Mitochondrial Magic: Tips for revitalising your mitochondrial health

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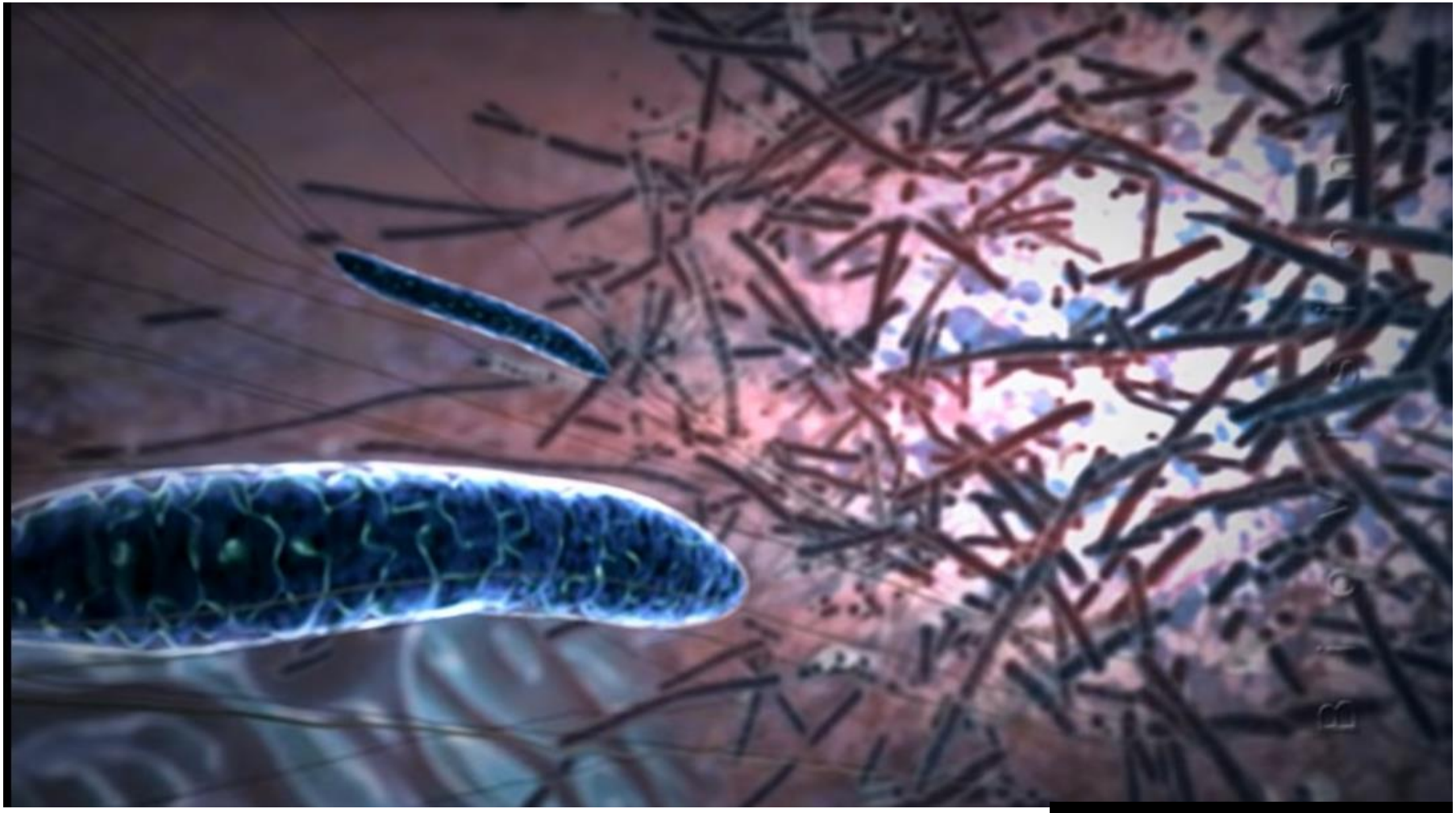
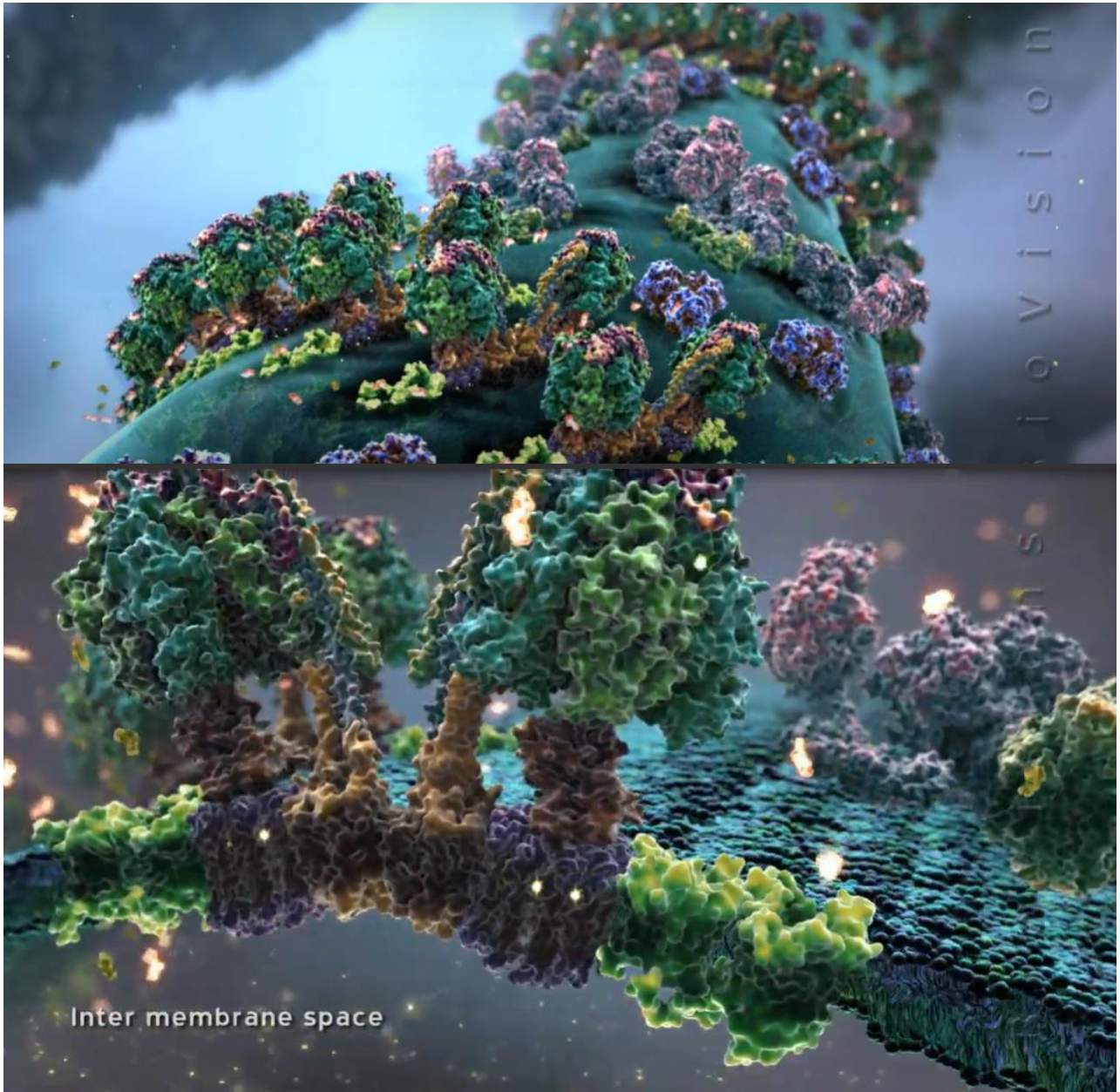
www.aonm.org

Mitochondria: Powering our cells



Biovisions Powering the Cell, Mitochondria, biovisions.mcb.harvard.edu
https://www.youtube.com/watch?v=RrS2uROUjK4

The electron transport chain (ETC) – 5 complexes



Agenda

- **What pathways may have become compromised?**
- Address the “Removes“
- Add/support according to the pathways that need work

What pathways may have become compromised?

Macronutrients

Are macronutrient fuels accessing the cell sufficiently?
Are the fuels the most efficient for generating mitochondrial energy?

Membranes

Are the cellular membranes of the right composition/sufficiently intact?
Any blockages in the membranes?

Micronutrients/cofactors

Correct substrates for the Krebs cycle?
Are the mitochondria able to metabolise the substrates? If not, why not?
Do the complexes of the electron transport chain have the right substrates?

Oxidative stress

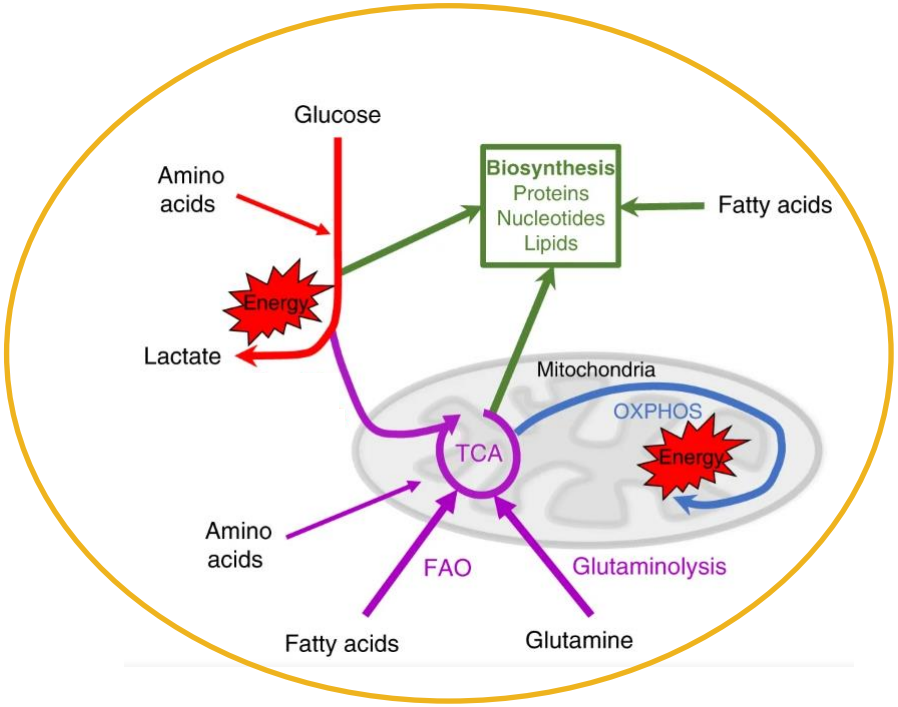
High ROS within the cell?
High ROS within the mitochondria?

