondria axis breaks down, a wide spectrum of clinical conditions can emerge. These are not isolated diseases — they reflect a shared underlying biology.

Five converging mechanisms across all conditions:

Mechanism	Result	Clinical Signal
↓ ATP production	Cells cannot meet energy demand	Fatigue, exercise intolerance, organ dysfunction
↑ Oxidative stress (ROS)	Damage to mtDNA, membranes, proteins	Inflammation, accelerated aging, pain
↓ Biogenesis (PGC-1α)	Fewer, older mitochondria	Worsening metabolic and hormonal function over time
Disrupted steroidogenesis	Reduced sex hormone synthesis	Reproductive, adrenal, and neurological symptoms
Insulin resistance	Glucose overload → mitochondrial ROS surge	Metabolic syndrome, PCOS, cognitive decline
Chronic inflammation	DAMPs activate immune cascade	Autoimmunity, neuroinflammation, cardiovascular risk

The tissue most vulnerable to energy deficit determines the clinical presentation — but the root biology is often the same.

Associated Pathologies — System Overview

Mitochondrial-hormonal dysfunction manifests across every organ system. The common thread is impaired energy metabolism and accumulated oxidative damage.

Supporting mitochondrial function may offer cross-system benefits — relevant across many diagnoses simultaneously.

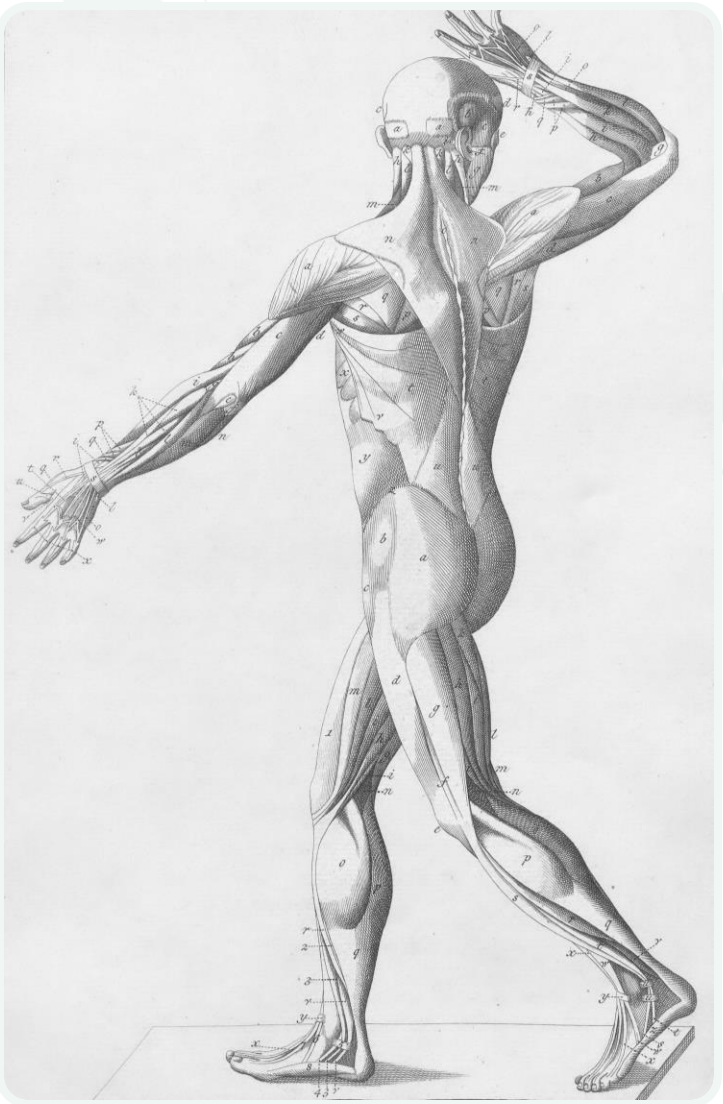
System	Key Conditions
Metabolic	Insulin resistance, T2DM, metabolic syndrome, MASLD/NAFLD, visceral obesity, dyslipidemia, glycemic instability
Reproductive & Endocrine	PCOS/PMOS, infertility (oocyte quality), POI, luteal phase dysfunction, hypogonadism, endometriosis, functional hypothalamic amenorrhea
Thyroid & Adrenal	Hypothyroidism, Hashimoto's, low T3 syndrome, reduced T4→T3 conversion, HPA dysregulation, burnout, PTSD
Neurological & Psychiatric	Depression (esp. treatment-resistant), bipolar disorder, Parkinson's, Alzheimer's, ALS, brain fog, TBI, migraine, autism spectrum
Cardiovascular	Heart failure (HFpEF), hypertension, atherosclerosis, arrhythmias, endothelial dysfunction, cardiomyopathy
Musculoskeletal & Fatigue	ME/CFS, fibromyalgia, sarcopenia, exercise intolerance, delayed recovery — real bioenergetic impairment, not psychosomatic
Immune & Inflammatory	Rheumatoid arthritis, SLE, MS, Type 1 diabetes, chronic low-grade inflammation, recurrent immune dysregulation
GI & Hepatic	IBS with dysmotility, intestinal dysbiosis, MASLD/NAFLD, impaired liver detoxification
Aging & Degenerative	Frailty, accelerated biological aging, sarcopenic obesity, osteoporosis, declining metabolic resilience
Cancer	Warburg effect: mitochondrial dysfunction → shift to glycolysis → uncontrolled proliferation

Wellness Wednesday

Mitochondrial Health Assessment

Wellness Wednesday

DOCTOR'S DATA INC.



Mitochondrial Health Assessment

No single test confirms or excludes dysfunction.
Diagnosis relies on a pattern-based integration of:

- Clinical phenotype
- Biochemical screening
- Functional capacity
- Genetic findings (when appropriate)

Bottom Line

Mitochondrial evaluation is a tiered, multimodal process: clinical suspicion → metabolic screening → functional testing → targeted genetics/tissue studies when indicated

Parikh S, Goldstein A, Koenig MK, Scaglia F, Enns GM, Saneto R, Anselm I, Cohen BH, Falk MJ, Greene C, Gropman AL, Haas R, Hirano M, Morgan P, Sims K, Tarnopolsky M, Van Hove JL, Wolfe L, DiMauro S. Diagnosis and management of mitochondrial disease: a consensus statement from the Mitochondrial Medicine Society. Genet Med. 2015 Sep;17(9):689-701. doi: 10.1038/gim.2014.177. Epub 2014 Dec 11. PMID: 25503498; PMCID: PMC5000852.

STEP 1 — Clinical Suspicion (Start Here)

No single test confirms or excludes mitochondrial dysfunction. Use clinical pattern + tiered testing.
Start with suspicion, escalate based on findings.

Symptom Cluster	Flag if Present
Fatigue / low stamina	Persistent, unrefreshing — not explained by thyroid or anemia alone
Exercise intolerance / post-exertional malaise	Symptoms worsen 12–48 hrs after exertion
Neurocognitive: brain fog, memory, concentration	Especially if disproportionate to life stressors
Muscle weakness or myalgias	Without clear structural cause
Multi-system involvement	≥ 3 body systems affected
Poor stress recovery / burnout physiology	HPA dysregulation pattern
Hormonal imbalance unresponsive to treatment	Despite optimized thyroid/sex hormones
Metabolic instability	Glycemic variability, weight gain despite lifestyle effort

Wellness Wednesday

≥ 3 symptoms present → proceed to Tier 1

DOCTOR'S DATA INC

TIER 1 — Core Metabolic Screen (All patients with clinical suspicion)

Category	Tests	What You're Looking For
Energy metabolism	Fasting glucose, insulin, HbA1c, lactate (fasting)	Insulin resistance; elevated lactate suggests impaired OXPHOS
Thyroid (mitochondrial driver)	TSH, Free T3, Free T4	Low T3 = impaired biogenesis even with 'normal' TSH
Core nutrients	Magnesium (RBC), ferritin + iron panel, B12, folate (RBC), vitamin D, CoQ10	Deficiency in any = direct ETC impairment
Inflammation / oxidative stress	hs-CRP	Proxy for ROS burden and DAMP-driven inflammation
Hormonal baseline	Sex hormones, diurnal cortisol + CAR, melatonin (saliva)	Bridges endocrine and mitochondrial assessment

Tier 1 positive or clinical suspicion persists → proceed to Tier 2

Tier 2 Functional Mitochondrial Profile (When Tier 1 is positive or suspicion is high)

Test	What It Assesses	Key Markers
Urine Organic Acids	Functional snapshot of all major mitochondrial pathways	Krebs cycle intermediates, lactate, ketones, fatty acid oxidation markers, 3-methylglutaconic acid — often most revealing
Fatty acid oxidation panel	Beta-oxidation capacity and carnitine status	Free carnitine, total carnitine, acylcarnitine profile; identifies specific block in fat burning
Oxidative stress markers	ROS burden and antioxidant reserve	Glutathione (reduced/oxidized ratio), 8-OH-dG (urine — mtDNA damage marker), oxidized LDL
NAD+/NADH ratio	Metabolic flexibility and redox status	Low ratio = metabolic impairment; high NADH = ETC dysfunction
Extended B vitamin status	Functional cofactor sufficiency	B1 (transketolase), B2 (EGR), B6 (PLP), B3 — not just serum levels

Tier 2 confirms dysfunction, rare presentation, or genetic suspicion → proceed to Tier 3

TIER 3 — Advanced / Specialist Testing (Targeted; when simpler tiers confirm dysfunction)

Test	Use When
mtDNA sequencing / nuclear mitochondrial gene panel	Family history of mitochondrial disease; multi-system presentation from childhood; unexplained neurodegenerative picture
Muscle biopsy (respiratory chain enzyme activity)	Gold standard for primary mitochondrial disease — specialist referral
Skin fibroblast mitochondrial respiration	Less invasive than biopsy; assesses live mitochondrial function
VO2 max / cardiopulmonary exercise testing (CPET)	Objective measure of aerobic capacity; post-exertional lactate response reveals ETC efficiency
Heart rate variability (HRV)	Autonomic proxy for mitochondrial and metabolic resilience
Circulating cell-free mtDNA (cfmtDNA)	Research setting; elevated in acute mitochondrial stress/injury

SCIENCE + INSIGHT

A clinical laboratory providing innovative, accurate specialty testing since 1972.

Doctor's Data Tests

- Sex hormone testing (either saliva or urine)
- HPA axis function – diurnal cortisol and CAR (saliva)
- Melatonin (saliva)
- NAD+/NADH ratio (blood)

NAD Profile; whole blood

DOCTOR'S DATA

Order: SAMPLE REPORT
Client #: 12345
Doctor: Sample Doctor
Doctor's Data, Inc.
3755 Illinois Ave.
St. Charles, IL 60174

Patient: Sample Patient
Age: 35
Sex: Female

Sample Collection	Date/Time
Date Collected	03/30/2026
Date Received	03/31/2026
Date Reported	04/01/2026

NADs: Metabolic Powerhouses

In the body, B3 vitamins manifest as NADs (nicotinamide adenine dinucleotides). NADs are crucial molecules central to diverse cellular processes, notably energy metabolism. Additionally, NADs are key players in regulatory pathways, influencing processes such as DNA repair and cell survival. For the clearest assessment of mitochondrial and metabolic function, it is essential to measure both the reduced and oxidized forms of NAD: NAD+ and NADH. Their significance in cellular activities makes them targets for research and interventions related to health, longevity, and disease.