Mitochondrial mass/composition

Insufficient numbers of mitochondria, or non-intact?

Obstacles along the electron transport chain

Blocks?
Proton leak?



Source: *MMD, O&M und Ernaehrung,* Mitochondrien – texts from 2016/No. 156 through to 2020/No. 171 Prof. Dr. rer. nat. Brigitte König; *mitochondrial research by Martin D. Brand and others (e.g. https://pubmed.ncbi.nlm.nih.gov/28270511/); https://www.nature.com/articles/s41467-019-10015-4; other references available on request*

Agenda

- What pathways may have become compromised?
- **Address the “Removes“**
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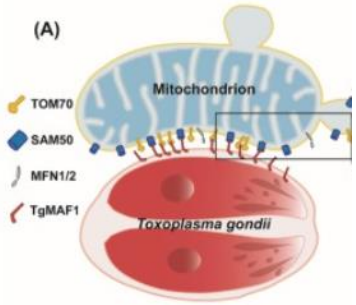
Removing is just as important supporting what is missing

Address, or at least log as key influencing factors:

Address the "Removes"

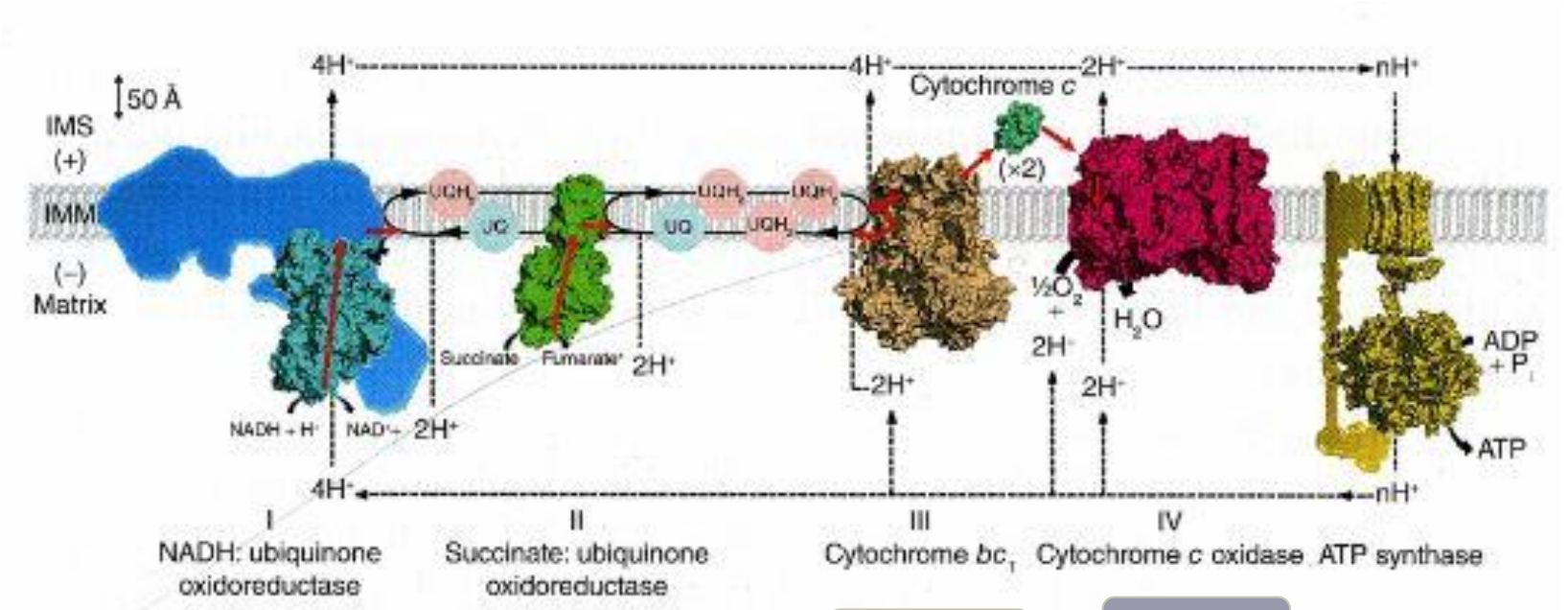
- Viral/bacterial infections: These increase non-mitochondrial respiration because the cell uses oxygen to try to kill the pathogens rather than for energy[1]; deplete the host's mitochondrial anti-viral defences to keep themselves alive[2]; Borrelia also steal ATP from their host to fuel their flagellum, etc.[3]
- Biotoxins/mycotoxins: Ochratoxin A uncouples the mitochondria and inhibits Complex 2[4]
- Some parasites: Especially Toxoplasma, which tethers and disables mitochondria[5]



- Heavy metals: Al induces permeability (MPT)[6], Hg induces mito dysfunction[7], Arsenic increases mitochondrial ROS formation, lipid peroxidation and mitochondrial membrane potential collapse[8]
- Pesticides, herbicides: e.g. glyphosate: blocks Shikimate pathway: bacterial energy generation,[9] it also chelates minerals, including copper …
- Chemical contaminants: e.g. Lindane[10]
- Household chemicals
- EMFs: See following chart
- Medications: See following chart
- GI issues: dysbiosis/SIBO: Chart follows

Source: 1. Naviaux RK. Metabolic features of the Cell Danger Response. Mitochondrion. 2014 May;16:7-17; 2. https://www.nature.com/ articles/s12276-021-00602-1; 3. https://pubmed.ncbi.nlm.nih.gov/22710875/; 4. https://pubmed.ncbi.nlm.nih.gov/5441684/; 5. https://www.sciencedirect.com/science/article/ pii/S1471492222000320; 6. https://link.springer.com/article/10.1007/s007750000144; 7. https://link.springer.com/chapter/10.1007/978-3-319-03777-6_1; 8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3813354/; 9. https://roundupprisks.com/2016/04/09/glyphosate-and-mitochondrial-dysfunction/; 10. https://europepmc.org/article/MED/6205709

“Most of the antidepressants and mood stabilizers tested inhibit the ETC complexes; CI and CIV were the most affected”



Proton pump inhibitors bind to Complexes 1, 3 and 4 and block electron transport ***

Complex 1

NADH

- **Amitriptyline**
- **Imipramine**
- **Citalopram**
- **Desipramine**
- **Mirtazapine**
- **Valproate**
- **Olanzapine**

Metformin*

Complex 2

Succinate Dehydrogenase

- **Amitriptyline**
- **Imipramine**
- **Citalopram**
- **Venlafaxine**

Complex 3

Cytochrome reductase

- **Paracetamol (Tylenol)****
- **Propofol ****

Complex 4

Cytochrome C oxidase

- Lithium
- Valproate
- Olanzapine
- Desipramine
- Amitriptyline
- Imipramine
- Venlafaxine
- Mirtazapine
- Tianeptine

Aspirin: “Salicylic acid is both an uncoupler and an inhibitor of mitochondrial electron transport” ****

*Source: Rich, R.P., Marechal, A., “The mitochondrial chain”, in “Essays in Biochemistry: Mitochondrial Function”, by Brown, G.C. et al., Portland Press Ltd., 2010, London, with permission; https://pubmed.ncbi.nlm.nih.gov/20588251/; *https://pubmed.ncbi.nlm. nih.gov/31133988/; **Thiamine Deficiency Disease, Dysautonomia and High Calorie Malnutrition, Derrick Lonsdale and Chandler Marrs, p. 87; Coffee, C, “Metabolism”, Quick Look Medicine, p. 47; ****https://www.ncbi.nlm.nih.gov/pmc/articles/PMC316328/*

Curb EMFs because they disrupt cellular homeostasis and the mitochondria so hugely

Electromagnetic fields have been proven to affect the voltage gated calcium channels on your cells, including allowing the influx of iron,[1] as well as excess calcium, which compromises ion exchange. This results in low intracellular magnesium, which cannot flow in because of the excess calcium. Yet magnesium is the rate-limiting substrate for the mitochondria: they cannot produce ATP without it.

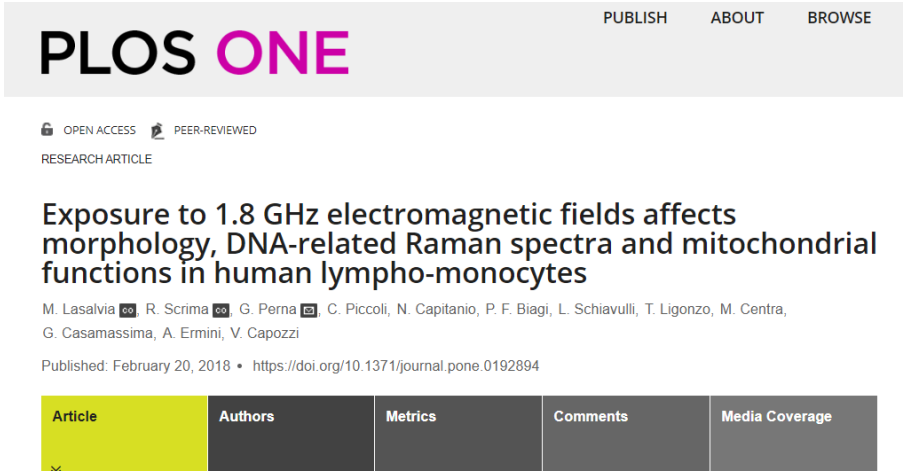
Actions we can take (selection):

Phones, iPads, routers off at night at least. Airplane mode when not needed during the day, hardwire your devices at home. **Anti-radiation airtubes** for the mobile phone.
Anti-radiation underwear
Grounding pad under the computer (groundology.com)
There is much more you can do if you are electrosensitive – fundamental to resolve this to regain mitochondrial function. Various companies can come to **check out your electrical networks** to reduce EMFs as much as possible.

Even wearing glasses with specific coloured lenses can help – **blue-light blockers** in the evening, for example.

https://www.youtube.com/watch?v=8tqYVpC4I1M

Professor Martin Pall – "A Mechanism for Health Impacts of Electromagnetic Fields"



Sources: *1. Gaasch, J.A., Geldenhuys, W.J., Lockman, P.R. et al. Voltage-gated Calcium Channels Provide an Alternate Route for Iron Uptake in Neuronal Cell Cultures. Neurochem Res* ***32,*** *1686–1693 (2007).*

Lipopolysaccharides from gram negative bacteria disable Complex 4 of the electron transport chain

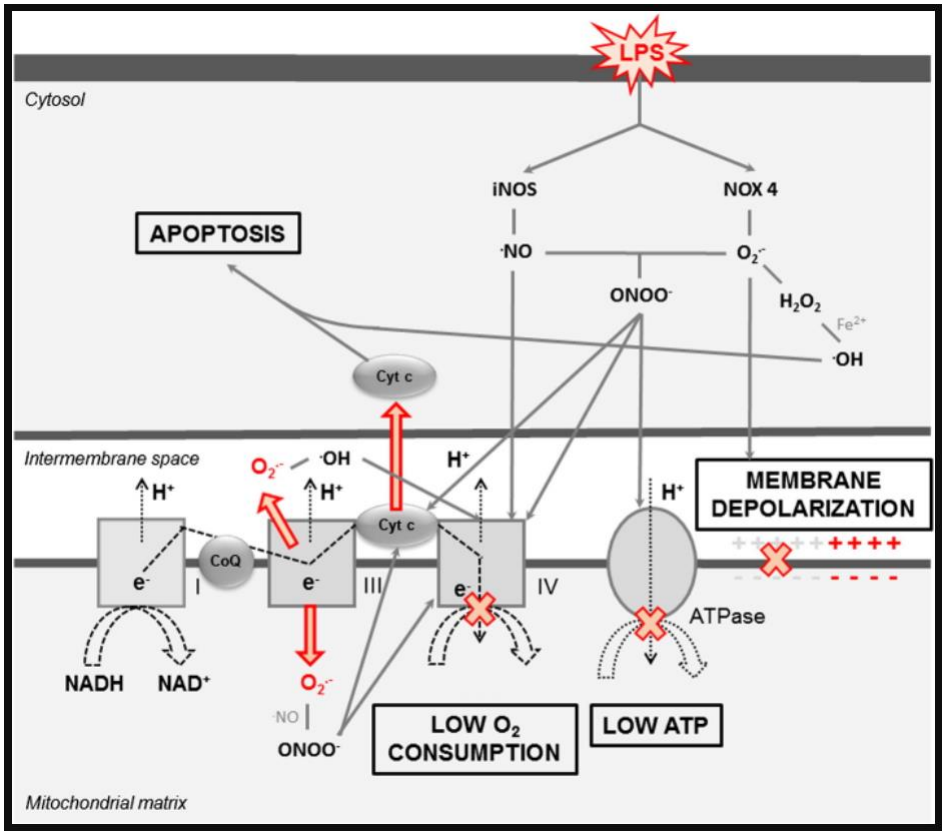
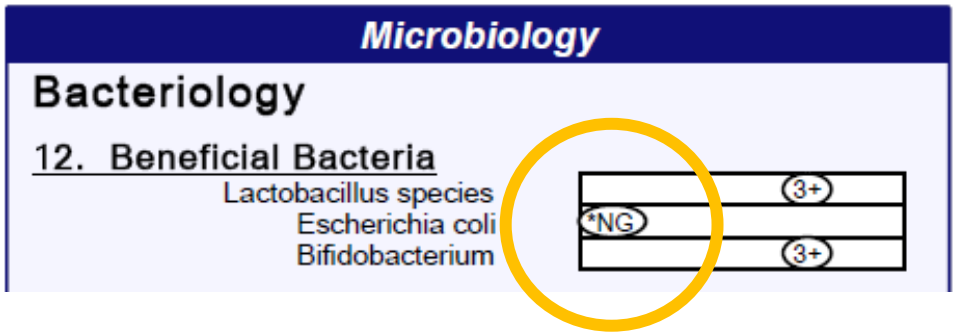


Fig. 8. Proposed mechanism of cytopathic hypoxia according to our experimental results. LPS treatment resulted in a cytosolic oxidative stress induced by the overexpression of NOX-4 and iNOS. **This primary oxidant state interrupted mitochondrial oxidative phosphorylation by reducing cytochrome c oxidase activity. As a consequence, disruptions in the electron transport and the proton pumping across the mitochondrial inner membrane occurred, leading to a decrease of the mitochondrial membrane potential, a release of apoptotic-inducing factors and a depletion of cellular ATP production from ATP synthase.**

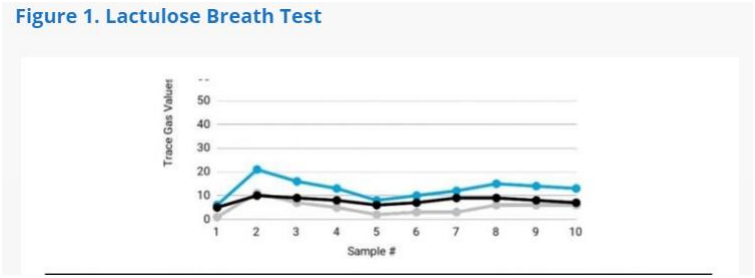
Source: https://www.sciencedirect.com/science/article/pii/S0005272814005313;
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7910823/pdf/pharmaceutics-13-00144.pdf

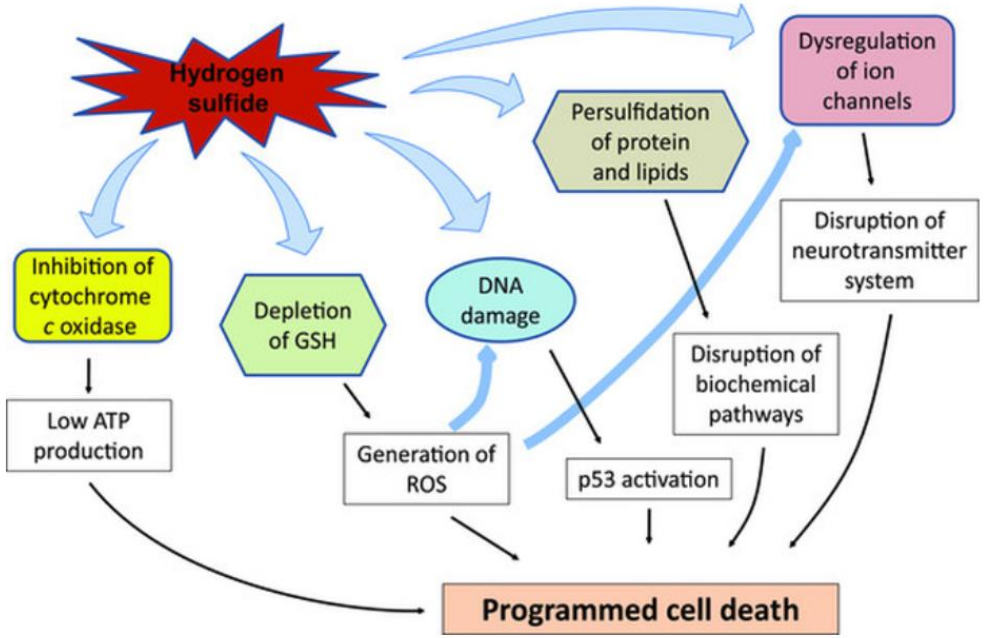
GI issues: dysbiosis and SIBO can block the mitochondria



If your patient has insufficient E Coli, so many of his/her pathways will be disabled for synthesising cofactors essential for the mitochondria

Hydrogen sulphide SIBO causes cytochrome C oxidase deficiency and is toxic to the mitochondria





Rumbeiha, Wilson & Whitley, Elizabeth & Anantharam, Poojya & Kim, Dong-Suk & Kanthasamy, Arthi. (2016). Acute hydrogen sulfide-induced neuropathology and neurological sequelae: Challenges for translational neuroprotective research. Annals of the New York Academy of Sciences. 1378. 10.1111/nyas.13148.

Source: Professor Henry Butt, seminar January 13, 2015; Makowski, GS. Metabolism in chronic fatigue syndrome. Advances in Clinical Chemistry Volume 66, 2014, Pages 121 – 172; http://chemgroups.ucdavis.edu/~toney/Chorismate.html ;
** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5063008/*

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- Address the “Removes“
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Low total, glycolytic and mitochondrial ATP: one key initiative is to improve nutrient access to your cells

Uptake issues

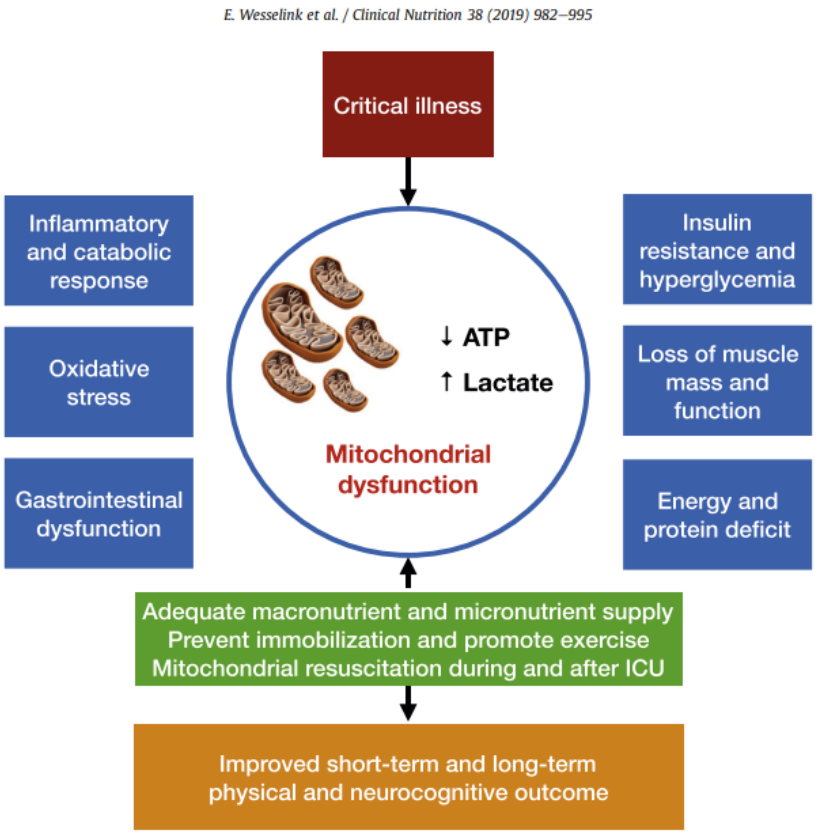
Insulin resistance? An estimated 1 in 3 in the UK are estimated to have prediabetes[1]; the CDC estimates that 85% of those are unaware they have the condition[2]

Digestive issues

Nutritional quality? High-quality natural fats; meat from grass-fed animals
Digestive enzymes for carbohydrates, fats and proteins?
Peristalsis? Upper fermenting gut? Bacterial dysbiosis?