LEGEND

less ← → more

The web image shows the relative levels among NADs and their ratios to each other. The white shaded area represents the patient's results compared to a reference population. The blue center of the web represents lower levels while the red outer edges represent higher levels.

NAD+/NADH

NAD+

NADH

Total NAD

Analytes	Result	Unit	L WRI H	Reference Interval
NAD+*	28	µmol		20 – 36
NADH*	1.7	µmol		0.6 – 1.8

Calculations	Result	Unit	L WRI H	Reference Interval
Total NAD	29.7	µmol		20.5 – 38.0
NAD+/NADH	16.5			16.3 – 46.0

Notes:
WRI – Within Reference Interval - represented by bracket and stated ranges on report, Dark Blue = Below RI, Light Blue = WRI low, Green = Optimal, Yellow = WRI high, Red = Above RI, <dl = result below detection limit
*This test was developed and its performance characteristics determined by Doctor's Data Laboratories in a manner consistent with CLIA requirements. The U. S. Food and Drug Administration (FDA) has not approved or cleared this test; however, FDA clearance is not currently required for clinical use. The results are not intended to be used as a sole means for clinical diagnosis or patient management decisions.

Methodology: Colorimetric

Page: 1 of 1

Analyzed by DOCTOR'S DATA, INC. • 3755 Illinois Avenue, St. Charles, IL 60174-2420 USA • LAB DIR: Saim Qazi, MD • CLIA ID: 14D0646470

NAD+ deserves its own section...

DOCTOR'S DATA INC

NAD+

- Vitamin B3 exists in several NAD-related forms in the body, with NAD^+ being the most abundant.
- NAD^+ acts as a coenzyme in more than 500 biochemical reactions involving metabolism, DNA repair, and nutrient processing, including glycolysis, the citric acid cycle, fatty acid oxidation, and oxidative phosphorylation.
- NAD^+ is crucial for energy metabolism, enabling the conversion of energy stored in food into ATP. Together with NADH, it maintains the body's overall energy balance.
- Additionally, NAD^+ supports the body in adapting to environmental changes and physiological stress.
- It also regulates nutrient-sensing enzymes such as sirtuins, which influence metabolism and gene expression, and PARPs, which are involved in DNA repair. Both types of enzymes consume NAD^+ upon activation. In cells containing mitochondria, oxidative respiration regenerates NAD^+ from NADH to help maintain redox balance.
- NAD^+ is also required for the synthesis of $NADP^+$, which, along with NADPH, plays a vital role in biosynthesis and antioxidant defense.

Yang Y, Sauve AA. NAD(+) metabolism: Bioenergetics, signaling and manipulation for therapy. Biochim Biophys Acta. 2016 Dec;1864(12):1787-1800. doi: 10.1016/j.bbapap.2016.06.014. Epub 2016 Jun 29. PMID: 27374990; PMCID: PMC5521000.

NAD+ Deficiency

- In healthy individuals, NAD^+ synthesis and consumption are balanced. However, in disease states, NAD^+ consumption often increases, leading to a secondary deficiency, even with an adequate dietary intake of vitamin B3.
- Based on scientific data, secondary NAD^+ deficiency is associated with several conditions, including:
  - Mitochondrial disorders (e.g. mitochondrial myopathies)
  - Muscle diseases and exercise intolerance
  - Neurodegenerative disorders such as Parkinson's disease and ALS
  - Metabolic disorders (e.g. diabetes)
  - Chronic Fatigue Syndrome and Long COVID
  - Cancers
  - Glaucoma

Wellness Wednesday

Reiten OK et al. (2021) Preclinical and clinical evidence of NAD^+ precursors in health, disease, and aging. Mechanisms of Ageing and Development. 199:111567

DOCTOR'S DATA INC

NAD+ High or Low?

- NAD^+ levels reflect the active form of vitamin B3 available in the body. *It is akin to a battery that has gone dead*; it is ready to be charged:
  - Low NAD^+ indicates a deficiency state due to disease, stress, or poor intake.
  - Low NAD^+ levels may contribute to fatigue and can be improved with supplementation.
  - Very high NAD^+ may suggest excessive supplementation.

Wellness Wednesday

- Heiskanen V & Pirinen E. (2020) Mitochondrial dysfunction in metabolic diseases – will B3 vitamins become helpful in the future? Duodecim; 136:1005–1012
- Murata MM et al. (2019) NAD^+ consumption by PARP1 in response to DNA damage triggers metabolic shift critical for damaged cell survival. Molecular Biology of the Cell; 30(20): 2584–2597

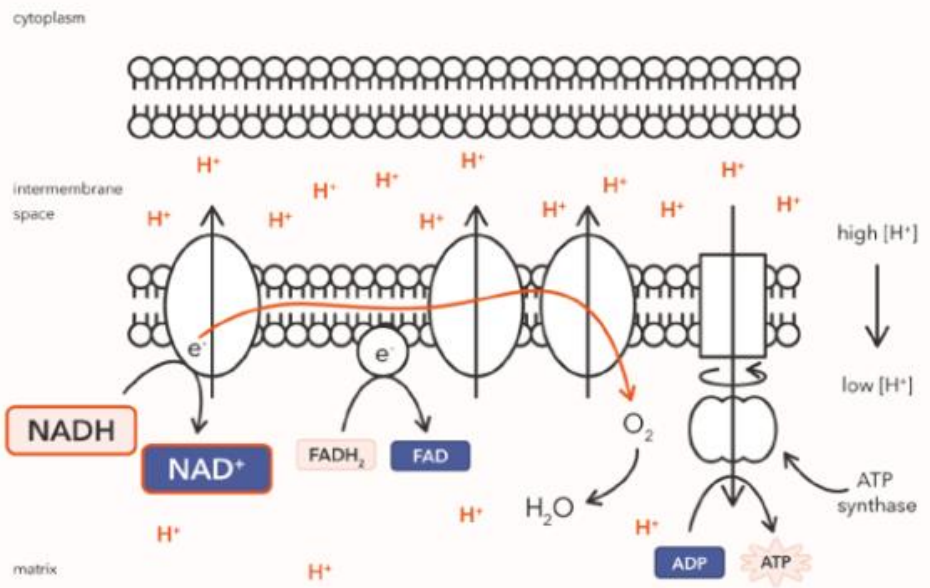
DOCTOR'S DATA INC

NADH – High or Low?

- NADH can be compared to a *charged battery,* ready to power things by donating a Hydrogen.
- NADH, the lower the better
- **Low NADH** may occur when mitochondria are efficiently oxidizing NADH to generate ATP. In this case, NADH is being consumed rather than accumulating. Often a normal finding.
- Examples: Exercise, fasting/caloric deficit, high metabolic rate, and stress response. In these cases, NADH drops because it is being used efficiently.
- **When NADH is elevated**, it means the body is accumulating it, rather than making ATP.
- Measuring NADH provides insight into how efficiently the body converts food into usable energy.

Walker MA, Tian R. NAD(H) in mitochondrial energy transduction: implications for health and disease. Curr Opin Physiol. 2018 Jun;3:101-109. doi: 10.1016/j.cophys.2018.03.011. Epub 2018 Apr 11. PMID: 32258851; PMCID: PMC7112453.

NAD+/NADH Ratio



- *When NADH is lower than NAD, it is a good sign of an active metabolism*
- Ratio - the higher, the better
- The NAD^+/NADH ratio serves as a marker of metabolic flexibility:
- A balanced ratio reflects effective energy metabolism and redox balance.
- A low ratio (reductive stress) may indicate impaired energy production and chronic disease states.

Chakraborty A, Minor KE, Nizami HL, Chiao YA, Lee CF. Harnessing NAD+ Metabolism as Therapy for Cardiometabolic Diseases. Curr Heart Fail Rep. 2022 Aug;19(4):157-169. doi: 10.1007/s11897-022-00550-5. Epub 2022 May 13. PMID: 35556214; PMCID: PMC9339518.

Sources of NAD+

- Sources of NAD^+ include dietary forms of vitamin B3: niacin, nicotinamide, nicotinamide riboside, and nicotinamide mononucleotide from meat, fish, poultry, nuts, legumes, brown rice, mushrooms, green peas, avocados, potatoes and some fortified/enriched foods.
- NAD+ can also be synthesized from tryptophan, an essential amino acid found in eggs, dairy, meat, nuts, and grains, though this pathway is less prominent.

Pirinen E et al. (2020) Niacin cures systemic NAD^+ deficiency and improves muscle performance in adult-onset mitochondrial myopathy. Cell Metabolism. 31(6):1078–1090.

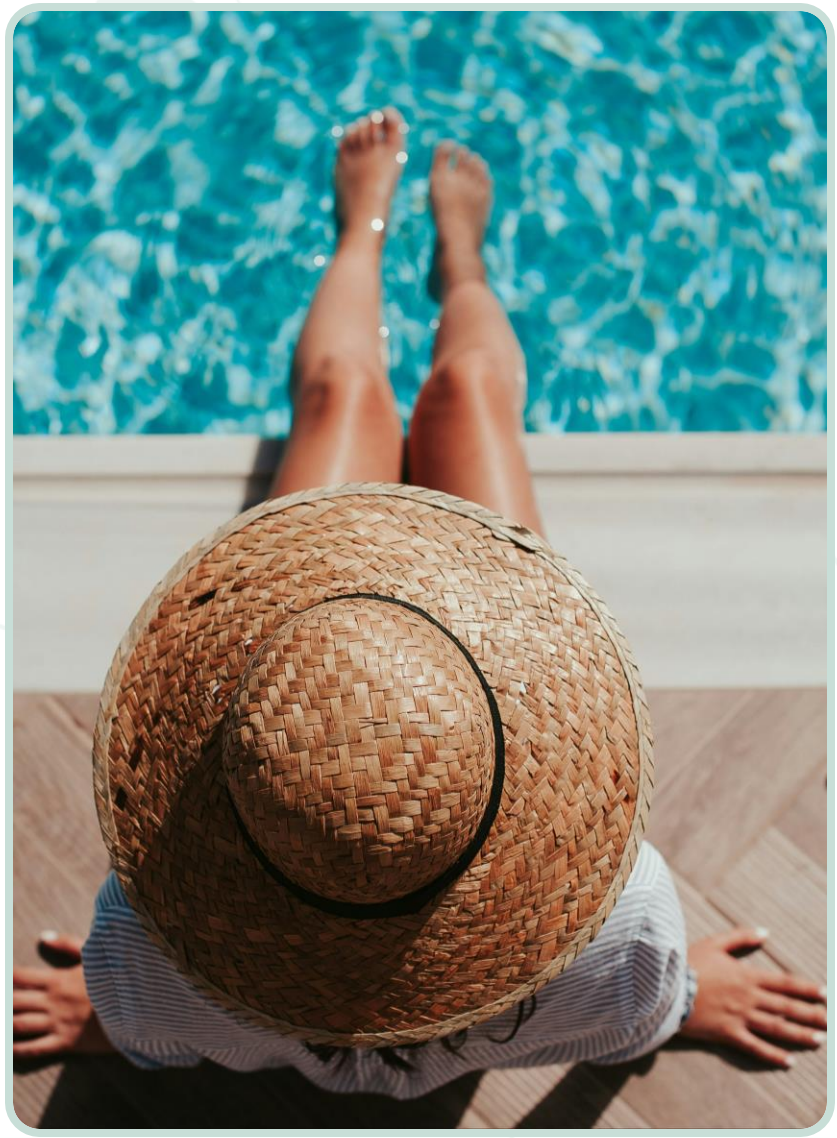
Wellness Wednesday

DOCTOR'S DATA INC.