Membrane health

Phospholipids make up 75% of cell membranes
A phospholipid bilayer surrounds all cells and controls what enters and leaves the cell
If this membrane is corrupt, no proper cellular exchange – even excellent nutrition will have limited access to cells
50% of this is phosphotidylcholine



Food sources: e.g. egg yolks, liver, beef cuts, cod, salmon, shrimps, krill oil, soy beans, sunflower seeds

Source: Kane E, Kane P. BodyBio Bulletin: Phosphotidylcholine: Life's Designer Molecule; Nicolson G, Singer SJ (1972). The fluid mosaic model of the structure of cell membranes. Science, 175(4023):720-31; https://pubmed.ncbi.nlm.nih.gov/30201141/

High anaerobic glycolysis

High non-mitochondrial ATP

Glucose can get into the cell, but fuels are not getting into the mitochondria sufficiently – neither glucose nor fats. Lots of lactic acid is formed (pain when high)

High stress (activation of the adrenal pathway/cortisol)

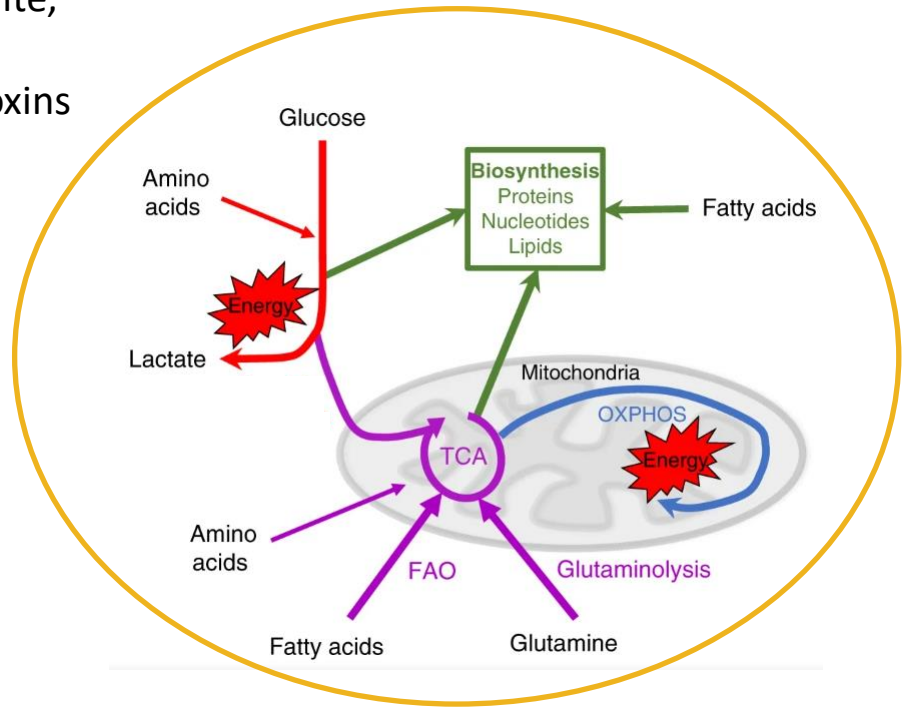
Lack of substrates?

High ROS, forming hydrogen peroxide, peroxynitrite, ferroptosis?

Intracellular pathogens: viruses, bacteria, mycotoxins

Insufficient mitochondria?

Heavy metals, esp. Hg, As, Sb

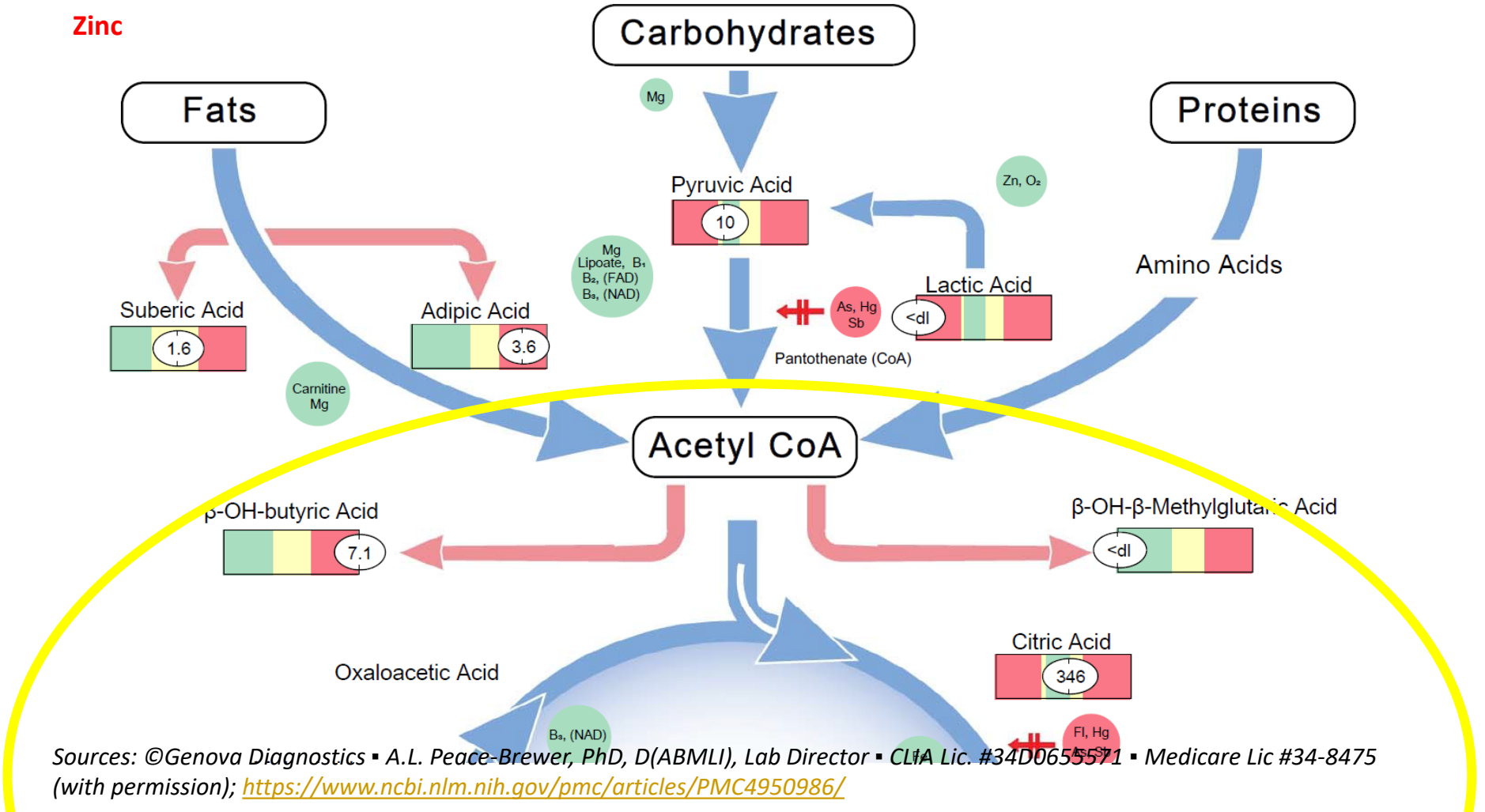


Source: *MMD, O&M und Ernaehrung,* Mitochondrien – texts from 2016/No. 156 through to 2020/No. 171 Prof. Dr. rer. nat. Brigitte König; *mitochondrial research by Martin D. Brand and others (e.g. https://pubmed.ncbi.nlm.nih.gov/28270511/); https://www.nature.com/articles/s41467-019-10015-4*

High non-mitochondrial ATP = strong anaerobic glycolysis: one reason: lack of the right substrates

Particularly important substrates:

Magnesium
Alpha lipoic acid
B1, 2, 3, 5
Carnitine
Zinc

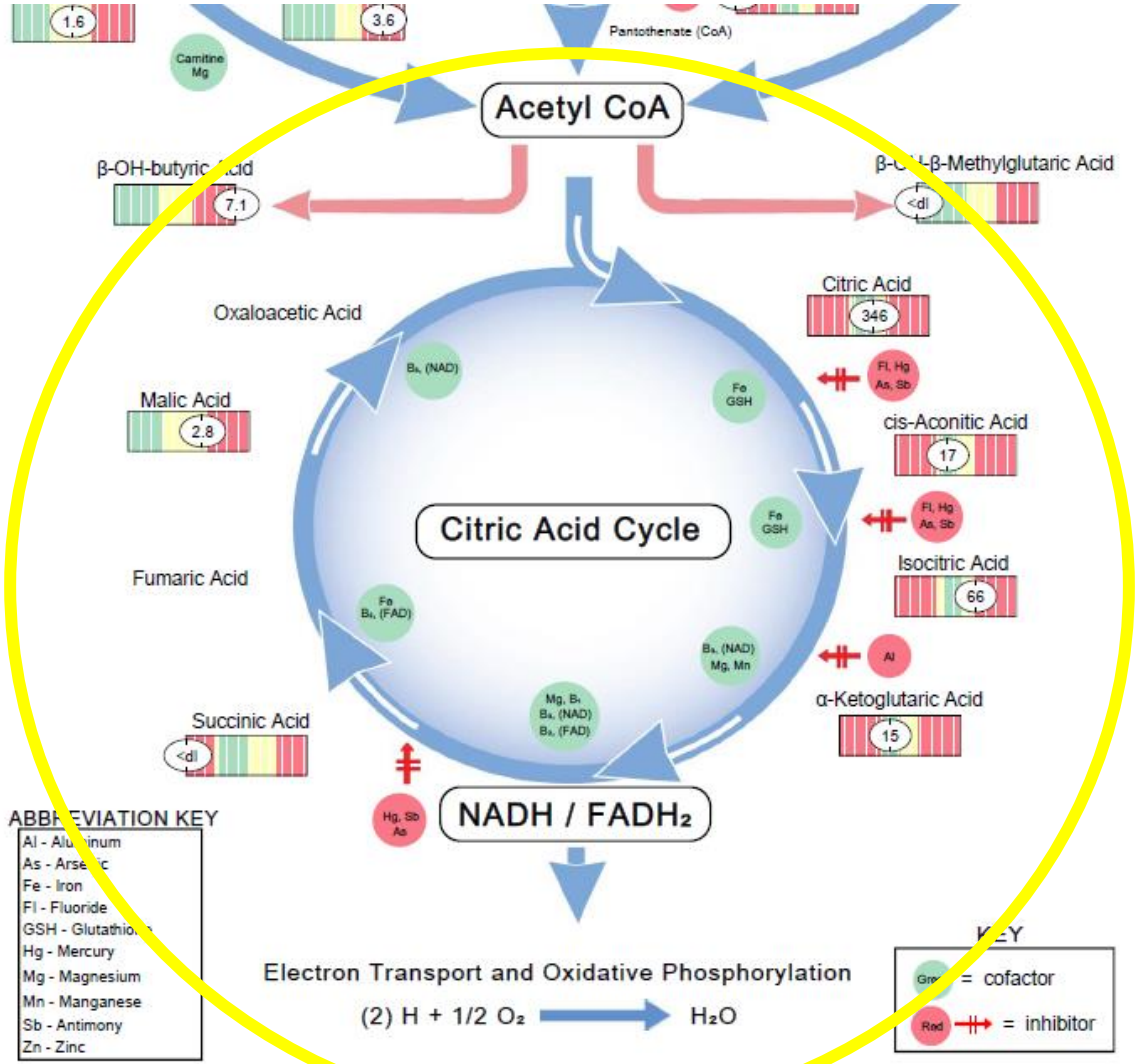


Sources: ©Genova Diagnostics ▪ A.L. Peace-Brewer, PhD, D(ABMLI), Lab Director ▪ CLIA Lic. #34D0655571 ▪ Medicare Lic #34-8475 (with permission); https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4950986/

Intramitochondrial blocks and substrates within the Citric Acid Cycle

Heavy metals:
Fluoride
Mercury
Arsenic
Antimony
Aluminium
Zinc

Substrates mentioned here:
Glutathione
B1
B2
B3
Mg
Mn
Fe
Malic acid/malate



Nicotinamide adenine dinucleotide

Flavin adenine dinucleotide (riboflavin)

Sources: ©Genova Diagnostics ▪ A.L. Peace-Brewer, PhD, D(ABMLI), Lab Director ▪ CLIA Lic. #34D0655571 ▪ Medicare Lic #34-8475 (with permission); https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4950986/

B vitamins vital throughout the entire cycle ... pantothenic acid often neglected

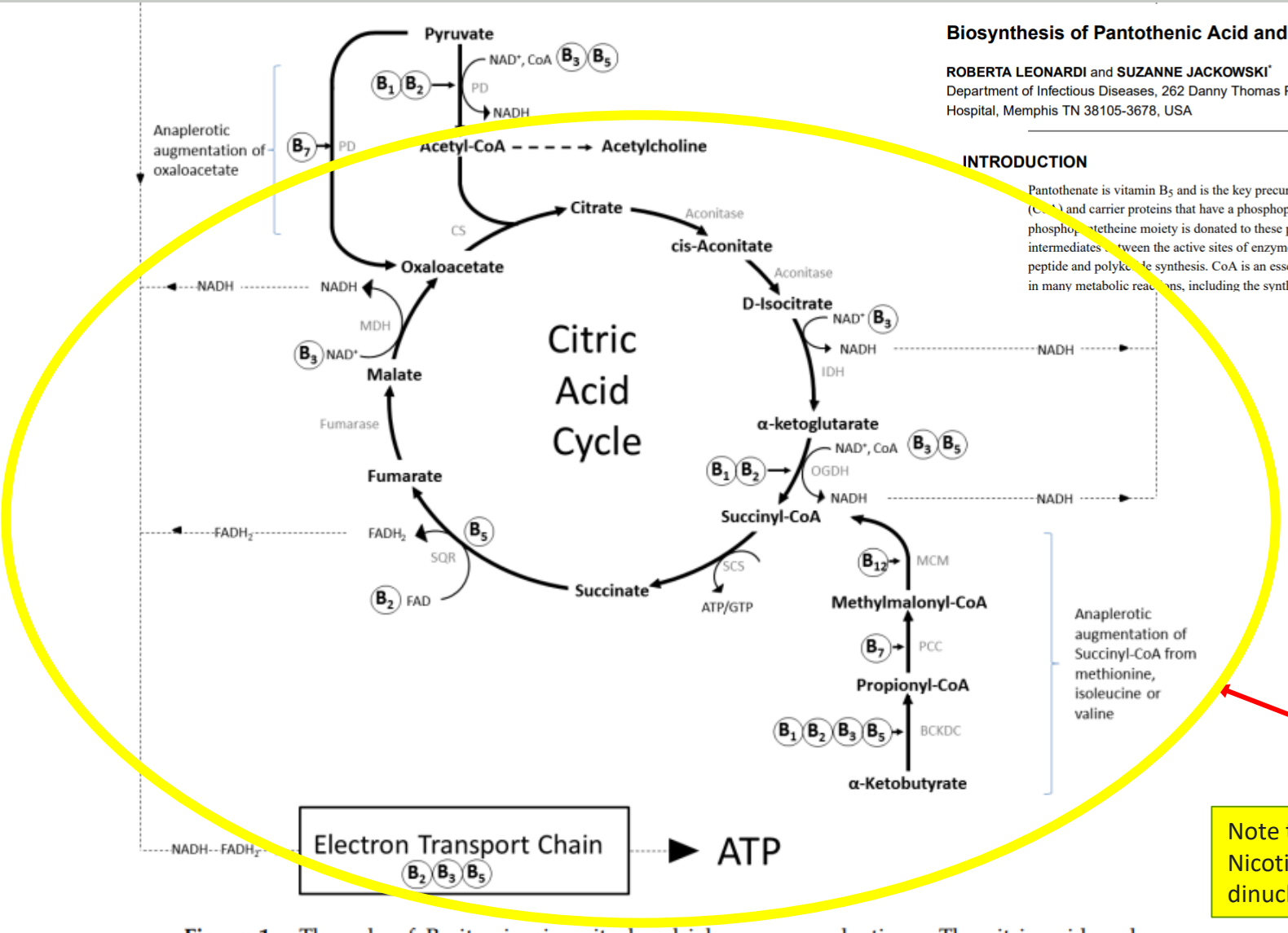


Figure 1. The role of B-vitamins in mitochondrial energy production. The citric acid cycle

Biosynthesis of Pantothenic Acid and Coenzyme A

ROBERTA LEONARDI and **SUZANNE JACKOWSKI***
Department of Infectious Diseases, 262 Danny Thomas Place, St. Jude Children's Research Hospital, Memphis TN 38105-3678, USA

INTRODUCTION

Pantothenate is vitamin B_5 and is the key precursor for the biosynthesis of coenzyme A (CoA) and carrier proteins that have a phosphopantetheine prosthetic group. The phosphopantetheine moiety is donated to these proteins by CoA and is used to shuttle intermediates between the active sites of enzymes involved in fatty acid, non-ribosomal peptide and polyketide synthesis. CoA is an essential cofactor for cell growth and is involved in many metabolic reactions, including the synthesis of phospholipids, synthesis and

B1
B2
B3
B5
B7 (Biotin)
B12

Mitochondrion

Note the huge role of Nicotinamide adenine dinucleotide (NAD)

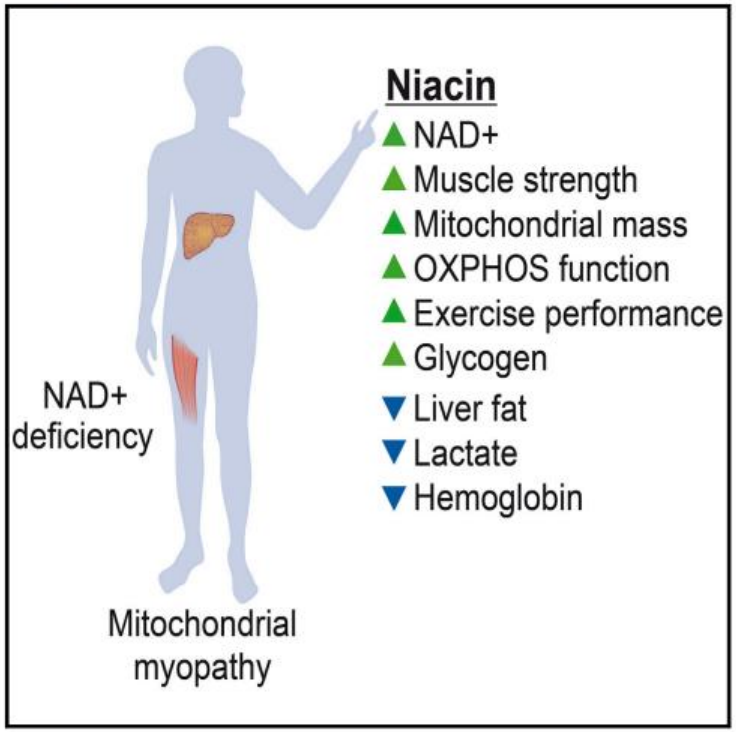
Source: https://www.mdpi.com/2072-6643/8/2/68; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4950986/