Blood Draw Services Now Available Through MOMS (U.S. Only)

- Doctor's Data now offers access to blood draw services through MOMS (My One Medical Source), a nationwide network of credentialed collection providers and mobile phlebotomists throughout the United States.
- Patients can easily locate a nearby collection site or schedule a mobile blood draw in many areas, helping make testing more accessible and convenient.
- Patients pay the collection provider directly for blood draw services at the time of their appointment.

Mitochondrial Treatments



Lifestyle Inputs Essential for Mitochondrial Health

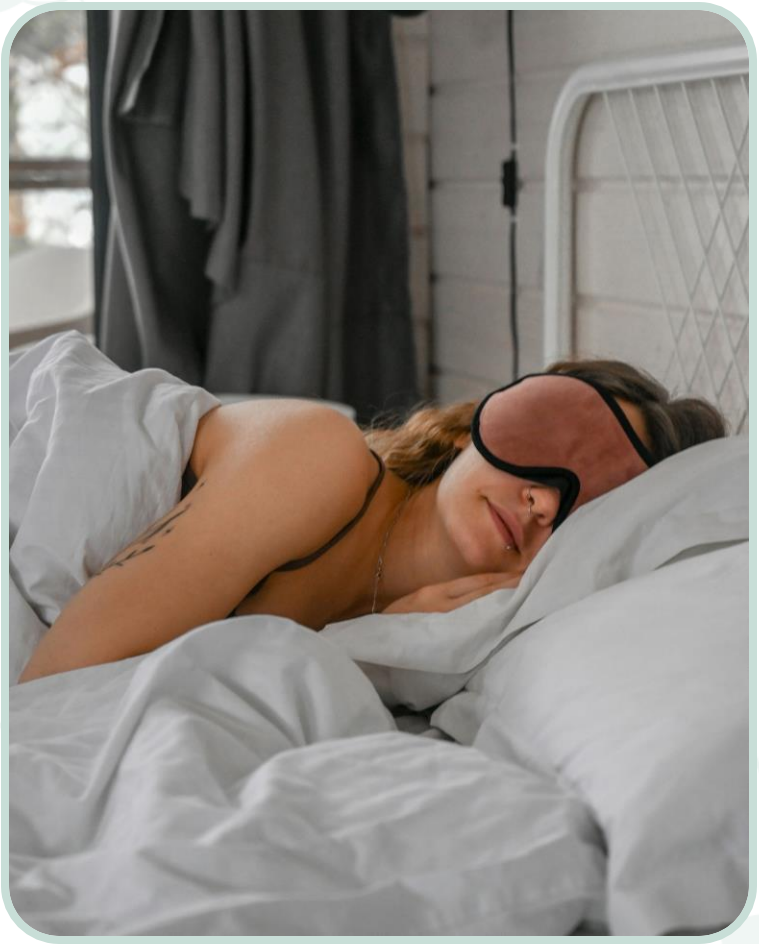
- Adequate oxygen delivery
- Regular physical activity
- Resistance training
- Sufficient protein intake
- Healthy Diet for substrates, cofactors and antioxidants
- Healthy circadian rhythms (i.e. sunlight exposure)
- Restorative sleep
- Stress management
- Blood sugar regulation
- Avoidance of smoking and excessive alcohol
- Minimization of environmental toxin exposure

Kyriazis ID, Vassi E, Alvanou M, Angelakis C, Skaperda Z, Tekos F, Garikipati VNS, Spandidos DA, Kouretas D. The impact of diet upon mitochondrial physiology (Review). Int J Mol Med. 2022 Nov;50(5):135.doi: 10.3892/ijmm.2022.5191. Epub 2022 Sep 21. PMID: 36129147; PMCID: PMC9542544.

Mitochondrial Treatment – Circadian Rhythm

Circadian and Rest Patterns (The Cleanup Window)

- **Deep, Uninterrupted Sleep:** Your mitochondria undergo their most intensive structural repairs while you sleep. Sleep deprivation causes rapid electron leakage, membrane degradation, and severe oxidative stress. Aiming for 7 to 8 hours of high-quality rest in a cool, dark environment is necessary to let the body run its natural cellular maintenance cycle.

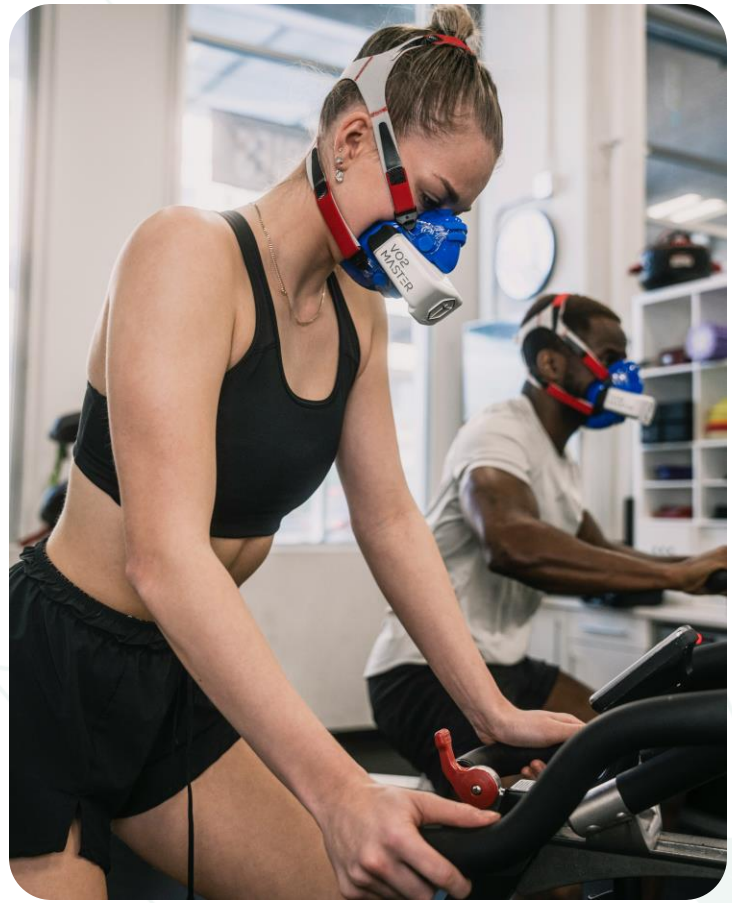


Richardson RB, Mailloux RJ. Mitochondria Need Their Sleep: Redox, Bioenergetics, and Temperature Regulation of Circadian Rhythms and the Role of Cysteine-Mediated Redox Signaling, Uncoupling Proteins, and Substrate Cycles. Antioxidants (Basel). 2023 Mar 9;12(3):674. doi: 10.3390/antiox12030674. PMID: 36978924; PMCID: PMC10045244.

Mitochondrial Biogenesis Treatments

- Exercise (resistance and aerobic, but especially endurance training)
- Cold or heat exposure
- Caloric restriction (mild stress)
- Increased energy demand (e.g., muscle use)
- Hormonal signals (thyroid hormone, estrogen, insulin signaling balance)

- Regulate mitochondrial fission by reducing:
- Oxidative stress
- Inflammation
- Metabolic dysfunction



Ball M, van Bergen NJ, Compton AG, Thorburn DR, Rahman S, Christodoulou J. Therapies for Mitochondrial Disease: Past, Present, and Future. J Inherit Metab Dis. 2025 Jul;48(4):e70065. doi: 10.1002/jimd.70065. PMID: 40714961; PMCID: PMC12301291.

Wellness Wednesday

DOCTOR'S DATA INC.

Mitochondrial Nutrients — The Complete Toolkit

Every major mitochondrial pathway has specific cofactor requirements. These are not generic antioxidants — each has a defined role in a defined pathway. Depletion in any one creates a specific bottleneck

Category	Key Nutrients	Primary Mitochondrial Role
B Vitamins (HIGHEST PRIORITY)	B1 (thiamine), B2 (riboflavin), B3 (niacin), B5 (pantothenic acid)	TCA cycle entry enzymes + ETC Complex I and II cofactors. Deficiency mimics primary mitochondrial disease.
B Vitamins (continued)	B6 (PLP), B7 (biotin), B9 (folate), B12 (cobalamin)	Amino acid metabolism, methylation, one-carbon metabolism, neurological function. Use RBC folate.
Key Minerals	Magnesium (RBC), Iron, Copper, Zinc, Manganese, Selenium, Chromium	Mg: ATP stabilization + 300+ reactions. Fe: cytochromes. Cu: Complex IV. Mn: MnSOD. Se: glutathione peroxidase. Test before supplementing iron.
Mitochondrial Cofactors	CoQ10, Alpha-Lipoic Acid (ALA), NAD+, FAD, Acetyl-CoA	CoQ10: electron shuttle + antioxidant (depleted by statins). ALA: TCA cofactor + antioxidant regeneration. NAD+: central to all energy pathways.
Amino Acids	L-Carnitine, Glycine, Cysteine (NAC), Taurine, Glutamine, Arginine, BCAAs	L-Carnitine: fatty acid transport into mitochondria (depleted in vegans/chronic illness). Glycine + Cysteine: glutathione precursors. Taurine: membrane stabilization.
Structural Lipids	Omega-3s (EPA, DHA), Phosphatidylcholine, Cardiolipin	Membrane fluidity + anti-inflammation. Cardiolipin: inner membrane integrity — critical for proton gradient and ETC efficiency.
Antioxidants	Glutathione, Melatonin, Vitamin C, Vitamin E, Polyphenols (resveratrol, quercetin, curcumin)	Glutathione: master intracellular antioxidant. Melatonin: produced IN mitochondria — most targeted protection. Polyphenols: activate PGC-1α → biogenesis.
Additional	Vitamin D, Vitamin K2, Creatine, Choline, Inositol, Calcium	Vitamin D: mitochondrial regulation. Creatine: ATP buffering in muscle/brain. Calcium: critical signaling — requires precise homeostasis (excess = damage).

Clinical Priorities — The Mitochondrial Stack

If a patient can only address a limited number of interventions, these are the highest-yield priorities — the ones with the strongest evidence and broadest mitochondrial impact.

Key message: supplements cannot compensate for absent sleep, sedentary lifestyle, or protein deficiency. Address lifestyle foundations first, then layer targeted nutrients.

Priority	Nutrient / Intervention	Why It Matters
1	B Complex (especially B1, B2, B3, B5)	TCA cycle and ETC cannot function without these — true rate-limiting cofactors
2	Magnesium	Required for ATP production and stabilization; cofactor for 300+ reactions; almost universally depleted
3	CoQ10	Electron shuttle between Complexes I/II and III; potent antioxidant; critical with statin use and in aging
4	L-Carnitine	Without it, long-chain fatty acids cannot enter the mitochondria — fat burning fails even with fat available
5	Alpha-Lipoic Acid	Dual role: TCA cycle cofactor + regenerates glutathione, vitamin C, and vitamin E
6	Glutathione (or NAC + glycine precursors)	Master antioxidant protecting mtDNA and membranes — cannot be replaced by exogenous antioxidants alone
7	Omega-3 fatty acids (EPA + DHA)	Membrane integrity, anti-inflammation, biogenesis support — structural, not optional
8	Exercise (endurance + resistance)	Activates AMPK → PGC-1α → biogenesis. Cannot be replaced by supplements.
9	Sleep + circadian rhythm	Mitochondrial repair, mitophagy, and melatonin production occur during sleep — non-negotiable
10	Adequate protein + caloric intake	Building material for all mitochondrial proteins — deficiency limits every other intervention

Wellness Wednesday

Estrogen & Mitochondria — How It Works

Of all sex steroid hormones, estrogen's relationship with mitochondria is the best studied. It acts through two distinct receptor-mediated pathways that together make mitochondria more efficient, more resilient, and less prone to apoptosis.

Pathway	Receptor	Mechanism	Net Effect
Genomic (indirect)	ERα in nucleus	Activates nuclear genes → upregulates biogenesis (via NRF-1), ETC/OXPHOS gene expression, mtDNA transcription	More mitochondria; better energy output over time
Non-genomic (direct)	ERβ inside mitochondria	Directly modulates ATP synthase; regulates ROS production; stabilizes Bcl-2 (anti-apoptotic); controls mitochondrial calcium handling	Faster ATP production; reduced oxidative damage; prevents apoptosis

Ventura-Clapier R, Piquereau J, Veksler V, Garnier A. Estrogens, Estrogen Receptors Effects on Cardiac and Skeletal Muscle Mitochondria. Front Endocrinol (Lausanne). 2019 Aug 14;10:557. doi: 10.3389/fendo.2019.00557. PMID: 31474941; PMCID: PMC6702264.

Estrogen and Mitochondria

What happens when estrogen declines (menopause)?

- Mitochondrial biogenesis slows (fewer new mitochondria)
- OXPHOS efficiency drops (less ATP per cell)
- ROS accumulation rises (less antioxidant protection)
- Mitochondrial calcium dysregulation increases apoptosis risk

These changes are measurable — and help explain the metabolic shifts, cognitive changes, and cardiovascular risk increase seen at menopause.

Wellness Wednesday

Key references: Chen et al. 2009 (BBA Mol Cell Res); Klinge 2017 (J Bioenerg Biomembr); Shaw 2021 (Brain Behav Immun Health)

DOCTOR'S DATA INC

Estrogen as Neuroprotector — The Brain Connection

The brain uses ~20% of body ATP despite being only 2% of body weight. Neurons are exquisitely sensitive to mitochondrial decline. Estrogen's mitochondrial effects in the brain are among its most important clinical actions.

How estrogen protects the brain through mitochondria:

- Stimulates NRF-1 → mitochondrial biogenesis → more energy-producing capacity in neurons
- Improves OXPHOS and ATP production (supports Complex IV function)
- Regulates mitochondrial calcium handling via ERβ → prevents apoptotic cascade
- Increases Bcl-2 (anti-apoptotic protein) → buffers calcium overload during ischemia or excitotoxicity
- Limits neuroinflammation: suppresses microglial and astrocyte activation
- Modulates the mitochondrial permeability transition pore (mPTP) — preventing catastrophic neuronal death

Clinical relevance:

Condition	Estrogen's Mitochondrial Role
Post-TBI recovery	Supports mitochondrial regeneration in injured neurons; reduces fission-driven respiration loss
Cognitive aging / menopause	Loss of estrogen → neuronal energy deficit → brain fog, memory decline, fatigue
Alzheimer's prevention	'Critical window' hypothesis — early hormone therapy maintains mitochondrial reserve before irreversible decline
Neuroinflammation	Estrogen suppresses DAMP-driven microglial activation (which is itself mitochondrially mediated)
Parkinson's risk	Women have lower Parkinson's rates pre-menopause; risk rises post-menopause — PINK1/Parkin mitophagy impaired by estrogen loss

Key references: Nilsen & Brinton 2003 (PNAS); Burstein et al. 2018 (BBA Bioenerg); Kövesdi et al. 2021 (IJMS); Mattingly et al. 2008 (Mol Endocrinol); Liao et al. 2019 (Free Radic Biol Med)

Progesterone Clinical Takeaways

Progesterone — The Overlooked Neurosteroid

- Progesterone is a metabolic regulator of the brain, not just a reproductive hormone. Together with estradiol, it upregulates mitochondrial oxidative capacity, enhances ATP production machinery, and supports neuronal energy demand.
- After acute brain injury (stroke, TBI), progesterone:
  - Reduces mitochondrial oxidative injury
  - Improves ETC and ATP-related respiration
  - Stabilizes mitochondrial membrane potential
  - Reduces mPTP opening and downstream apoptosis

Wellness Wednesday

Natural micronized progesterone may have neurological benefits beyond its reproductive role. (Andrabi et al. 2017, DMM; Irwin et al. 2008, Endocrinology)

DOCTOR'S DATA INC

Testosterone Clinical Takeaways

Testosterone — Context-Dependent Mitochondrial Support

- Testosterone shares significant mechanisms with estrogen in supporting mitochondrial function:
  - Supports OXPHOS and ATP production
  - Reduces ROS and oxidative damage
  - Stabilizes calcium homeostasis
  - Reduces mitochondrial apoptosis — preserving neuronal survival in TBI, stroke, neurodegeneration
- Brain effects (reduced anxiety, antidepressant-like, improved spatial cognition) are real but highly context-dependent — dose, age, sex, and whether testosterone converts to DHT or estradiol all affect outcome.

Wellness Wednesday

(Mohajeri et al. 2019, Prog Neurobiol; Celec et al. 2015, Front Neurosci)

DOCTOR'S DATA INC

Insulin

- Diabetic peripheral neuropathy is one of the most common complications of diabetes, but for a long time the mitochondrial story was framed mostly as:
- hyperglycemia
  → excess electron donors
  → excess mitochondrial ROS
  → nerve injury
- This paper adds an important layer: in **sensory neuron cell bodies of the DRG**, diabetes can eventually lead to **respiratory chain failure itself**, not just oxidative overload. In other words, by later stages of diabetes, mitochondria are not merely “overactive and oxidatively stressed”; they may become **bioenergetically impaired**.
- Insulin substantially improved the mitochondrial defect. **Insulin improved mitochondrial function even without fully normalizing diabetes**
- insulin may help sensory neuron mitochondria through more than just “glucose lowering”

Chowdhury S.K.R., Zherebitskaya E., Smith D.R., Akude E., Chattopadhyay S., Jolivalt C.G., Calcutt N.A., Fernyhough P. Mitochondrial respiratory chain dysfunction in dorsal root ganglia of streptozotocin-induced diabetic rats and its correction by insulin treatment. Diabetes. 2010;59:1082–1091. doi: 10.2337/db09-1299.

Thyroid Hormone and Mitochondria

- Thyroid hormone helps regulate mitochondrial function
- T3 is the most active thyroid hormone at the cellular level
- T3 turns on genes involved in:
  - energy production
  - heat production (thermogenesis)
  - mitochondrial repair and turnover

Key mitochondrial effects of T3

- Supports mitochondrial biogenesis
  → helps make new mitochondria
- Supports mitophagy
  → helps remove damaged mitochondria
- Increases thermogenesis in brown fat
  → boosts calorie burning and heat production
- May protect neurons after brain injury
  → helps clear damaged mitochondria and reduce oxidative stress
- May protect heart cells after ischemia-reperfusion injury
  → supports mitochondrial cleanup and recovery

Clinical takeaway

- Healthy thyroid signaling supports mitochondrial quality, energy production, and metabolic resilience
- Too little thyroid hormone may impair energy production
- Too much thyroid hormone may disrupt mitochondrial balance and damage cardiac mitochondrial function
- Even subclinical hypothyroidism (elevated TSH with normal T4) may impair free T3 availability at the mitochondrial level — consider full thyroid panel including free T3 in fatigued patients

Wellness Wednesday

- W.W. Yau, B.K. Singh, R. Lesmana et al. Thyroid hormone (T(3)) stimulates brown adipose tissue activation via mitochondrial biogenesis and MTOR-mediated mitophagy Autophagy, 15 (1) (2019), pp. 131-150
- H.C. Chi, S.L. Chen, S.L. Lin, et al. Thyroid hormone protects hepatocytes from HBx-induced carcinogenesis by enhancing mitochondrial turnover Oncogene, 36 (37) (2017), pp. 5274-5284

DOCTOR'S DATA INC

The Big Clinical Takeaway

Sex hormone optimization IS mitochondrial medicine.

Treating hormonal deficiency protects mitochondria — and vice versa.

Hormone	Mitochondrial Effect	Clinical Priority
Estrogen (E2)	Biogenesis, OXPHOS, calcium regulation, anti-apoptotic, anti-inflammatory	Critical in perimenopause/menopause — timing matters
Progesterone	Oxidative metabolism, neuroprotection after injury, mPTP stabilization	Especially relevant in neurological presentations
Testosterone	OXPHOS support, ROS reduction, calcium stability, neuronal survival	Both men and women — context-dependent dosing
Thyroid (T3)	Direct PGC-1α activation → biogenesis; OXPHOS upregulation	Treat subclinical dysfunction; low T3 = mitochondrial brake
Melatonin	Produced IN mitochondria; mitophagy regulation; antioxidant	Circadian health = mitochondrial health
Cortisol (balance)	Acute: adaptive. Chronic excess or deficiency: mitochondrial exhaustion	HPA optimization = mitochondrial optimization

Mitochondrial Mitophagy Treatments

- Estrogen
- Progesterone
- Melatonin
- Cortisol
- Thyroid

Wellness Wednesday

DOCTOR'S DATA INC.