... particularly B3 in the form of niacin, in some studies and protocols

Cell Metabolism
Clinical and Translational Report

Niacin Cures Systemic NAD+ Deficiency and Improves Muscle Performance in Adult-Onset Mitochondrial Myopathy

Graphical Abstract



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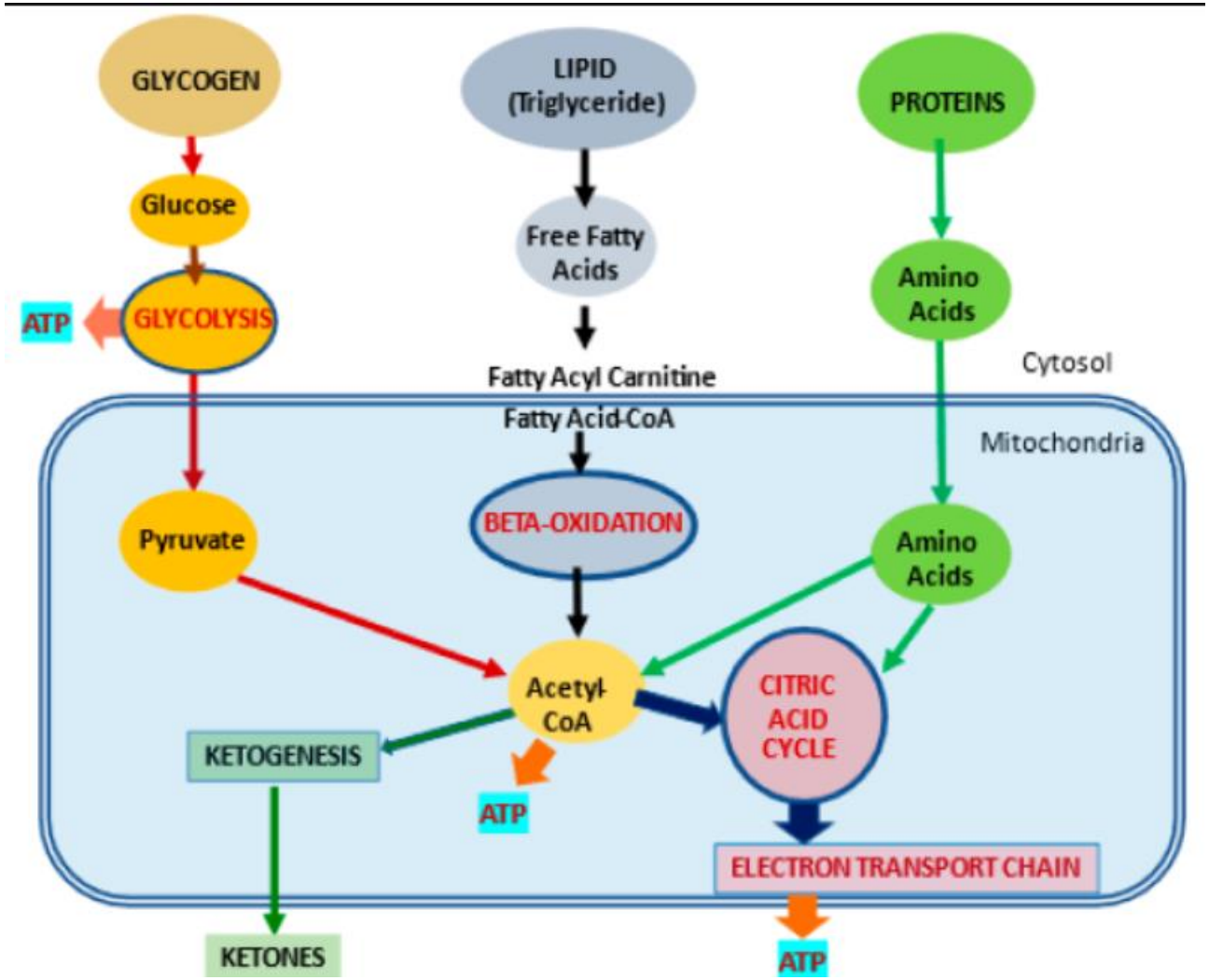
In Brief

Pirinen et al. report that niacin, a vitamin B3, can efficiently rescue NAD+ levels in the muscle and blood of patients with mitochondrial myopathy, improving disease signs and muscle strength. NAD+ levels increased also in healthy subjects. The evidence suggests that niacin is an effective NAD+ booster in humans.

Carnitine is essential to get fatty acids into the mitochondria for beta oxidation



L-carnitine is one of the key nutrients for proper mitochondrial function and is notable for its role in fatty acid oxidation. L-carnitine also plays a major part in protecting cellular membranes, preventing fatty acid accumulation, modulating ketogenesis and glucogenesis and in the elimination of toxic metabolites.

Meat, fish, poultry and milk – dairy products primarily in the whey fraction – also cereals and legumes

Source: https://www.mdpi.com/1422-0067/23/5/2717/htm

Right balance of electrolytes and especially magnesium – the rate-limiting mineral at the end of the ETC – in the “metallome”

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Invited Review Article

Mineral requirements for mitochondrial function: A connection to redox balance and cellular differentiation

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ARTICLE INFO

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Minerals
Metals
Redox
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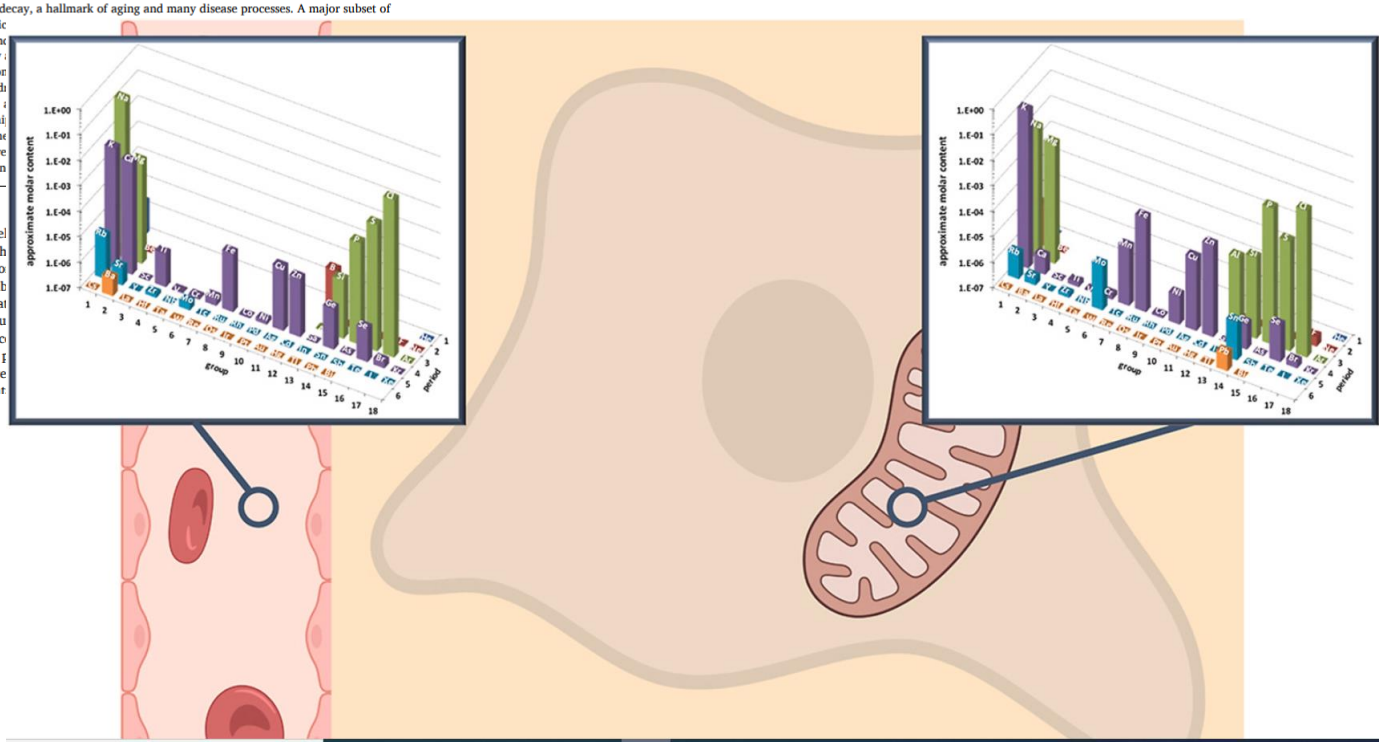
ABSTRACT

Professor Bruce Ames demonstrated that nutritional recommendations should be adjusted in order to ‘tune-up’ metabolism and reduce mitochondria decay, a hallmark of aging and many disease processes. A major subset of tunable nutrients are the minerals, whic
in the typical Western diet. Mitochon
cofactors for mitochondrial physiology
understanding of the form and functio
have known activities in the mitochondr
established mitochondrial function at
understand the patterns and relationshi
brief overview serves to highlight the
mitochondria and to encourage more re
the amounts of specific nutritional min

1. Introduction

In a series of papers beginning 20 years ago, Professor Bruce Ames proposed that the recommended intake for essential micronutrients should be reset to promote optimal health rather than just avoiding acute disease – a campaign he called ‘tuning up metabolism’ [1–3]. Central to this proposal is boosting the metabolism of the mitochondria [4], which Professor Ames and others postulated was the fulcrum for the pathological processes that drive aging and senescence [5–8]. Of the 40–50 micronutrients required for human physiology, most can be



Source: https://www.sciencedirect.com/science/article/pii/S0891584922000752

The CDR: "An evolutionarily conserved response activated when a cell encounters a threat that could injure or kill it"

Contents lists available at ScienceDirect

Mitochondrion

journal homepage: www.elsevier.com/locate/mito

Metabolic features of the cell danger response

Threats:

- **Biological** – viruses, bacteria, fungi, parasites
- **Chemical** – e.g. heavy and trace metals like lead, mercury, cadmium, arsenic, and nickel, gadolinium*, certain electrophilic aromatic chemicals like the plasticizer bisphenol A, chemical flame retardants like brominated diphenyl ethers (BDEs), and certain halogenated pesticides like chlorpyrifos and DDT.
- **Physical** – e.g. heat, salt, pH shock, UV/ionising radiation ...