Estrogen & Progesterone Mitophagy

Ovarian Hormones & Mitochondrial Aging

- Loss of ovarian hormones over time affects **mitochondrial health**

What happens with chronic hormone decline

- Leads to:
  - **Mitochondrial dysfunction**
  - Changes in **mitochondrial membrane lipids**
- These changes resemble a **cellular aging pattern**

Clinical implications

- May contribute to increased risk of:
  - **Postmenopausal cognitive decline**
  - **Alzheimer's disease**
  - Other **age-related conditions**

Bottom line

- **Long-term loss of ovarian hormones may accelerate mitochondrial aging, which could contribute to brain and systemic aging processes.**

S.S. Han, M.Y. Zhang, Y.Y. Jeong, D.J. Margolis, Q. Cai The role of mitophagy in the regulation of mitochondrial energetic status in neurons Autophagy, 17 (12) (2021), pp. 4182-4201

Progesterone & Mitophagy

Parameter	Natural P4	MPA (synthetic)	ALLO (metabolite)
Mitochondrial respiration	Improves	Inhibits	Supports
	Increases	No benefit	Enhances
Antioxidant defense	↑ MnSOD	No effect	Not studied
Biogenesis	Supports	No effect	Promotes (CNS)
Clinical implication	Use bioidentical P4	Avoid when possible	Neurosteroid benefit

Progesterone vs Synthetic Progestins & Mitochondria

- Different forms of progesterone have **very different effects on mitochondria**

Natural progesterone (P4)

- Supports mitochondrial function by:
  - Improving mitochondrial respiration
  - Increasing ATP production
  - Boosting energy-related proteins (COX IV, ATP synthase)
  - Increasing antioxidant defense (MnSOD)

Medroxyprogesterone acetate (MPA) – synthetic progestin

- Does not improve mitochondrial function
- Can **inhibit mitochondrial respiration**
- Lacks the beneficial metabolic effects seen with natural progesterone

Allopregnanolone (ALLO) – progesterone metabolite

- Acts as a **neurosteroid**
- Supports brain mitochondria by:
  - Enhancing mitochondrial function
  - Promoting mitochondrial biogenesis (new mitochondria)

Bottom line

- Natural progesterone and its metabolite (ALLO) support mitochondrial health, while synthetic MPA does not and may impair mitochondrial respiration.
- Progesterone supports brain mitochondrial function by improving energy output and reducing oxidative stress, in a way that is distinct from estrogen.
- 'This suggests that progesterone — not just estrogen — should be part of any neuroprotective hormone strategy

Wellness Wednesday

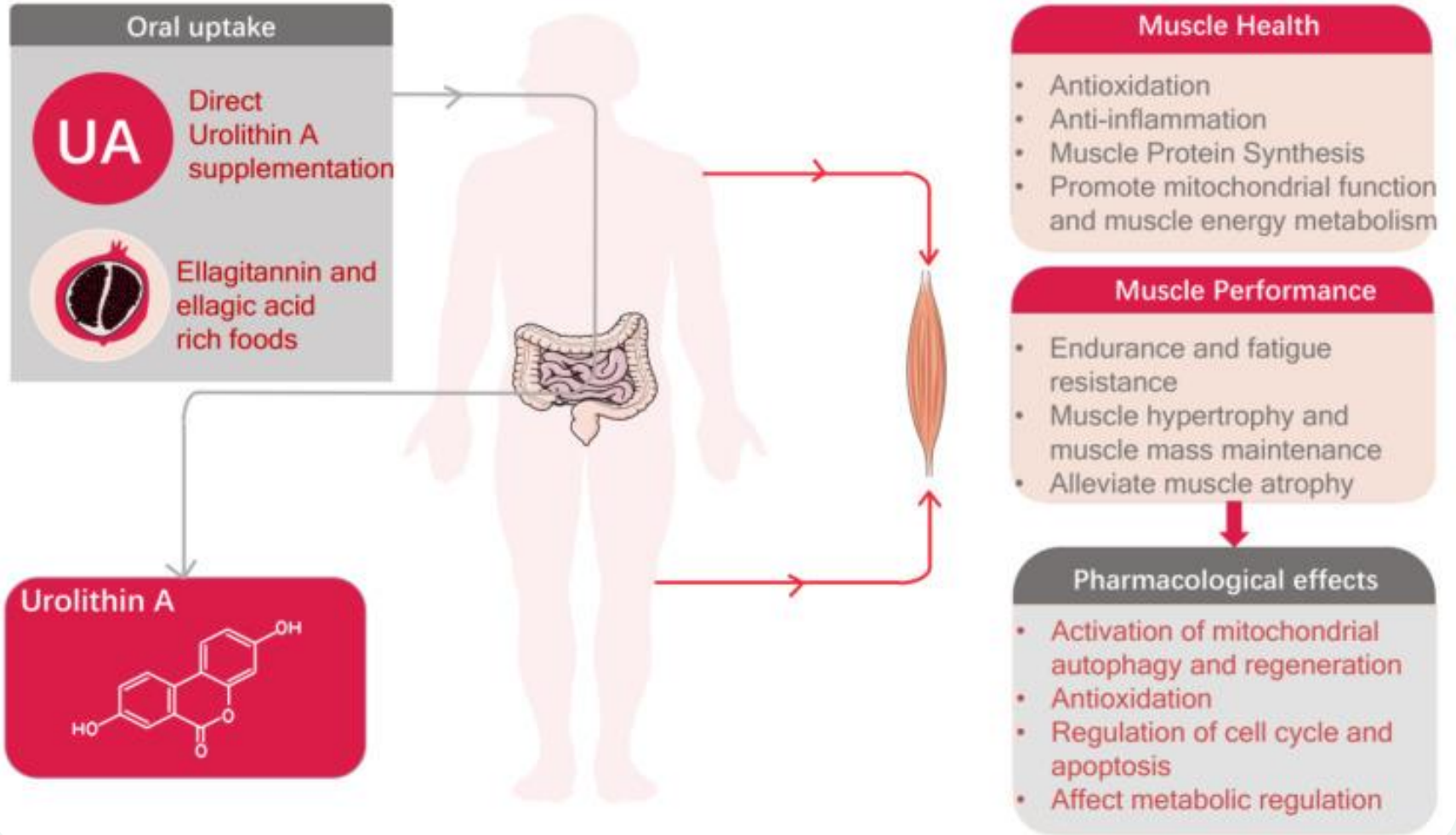
- R.W. Irwin, J. Yao, S.S. Ahmed, R.T. Hamilton, E. Cadenas, R.D. Brinton Medroxyprogesterone acetate antagonizes estrogen up-regulation of brain mitochondrial function Endocrinology, 152 (2) (2011), pp. 556-567
- T. Wang, J. Yao, S.H. Chen, Z.S. Mao, R.D. Brinton Allopregnanolone reverses bioenergetic deficits in female triple transgenic Alzheimer's mouse model Neurotherapeutics, 17 (1) (2020), pp. 178-188

DOCTOR'S DATA INC

Urolithin A

- **1980:** Researchers Doyle and Griffiths identified the compound in rats, showing that gut bacteria convert ellagic acid into urolithins.
- **2005:** A study led by Tomás-Barberán and colleagues explicitly identified urolithin A as a product of human colon microflora (postbiotic) after consuming items like with polyphenols such as walnuts, berries, and pomegranates.
- **Recent Aging Discoveries:** Modern studies expanded on how it stimulates mitophagy (recycling damaged cell parts) to improve muscle and cellular health.
- **Muscle health: Human clinical trials show that daily supplementation (500 mg to 1000 mg) can improve muscle strength and endurance in middle-aged and older adults**
- **Anti-inflammatory:** Studies also note decreases in specific blood markers linked to chronic inflammation.

- Cerdá B, Periago P, Espín JC, Tomás-Barberán FA. Identification of urolithin a as a metabolite produced by human colon microflora from ellagic acid and related compounds. J Agric Food Chem. 2005 Jul 13;53(14):5571-6. doi: 10.1021/jf050384i. PMID: 15998116.
- D'Amico D, Olmer M, Fouassier AM, Valdés P, Andreux PA, Rinsch C, Lotz M. Urolithin A improves mitochondrial health, reduces cartilage degeneration, and alleviates pain in osteoarthritis. Aging Cell. 2022 Aug;21(8):e13662. doi: 10.1111/acel.13662. Epub 2022 Jul 1. PMID: 35778837; PMCID: PMC9381911.
- Zhao H, Song G, Zhu H, Qian H, Pan X, Song X, Xie Y, Liu C. Pharmacological Effects of Urolithin A and Its Role in Muscle Health and Performance: Current Knowledge and Prospects. Nutrients. 2023 Oct 19;15(20):4441. doi: 10.3390/nu15204441. PMID: 37892516; PMCID: PMC10609777.



Wellness Wednesday

Zhao H, Song G, Zhu H, Qian H, Pan X, Song X, Xie Y, Liu C. Pharmacological Effects of Urolithin A and Its Role in Muscle Health and Performance: Current Knowledge and Prospects. Nutrients. 2023 Oct 19;15(20):4441. doi: 10.3390/nu15204441. PMID: 37892516; PMCID: PMC10609777.

DOCTOR'S DATA INC

Emerging Mitochondrial Treatments

1. Mitoceuticals including MitoQ
2. Mitochondrial transplantation
3. Gene therapies
4. External therapies

Wellness Wednesday

SS-31 (Elamipretide)

- **What it is:** A mitochondrially-targeted, synthetic peptide
- **Mechanism:** Binds to cardiolipin on the inner mitochondrial membrane to stabilize structure, optimize electron transfer, and reduce oxidative stress.
- **Delivery**: Typically studied as an injectable peptide or targeted therapeutic for specific mitochondrial and cardiac conditions.
- **Conditions studied**: Kidney disease, Alzheimer's, cardiomyopathy, TBI, retinopathy, endothelial injury, skeletal muscle aging

- Zhu Y, Luo M, Bai X, Li J, Nie P, Li B, Luo P. SS-31, a Mitochondria-Targeting Peptide, Ameliorates Kidney Disease. Oxid Med Cell Longev. 2022 Jun 6;2022:1295509. doi: 10.1155/2022/1295509. PMID: 35707274; PMCID: PMC9192202.
- Reddy P. H., Manczak M., Kandimalla R. Mitochondria-targeted small molecule SS31: a potential candidate for the treatment of Alzheimer's disease. Human Molecular Genetics . 2017;26(8):1483–1496. doi: 10.1093/hmg/ddx052.
- Lu H.-I., Lee F.-Y., Wallace C. G., et al. SS31 therapy effectively protects the heart against transverse aortic constriction-induced hypertrophic cardiomyopathy damage. American Journal of Translational Research . 2017;9(12):5220–5237.
- Zhu Y., Wang H., Fang J., et al. SS-31 provides neuroprotection by reversing mitochondrial dysfunction after traumatic brain injury. Oxidative Medicine and Cellular Longevity . 2018;2018:12. doi: 10.1155/2018/4783602.4783602
- Li J., Chen X., Xiao W., et al. Mitochondria-targeted antioxidant peptide SS31 attenuates high glucose-induced injury on human retinal endothelial cells. Biochemical and Biophysical Research Communications . 2011;404(1):349–356. doi: 10.1016/j.bbrc.2010.11.122.
- Siegel M. P., Kruse S. E., Percival J. M., et al. Mitochondrial-targeted peptide rapidly improves mitochondrial energetics and skeletal muscle performance in aged mice. Aging Cell . 2013;12(5):763–771. doi: 10.1111/acel.12102.

Mitoceuticals Targeting MitoNEET

- MitoNEET, a protein located on the outer membrane of mitochondria, was first identified in 2004 by Colca et al.
- Studies have shown diagnostic associations between not only mitoNEET and T2D, but also Parkinson's disease, cystic fibrosis, Alzheimer's disease, cardiac function, as well as deficits in mitochondrial oxidative stress.
- Development of pharmaceuticals designed to target mitoNEET seems like a logical step in mitoceutical development.
- Currently a drug discovery target — not yet available as a therapeutic. Watch this space.

Colca J.R., McDonald W.G., Waldon D.J., Leone J.W., Lull J.M., Bannow C.A., Lund E.T., Mathews W.R. Identification of a novel mitochondrial protein ("mitoNEET") cross-linked specifically by a thiazolidinedione photoprobe. Am. J. Physiol. Metab. 2004;286:E252–E260. doi: 10.1152/ajpendo.00424.2003.

Mitoceuticals – MitoQ

- The mitoceutical MitoQ, a compound based on coenzyme Q10 (CoQ10), is an antioxidant specifically targeted to the mitochondria with a number of studies completed *in vitro* and *in vivo* in both rodents and humans.
- Notably, *in vitro* and *in vivo* rodent studies have shown that MitoQ treatment minimized neurodegeneration caused by Aß-accumulation, prevented cognitive decline, and synaptic mitochondrial dysfunction.
- High-intensity interval exercise increases **mitochondrial and nuclear DNA damage** via oxidative stress
- **Mitochondria-targeted antioxidant (MitoQ, 20 mg/day)** for 21 days **attenuated DNA damage** in blood and skeletal muscle
- Suggests **mitochondrial oxidative injury in humans is modifiable** with targeted antioxidant strategies

- Smith R.A.J., Murphy M.P. Animal and human studies with the mitochondria-targeted antioxidant MitoQ. Ann. N. Y. Acad. Sci. 2010;1201:96–103. doi: 10.1111/j.1749-6632.2010.05627.x.
- Tauskela J.S. MitoQ--a mitochondria-targeted antioxidant. IDrugs. 2007;10:399–412.
- Williamson J, Hughes CM, Cobley JN, Davison GW. The mitochondria-targeted antioxidant MitoQ, attenuates exercise-induced mitochondrial DNA damage. Redox Biol. 2020 Sep;36:101673. doi: 10.1016/j.redox.2020.101673. Epub 2020 Aug 6. PMID: 32810739; PMCID: PMC7452004.

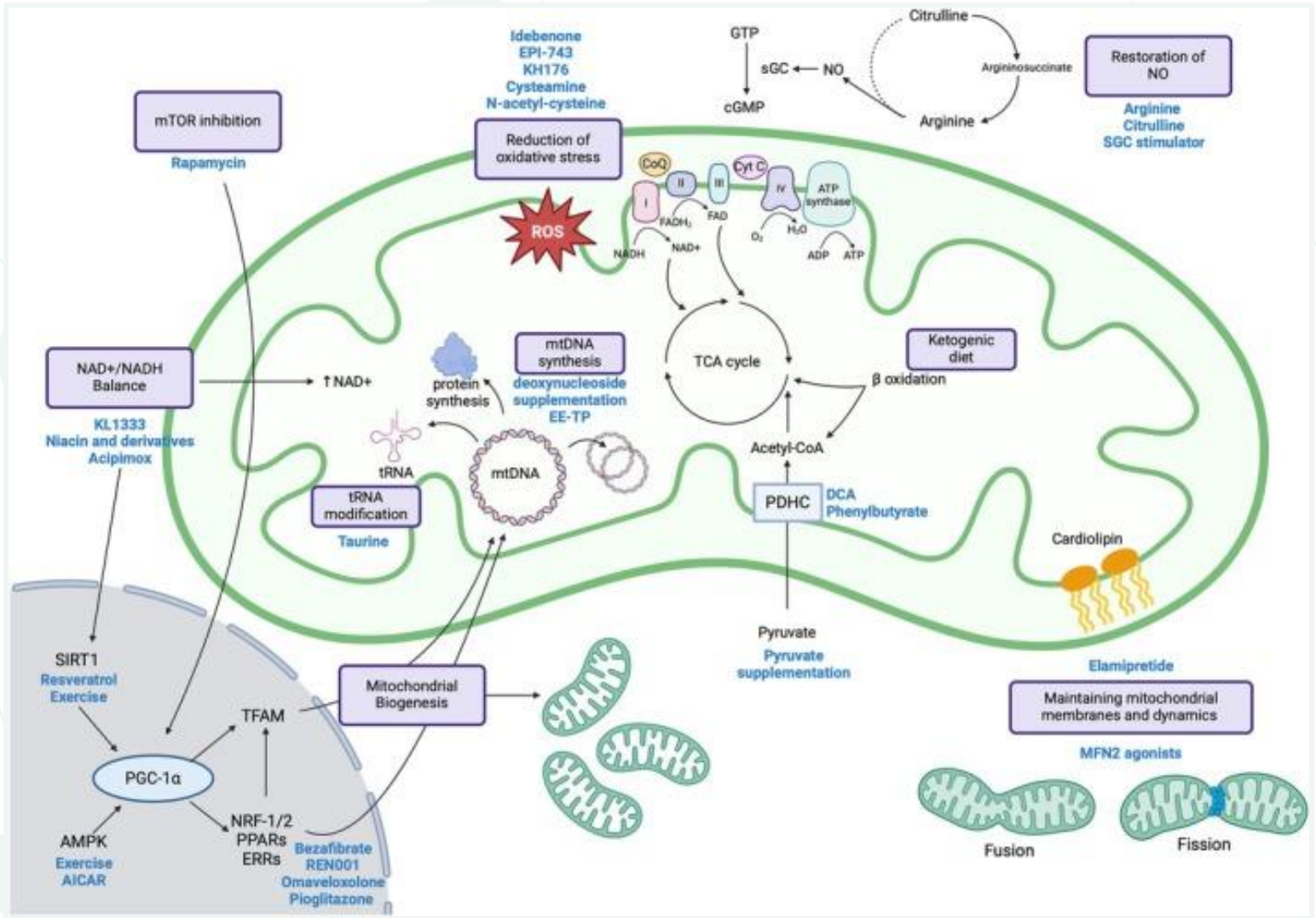
Estrogen-Mitoceuticals

Treatment	Core Mechanism	Target Conditions
Estrogen + CoQ10	Combines ER driven respiratory chain assembly with targeted mitochondrial antioxidants to halt the “oxidative storm”	Cardiovascular disease
ERR Agonists + NAD+ Boosters	Activating estrogen-related receptors (ERRs) alongside NAD+ precursors to repair energy metabolism	Severe muscle fatigue, genetic mitochondrial mutations, and metabolic inflexibility
Phytoestrogens + Mitochondrial Primers	Utilizing plant derived estrogens (i.e. resveratrol) that concurrently act as mitoceuticals to bypass standard hormone therapy risks	Female brain aging, Alzheimer's, Parkinson’s disease
SIRT3 and AMPK Activators	Using compound combinations to mimic estrogen’s ability to clear out damaged cellular waste	Postmenopausal metabolic decline and systemic insulin resistance

Mitochondrial Transplantation

- This paper argues that mitochondrial transplantation is attractive because many neurodegenerative disorders share overlapping mitochondrial abnormalities, including:
  - reduced oxidative phosphorylation / ATP generation
  - increased reactive oxygen species
  - mtDNA damage
  - impaired calcium handling
  - abnormal fission/fusion and mitochondrial trafficking
  - activation of apoptosis and inflammatory signaling
- So instead of trying to block one downstream consequence at a time, mitochondrial transplantation aims to address the problem at a more upstream level by **supplying new, respiration-competent mitochondria**.

Fuente-Muñoz C.E.D. la, Arias C. The therapeutic potential of mitochondrial transplantation for the treatment of neurodegenerative disorders. Rev. Neurosci. 2021;32:203–217. doi: 10.1515/revneuro-2020-0068.



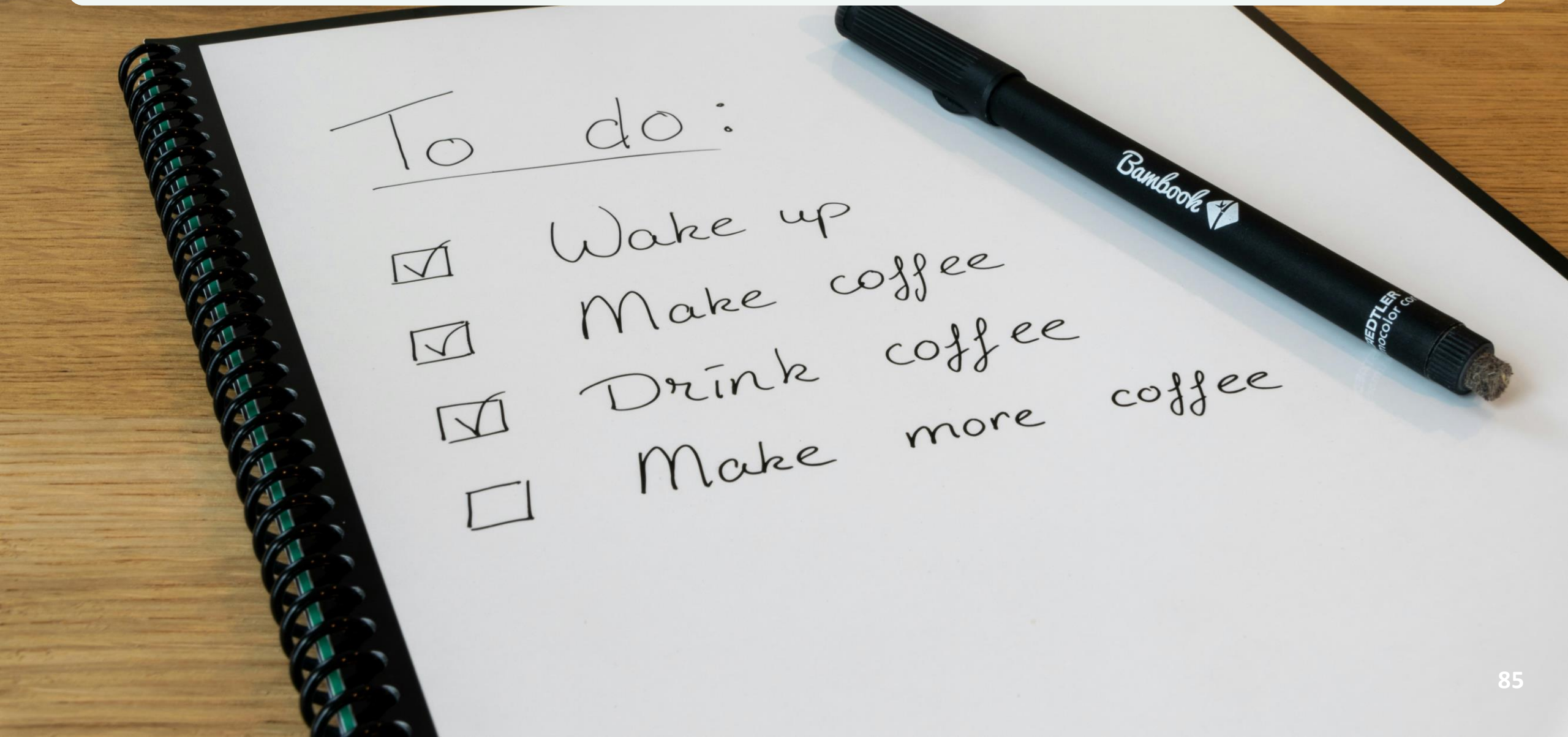
Ball M, van Bergen NJ, Compton AG, Thorburn DR, Rahman S, Christodoulou J. Therapies for Mitochondrial Disease: Past, Present, and Future. J Inherit Metab Dis. 2025 Jul;48(4):e70065. doi: 10.1002/jimd.70065. PMID: 40714961; PMCID: PMC12301291.