... Our mitochondria downregulate as a protective mechanism

*Source: Naviaux RK. Metabolic features of the Cell Danger Response. Mitochondrion. 2014 May;16:7-17; * Bower DV et al. Gadolinium-Based MRI Contrast Agents Induce Mitochondrial Toxicity and Cell Death in Human Neurons, and Toxicity Increases With Reduced Kinetic Stability of the Agent. Invest Radiol. 2019 Aug;54(8):453-463.*

The oxygen “switch”

“When mitochondrial electron transport decreases for any reason, fewer molecules of oxygen are converted to water (H2O) by cytochrome c oxidase. If capillary delivery of oxygen to the cell is unchanged, the concentration of dissolved oxygen rises in the cell like water in a bowl in response to instantaneous decreases in mitochondrial oxygen consumption.”

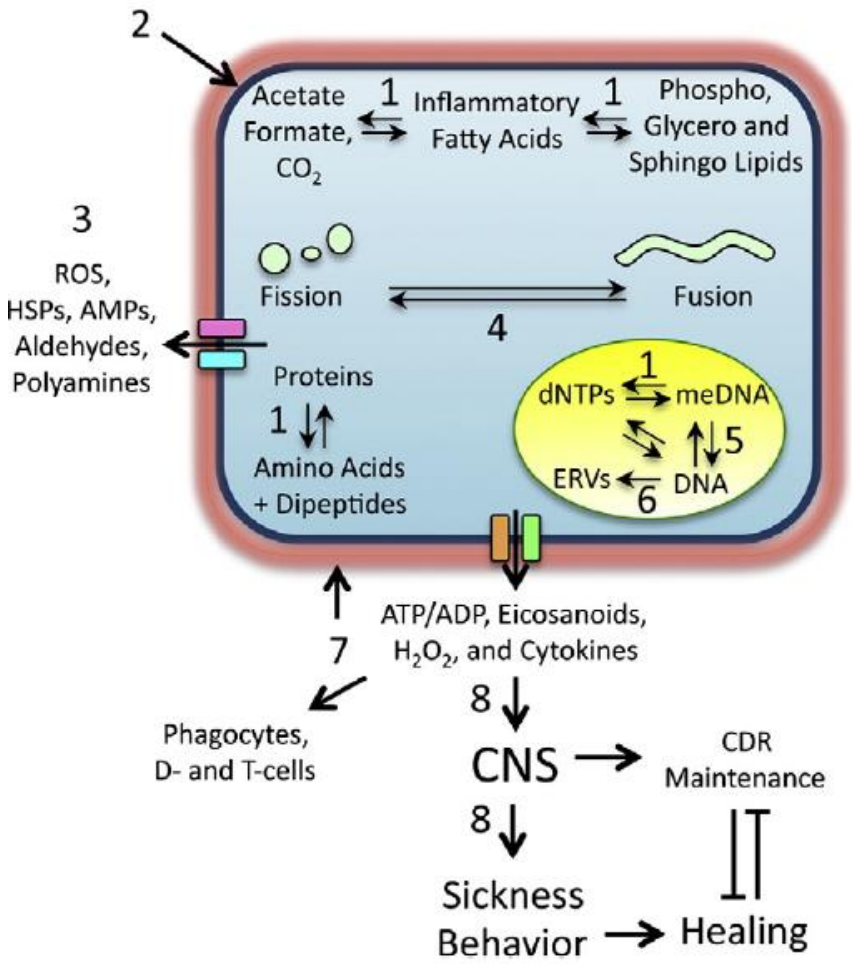
This change in pH alters the activity of the myriad of enzymes that are kinetically regulated by the availability of dissolved oxygen and can act as oxygen sensors.

“Some of these [that are upregulated] include NADPH oxidases like Nox4 (53) that make hydrogen peroxide (H2O2) from the excess diatomic oxygen (O2) to initiate the oxidative shielding response (6).”

Source: 1. Naviaux RK. Metabolic features of the Cell Danger Response. Mitochondrion. 2014 May;16:7-17; 2. Robert K. Naviaux. Oxidative Shielding. Journal of Pharmacology and Experimental Therapeutics September 1, 2012, 342 (3) 608-618

What are the immediate results of acute CDR?

1) Mitochondria decrease oxygen consumption to oxidise the cellular environment, inhibiting assembly of monomeric building blocks into polymers, thus decreasing efficiency of RNA, protein, and DNA synthesis by the infecting pathogen
2) Stiffen cell membranes to limit pathogen egress
3) Release of antiviral and antimicrobial chemicals
4) Increase in autophagy/mitochondrial fission/mitophagy
5) Changes in DNA methylation: SAM is directed to polyamine synthesis to assist ROS and antiviral/antimicrobial polyamine aldehyde synthesis and release, lowering the SAM/SAH ratio
6) ERVs mobilised
7) Warning with extracellular nucleotides
8) Altered host behaviour



Source: Naviaux RK. Metabolic features of the Cell Danger Response. Mitochondrion. 2014 May;16:7-17

Excess ATP utilisation in the mitochondria at rest, high nrf2: reduce oxidative stress

"Usually, iron release from a cell occurs via ferroportin (Fpn) [37–41] a membrane bound iron exporter, which is controlled by hepatocyte derived hepcidin [42,43], the hepcidin activity itself being regulated by the serine protease matriptase-2 [44,45]. The ferroportin-released iron is then directly transferred to transferrin by aid of the multi-copper ferroxidases hephaestin and caeruloplasmin [39,46–48]."[3]

"Release of iron from the liver relies on ferroportin and the ferroxidase activity of ceruloplasmin which is found in blood in a soluble form."[3]

Release of that trapped iron requires copper on its carrier, caeruloplasmin (Cp)

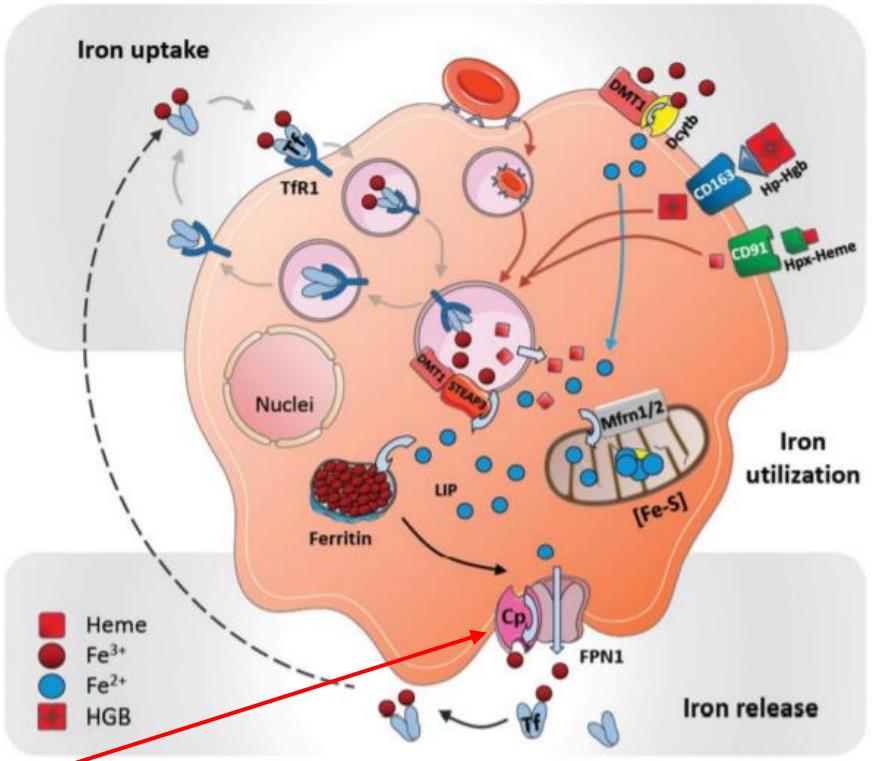


Figure 1. Iron metabolism by macrophages. General steps of iron uptake, acquisition, storage and release in the macrophage: In addition to iron extraction from red blood cells by erythrophagocytosis, macrophages express a variety of receptors to acquire iron from different sources. Transferrin-bound iron can be taken up by the transferrin receptor (TfR or CD71) and the complex is internalized by clathrin coated endocytosis followed by iron release at a low endosomal pH. Empty apo-transferrin and transferrin receptor complex are recycled again (grey arrows). Non-transferrin iron can be acquired

Source: www.rcp123.org; 2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4496698/pdf/biomolecules-05-00808.pdf; 3. Vashchenko, G.; MacGillivray, R. Multi-copper oxidases and human iron metabolism. Nutrients 2013, 5, 2289–2313

Retinol is the backbone of the multi-copper ferroxidase, caeruloplasmin

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"Retinol is the backbone of the ferroxidase enzyme that is so critical for chaperoning iron, and retinol loads copper into ferroxidase. Interestingly, studies of anemia have illustrated vitamin A's importance.[35] Although
we measure anemia via hemoglobin, adding iron does not meaningfully restore normal hemoglobin levels—
but vitamin A does. In addition to high-quality cod liver oil, good sources of retinol include liver, pastured eggs and butter (preferably from raw milk)."[1]

The FASEB Journal
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FASEB J. 2010 Feb; 24(2): 627–636.
doi: 10.1096/fj.09-142281

PMCID: PMC2812036
PMID: 19812372

Control of oxidative phosphorylation by vitamin A illuminates a fundamental role in mitochondrial energy homoeostasis

Rebeca Acin-Perez,[*] Beatrice Hoyos,[‡] Feng Zhao,[‡] Valerie Vinogradov,[‡] Donald A. Fischman,[†] Robert A. Harris,[§] Michael Leitges,[‖] Nuttaporn Wongsiriroj,[¶] William S. Blaner,[#] Giovanni Manfredi,[*] and Ulrich Hammerling[‡]

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"Here we show that retinol is essential for the metabolic fitness of mitochondria."