External Therapies

- Pulsed electromagnetic field (PEMF)
- Photobiomodulation (Red light therapy)
- Hyperbaric oxygen therapy (HBOT)

- Chianese D, Bonora M, Sambataro M, Sambato L, Paola LD, Tremoli E, Cappucci IP, Scatto M, Pinton P, Picari M, Ferroni L, Zavan B. Exploring Mitochondrial Interactions with Pulsed Electromagnetic Fields: An Insightful Inquiry into Strategies for Addressing Neuroinflammation and Oxidative Stress in Diabetic Neuropathy. Int J Mol Sci. 2024 Jul 16;25(14):7783. doi: 10.3390/ijms25147783. PMID: 39063025; PMCID: PMC11277522.
- Hamblin MR. Mechanisms and Mitochondrial Redox Signaling in Photobiomodulation. Photochem Photobiol. 2018 Mar;94(2):199-212. doi: 10.1111/php.12864. Epub 2018 Jan 19. PMID: 29164625; PMCID: PMC5844808.
- Schottlender N, Gottfried I, Ashery U. Hyperbaric Oxygen Treatment: Effects on Mitochondrial Function and Oxidative Stress. Biomolecules. 2021 Dec 3;11(12):1827. doi: 10.3390/biom11121827. PMID: 34944468; PMCID: PMC8699286.

Mitochondrial Health Cheat Sheets



Mitochondrial Treatment Overview – Physical

1. **Physical Stimuli (The Signaling Triggers):** Mitochondria adapt rapidly to metabolic stress. You can apply controlled, temporary stress (known as *mitohormesis*) to force them to adapt and multiply:

- **Zone 2 Aerobic Training:** Steady-state, low-intensity cardio (like brisk walking or slow cycling) relies almost exclusively on **beta-oxidation** for fuel. This continuous demand forces skeletal muscle to drastically increase its baseline mitochondrial density.
- **High-Intensity Interval Training (HIIT):** Short bursts of maximum effort rapidly deplete cellular ATP. This severe drop activates **AMPK**, the emergency signal that forces the nucleus to trigger biogenesis through **PGC-1\(\alpha \)**.
- **Thermal Hormesis:** Brief exposure to cold (e.g., cold showers) or heat (e.g., saunas) triggers the nervous system to release norepinephrine. This process upregulates PGC-1\(\alpha \), instructing the body to grow more mitochondria to assist with cellular resilience and temperature regulation.

Zhang X, Xiao J, Jiang M, Phillips CJC, Shi B. Thermogenesis and Energy Metabolism in Brown Adipose Tissue in Animals Experiencing Cold Stress. Int J Mol Sci. 2025 Mar 31;26(7):3233. doi: 10.3390/ijms26073233. PMID: 40244078; PMCID: PMC11989373.

Exercise Routine for Mitochondrial Health

Sample Weekly Routine: Zone 2 & HIIT Protocol

This schedule balances **Zone 2 cardio** (which expands your baseline mitochondrial volume and trains fat-burning efficiency) with **HIIT** (which forces the creation of new mitochondria via intense energy depletion), while including mandatory rest days for structural repair.

- **Monday (Zone 2 - Aerobic Base):** 45–60 minutes of steady-state cardio (brisk walking, cycling, or rowing). Keep your pace at a level where you can maintain a conversation but breathing is noticeably heavier.
- **Tuesday (Strength Training):** 45 minutes of resistance training focusing on major muscle groups. Building muscle mass provides more physical "real estate" for new mitochondria to grow.
- **Wednesday (HIIT - Biogenesis Trigger):** 20–25 minutes total. Perform a 5-minute warmup, followed by 4 to 6 rounds of 30 seconds at absolute maximum effort (sprinting, stationary bike, or kettlebell swings) paired with 2 to 3 minutes of complete active recovery.
- **Thursday (Active Recovery & Mobility):** Light walking, yoga, or stretching. Focus on getting deep, restorative sleep tonight to allow the cells to repair.
- **Friday (Zone 2 - Volume Building):** 45–60 minutes of low-intensity steady-state cardio. This trains your mitochondria to seamlessly utilize beta-oxidation for long periods.
- **Saturday (Full Body Strength or Zone 2):** Optional light full-body workout or an outdoor hike.
- **Sunday (Complete Rest):** No structured exercise. Allow your cells to rebuild membranes and replenish ATP reserves

Porter C, Reidy PT, Bhattarai N, Sidossis LS, Rasmussen BB. Resistance Exercise Training Alters Mitochondrial Function in Human Skeletal Muscle. Med Sci Sports Exerc. 2015 Sep;47(9):1922-31. doi: 10.1249/MSS.0000000000000605. PMID: 25539479; PMCID: PMC4478283.

Mitochondrial Treatment Overview -Diet

2. Dietary Strategies (Fuel Customization)

- How and when you eat dictates the efficiency of the inner mitochondrial membrane:
  - **Intermittent Fasting or Caloric Restriction:** Periodically withholding food lowers systemic glucose and elevates **NAD+/NADH ratio** levels. This activates **SIRT1**, a longevity protein that triggers mitophagy, causing the cell to dismantle leaky, underperforming mitochondria and recycle their parts into fresh, efficient ones.
- **Prioritizing Healthy Fats:** Shifting toward a Mediterranean-style pattern rich in monounsaturated fats (like olive oil and avocados) provides the raw materials needed to synthesize **cardiolipin**—the foundational lipid that prevents the inner membrane from leaking protons.

Wellness Wednesday

Pollicino F, Veronese N, Dominguez LJ, Barbagallo M. Mediterranean diet and mitochondria: New findings. Exp Gerontol. 2023 Jun 1;176:112165. doi: 10.1016/j.exger.2023.112165. Epub 2023 Apr 5. PMID: 37019345.

DOCTOR'S DATA INC

Grocery List for Mitochondrial Health

Mitochondrial Grocery List: Nutrient-Rich Foods

- To feed the specific enzymatic checkpoints we discussed (such as the Krebs Cycle and Electron Transport Chain), prioritize these nutrient-dense foods:
- **Organ Meats (Beef Liver & Heart):** The absolute highest natural source of **CoQ10**, **Iron**, and the entire **B-vitamin spectrum** (especially B1, B2, B3, and B5).
- **Sardines and Wild Salmon:** Exceptionally rich in **CoQ10**, **Omega-3 fatty acids** (essential for building the cardiolipin in the inner membrane), and **Iron**.
- **Grass-Fed Beef and Lamb:** High concentrations of **L-Carnitine** (the required vehicle for fat transport), **Iron**, and **Zinc**.
- **Spinach and Swiss Chard:** Packed with **Magnesium** (the mineral anchor for the ATP Synthase turbine) and dietary nitrates that improve electron transport efficiency.
- **Pumpkin Seeds and Almonds:** Excellent plant-based sources of **Magnesium**, **Vitamin E** (to protect lipid membranes from oxidation), and **B-vitamins**.
- **Cruciferous Vegetables (Broccoli, Brussels Sprouts):** Contain sulfur compounds that your body uses to synthesize its own master internal antioxidant, **Glutathione**.
- **Eggs (with the Yolk):** Rich in **Biotin (B7)**, **Pantothenic Acid (B5)**, and essential lipids needed for cellular membrane synthesis.

Wellness Wednesday

Pollicino F, Veronese N, Dominguez LJ, Barbagallo M. Mediterranean diet and mitochondria: New findings. Exp Gerontol. 2023 Jun 1;176:112165. doi: 10.1016/j.exger.2023.112165. Epub 2023 Apr 5. PMID: 37019345.

DOCTOR'S DATA INC

Clinical Priorities — The Mitochondrial Stack

If a patient can only address a limited number of interventions, these are the highest-yield priorities — the ones with the strongest evidence and broadest mitochondrial impact.

Key message: *supplements cannot compensate for absent sleep, sedentary lifestyle, or protein deficiency. Address lifestyle foundations first, then layer targeted nutrients.*

Priority	Nutrient / Intervention	Why It Matters
1	B Complex (especially B1, B2, B3, B5)	TCA cycle and ETC cannot function without these — true rate-limiting cofactors
2	Magnesium	Required for ATP production and stabilization; cofactor for 300+ reactions; almost universally depleted
3	CoQ10	Electron shuttle between Complexes I/II and III; potent antioxidant; critical with statin use and in aging
4	L-Carnitine	Without it, long-chain fatty acids cannot enter the mitochondria — fat burning fails even with fat available
5	Alpha-Lipoic Acid	Dual role: TCA cycle cofactor + regenerates glutathione, vitamin C, and vitamin E
6	Glutathione (or NAC + glycine precursors)	Master antioxidant protecting mtDNA and membranes — cannot be replaced by exogenous antioxidants alone
7	Omega-3 fatty acids (EPA + DHA)	Membrane integrity, anti-inflammation, biogenesis support — structural, not optional
8	Exercise (endurance + resistance)	Activates AMPK → PGC-1α → biogenesis. Cannot be replaced by supplements.
9	Sleep + circadian rhythm	Mitochondrial repair, mitophagy, and melatonin production occur during sleep — non-negotiable
10	Adequate protein + caloric intake	Building material for all mitochondrial proteins — deficiency limits every other intervention

Today's Takeaway

- Anytime you improve mitochondrial health, you improve hormone health

Exercise (PGC-1α activation) → better steroidogenesis → improved sex hormone levels

CoQ10 + carnitine supplementation → improved ovarian mitochondrial function → better egg quality and fertility

Better sleep (melatonin) → improved cortisol rhythm → better adrenal function

Improve hormone health → improve mitochondrial health

- Anytime you improve hormone health, you improve mitochondrial health

Thyroid optimization → T3 stimulates PGC-1α and biogenesis

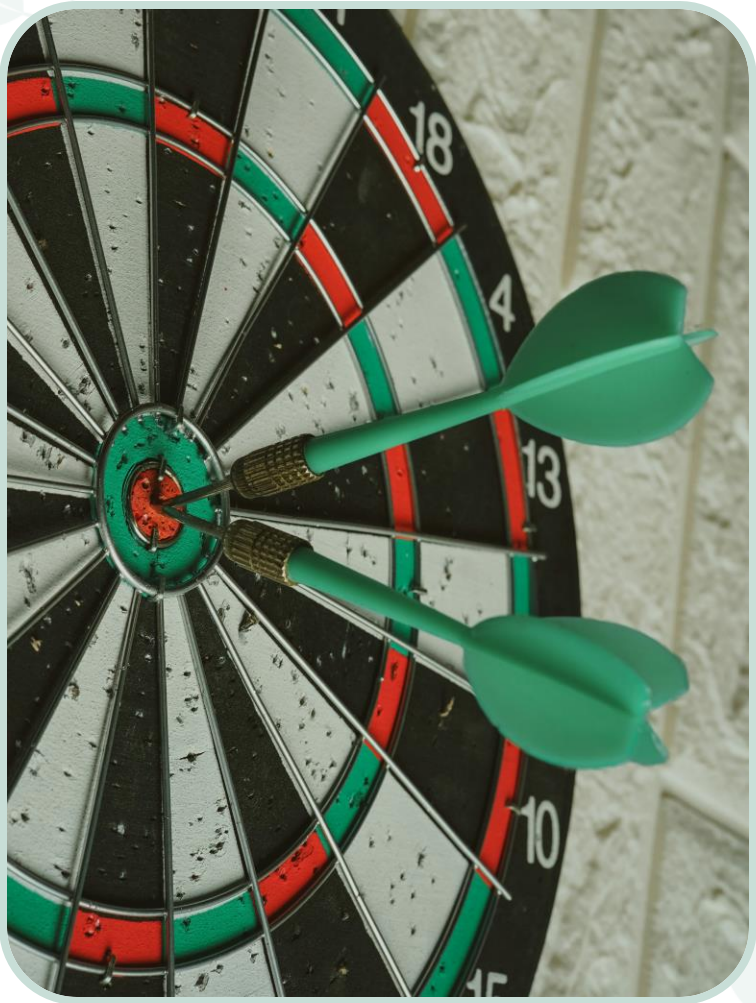
Estrogen replacement in perimenopause → restores mitochondrial efficiency in brain and heart

Progesterone support → reduces neuronal oxidative stress and supports mitochondrial respiration

Treating Hormones = Treating Mitochondria

- Amenorrhea
- Hypogonadism (male and female)
- Endometriosis
- Infertility
- Luteal phase dysfunction
- Premature ovarian insufficiency (POI)
- PMOS/PCOS
- Perimenopause
- Menopause
- Andropause

Treating any hormone-related pathology may include mitochondrial treatments for a more powerful outcome



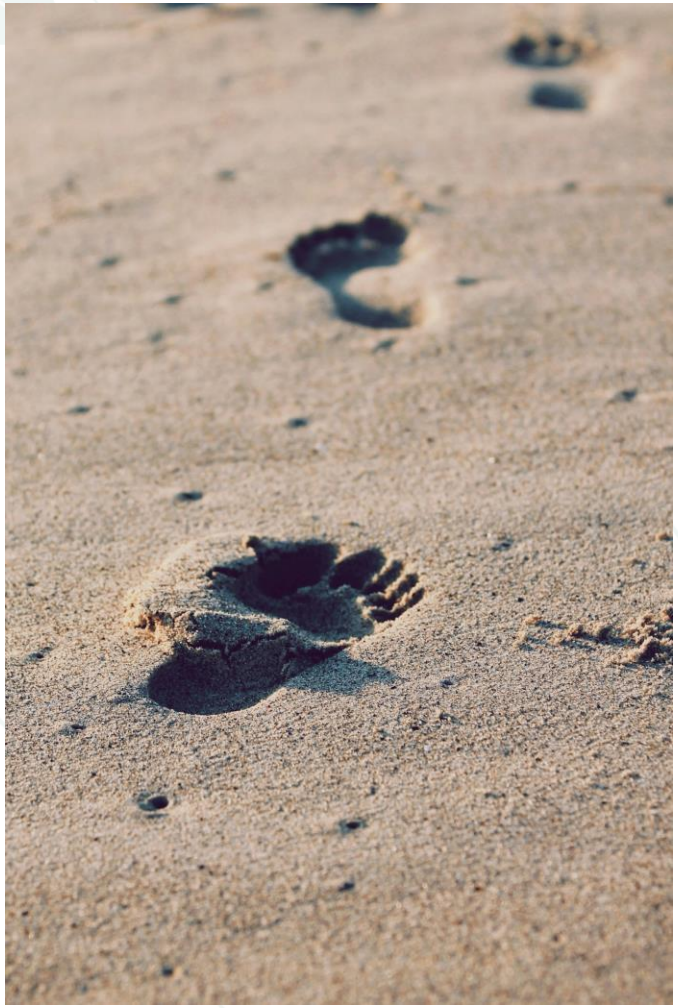
Wellness Wednesday

DOCTOR'S DATA INC.

Mitochondrial Treatment: Clinical Steps

The mitochondrial-hormonal treatment framework:

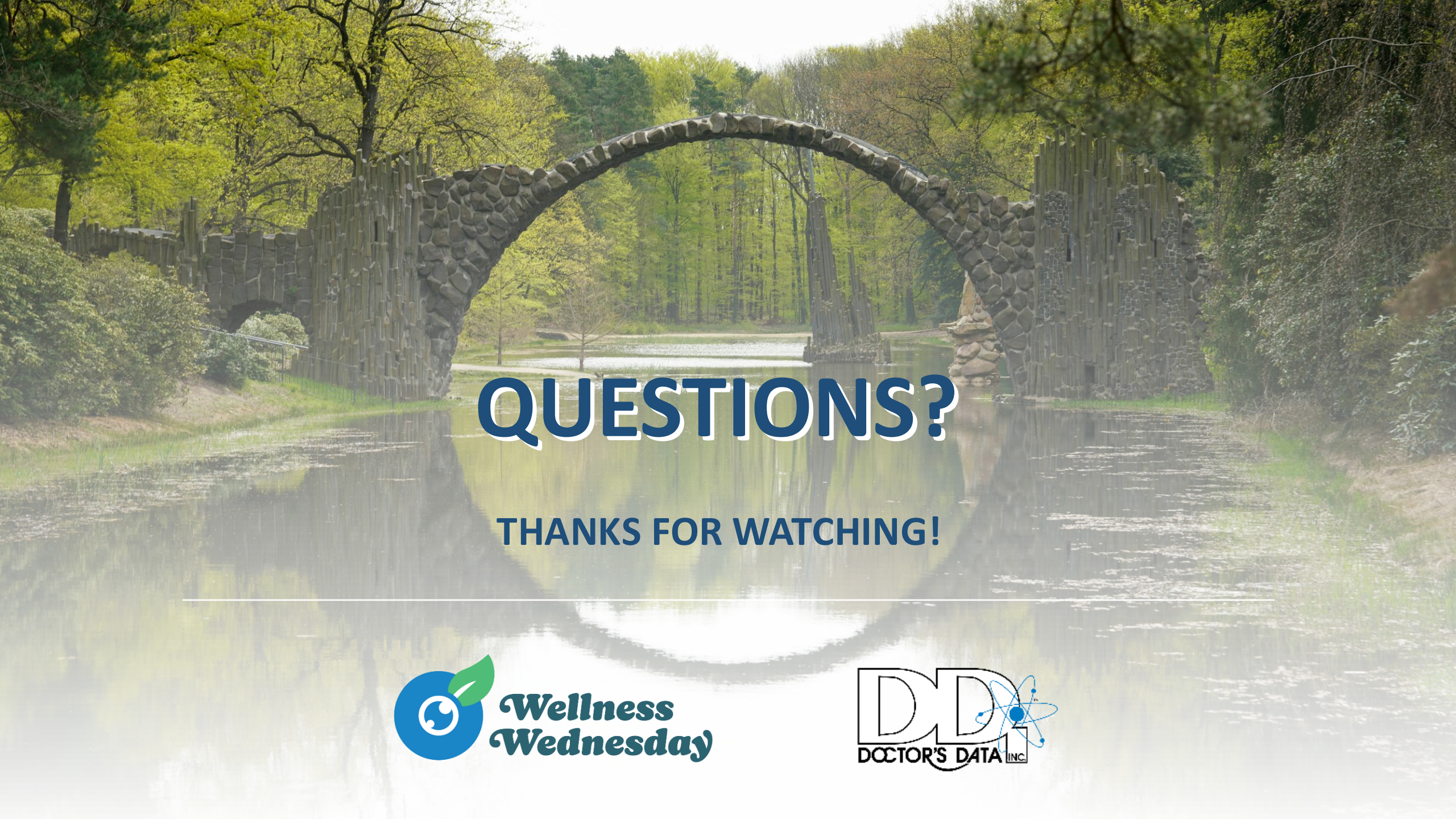
1. Assess for mitochondrial dysfunction (labs + clinical)
2. Address foundational lifestyle and nutritional needs
3. Optimize hormonal balance (thyroid, sex hormones, cortisol, melatonin)
4. Consider targeted mitochondrial interventions



Case Application — Post-Menopausal Female (Fatigue, Insomnia, Brain Fog, Joint Pain, Vaginal Dryness)

- Tier 1 — Lifestyle Foundation: Mediterranean diet + intermittent fasting | Zone 2 + resistance training | Sleep hygiene + morning light | Stress regulation (thermal hormesis, adaptogens)
- Tier 2 — Hormonal Optimization: Bioidentical estradiol (transdermal) | Vaginal estriol | Oral micronized progesterone | Low-dose testosterone (if indicated) | Assess thyroid (free T3) and cortisol
- Tier 3 — Mitochondrial Support: Mitochondrial nutrient stack (Mg, B-complex, CoQ10/MitoQ, L-carnitine) | Melatonin | NAC + antioxidant support | Maca for adrenal/HPA | Resveratrol/EGCG as mitophagy support

- **Key principle:** Sequence matters — establish lifestyle and hormonal foundation first; add mitochondrial nutraceuticals as targeted adjuncts, not first-line.



QUESTIONS?

THANKS FOR WATCHING!

Wellness Wednesday

DOCTOR'S DATA INC.