Associated Data

▸ Supplementary Materials

Abstract Go to: ▸

The physiology of two metabolites of vitamin A is understood in substantial detail: retinaldehyde functions as the universal chromophore in the vertebrate and invertebrate eye; retinoic acid regulates a set of vertebrate transcription factors, the retinoic acid receptor superfamily. The third member of this retinoid triumvirate is retinol. While functioning as the precursor of retinaldehyde and retinoic acid, a growing body of evidence suggests a far more fundamental role for retinol in signal transduction. Here we show that retinol is essential for the metabolic fitness of mitochondria. When cells were deprived of retinol, respiration and ATP synthesis defaulted to basal levels. They recovered to significantly higher energy output as soon as retinol was restored to physiological concentration, without the need for metabolic conversion to other retinoids.[2]

Source: 1. https://www.westonaprice.org/health-topics/toxic-iron-and-ferroxidase-the-master-antioxidant/, 2. https://pubmed.ncbi.nlm.nih.gov/3655940/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2812036/; www.rcp123.org

Evidence available on the retinol fraction of vitamin A – the science has been evident for decades

Table 1. *Weight gain, feed consumption, haemoglobin (HGB), relative liver weight, serum ceruloplasmin and cholesterol, and liver zinc–copper superoxide dismutase (EC 1.15.1.1) (Zn-CuSOD) in rats fed on diets containing various levels of retinyl acetate, zinc, and copper**

(Mean values and standard deviations for ten rats per group)

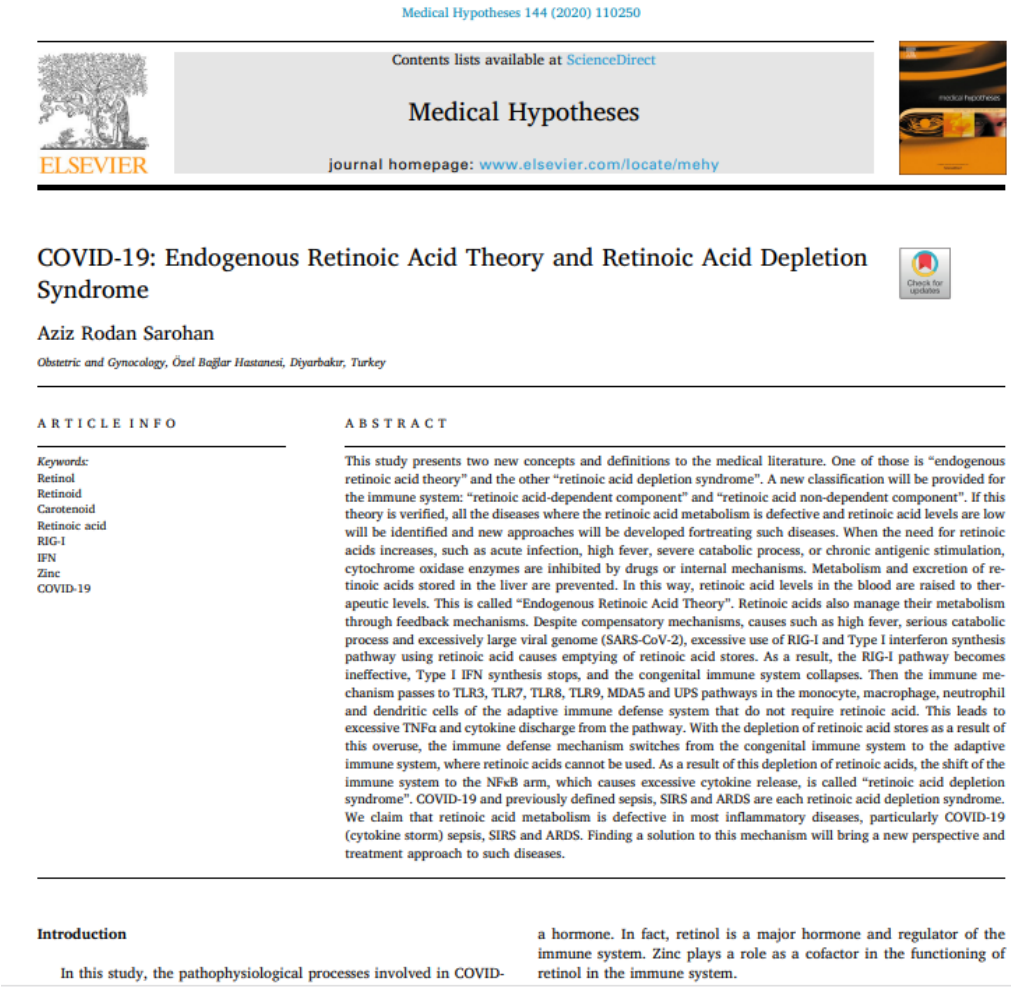
Dietary level (mg/kg)			Weight gain (g)		Feed intake (g)		HGB (g/l)		Liver weight (% of body wt)		Serum ceruloplasmin (Units/l)		Serum cholesterol (mmol/l)		Liver Zn-CuSOD (mg/g)	
Retinyl acetate	Zinc	Copper	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
1·4	12	5	123	10	401	25	139	22	4·0	0·3	79	15	2·41	0·26	1·16	0·25
1·4	12	50	125	10	403	21	148	33	4·0	0·3	85	11	2·41	0·18	1·13	0·32
1·4	240	5	119	11	394	36	136	17	3·9	0·3	43	31	2·90	0·36	0·90	0·29
1·4	240	50	114	6	374	17	159	14	4·0	0·2	104	13	2·85	0·47	1·08	0·28
34·4	12	5	121	12	403	34	161	12	4·1	0·3	100	8	2·82	0·28	1·16	0·32
34·4	12	50	118	8	398	31	159	20	3·9	0·2	113	17	3·21	0·57	1·14	0·30
34·4	240	5	125	6	406	26	151	13	4·0	0·3	59	49	3·39	0·49	0·85	0·33
34·4	240	50	125	11	411	34	151	9	3·9	0·2	109	18	3·18	0·59	1·02	0·22
206·4	12	5	120	8	413	35	144	12	4·2	0·2	162	24	3·34	0·59	1·10	0·28
206·4	12	50	116	11	411	19	157	6	4·1	0·3	185	15	3·31	0·52	1·14	0·25
206·4	240	5	118	8	410	32	147	9	4·2	0·2	126	53	2·95	0·39	1·01	0·17
206·4	240	50	116	14	424	38	146	10	4·2	0·2	159	16	3·00	0·59	1·15	0·26
Analysis of variance (2 × 2 × 3): *P* =																
Copper			NS		NS		0·0221		NS		0·0001		NS		NS	
Zinc			NS		NS		NS		NS		0·0001		NS		0·0075	
Copper × zinc interaction			NS		NS		NS		NS		0·0006		NS		NS	
Vitamin A			NS		0·0059		0·0285		0·0002		0·0001		0·0001		NS	
Copper × vitamin A interaction			NS		NS		NS		NS		NS		0·041		NS	
Zinc × vitamin A interaction			0·0234		NS		NS		NS		NS		0·0007		NS	
Copper × zinc × vitamin A interaction			NS		NS		NS		NS		NS		NS		NS	

* For details of diets and procedures, see pp. 916–918.

"Serum ceruloplasmin was significantly higher in rats fed on diets with increased dietary vitamin A (Table 1). A two-way interaction between Cu and Zn also affected serum ceruloplasmin activity"

Source: https://www.cambridge.org/core/journals/british-journal-of-nutrition/article/interactions-in-indices-of-vitamin-a-zinc-and-copper-status-when-these-nutrients-are-fed-to-rats-at-adequate-and-increased-levels/403AC96660C617812248DBBB9E90E538

Mitochondrial antiviral signalling (MAVS) is retinol-dependent



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COVID-19: Endogenous Retinoic Acid Theory and Retinoic Acid Depletion Syndrome

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Obstetric and Gynecology, Özel Bağlar Hastanesi, Diyarbakır, Turkey

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ABSTRACT

This study presents two new concepts and definitions to the medical literature. One of those is "endogenous retinoic acid theory" and the other "retinoic acid depletion syndrome". A new classification will be provided for the immune system: "retinoic acid-dependent component" and "retinoic acid non-dependent component". If this theory is verified, all the diseases where the retinoic acid metabolism is defective and retinoic acid levels are low will be identified and new approaches will be developed fortreating such diseases. When the need for retinoic acids increases, such as acute infection, high fever, severe catabolic process, or chronic antigenic stimulation, cytochrome oxidase enzymes are inhibited by drugs or internal mechanisms. Metabolism and excretion of retinoic acids stored in the liver are prevented. In this way, retinoic acid levels in the blood are raised to therapeutic levels. This is called "Endogenous Retinoic Acid Theory". Retinoic acids also manage their metabolism through feedback mechanisms. Despite compensatory mechanisms, causes such as high fever, serious catabolic process and excessively large viral genome (SARS-CoV-2), excessive use of RIG-I and Type I interferon synthesis pathway using retinoic acid causes emptying of retinoic acid stores. As a result, the RIG-I pathway becomes ineffective, Type I IFN synthesis stops, and the congenital immune system collapses. Then the immune mechanism passes to TLR3, TLR7, TLR8, TLR9, MDA5 and UPS pathways in the monocyte, macrophage, neutrophil and dendritic cells of the adaptive immune defense system that do not require retinoic acid. This leads to excessive TNFα and cytokine discharge from the pathway. With the depletion of retinoic acid stores as a result of this overuse, the immune defense mechanism switches from the congenital immune system to the adaptive immune system, where retinoic acids cannot be used. As a result of this depletion of retinoic acids, the shift of the immune system to the NFκB arm, which causes excessive cytokine release, is called "retinoic acid depletion syndrome". COVID-19 and previously defined sepsis, SIRS and ARDS are each retinoic acid depletion syndrome. We claim that retinoic acid metabolism is defective in most inflammatory diseases, particularly COVID-19 (cytokine storm) sepsis, SIRS and ARDS. Finding a solution to this mechanism will bring a new perspective and treatment approach to such diseases.

Introduction

In this study, the pathophysiological processes involved in COVID-

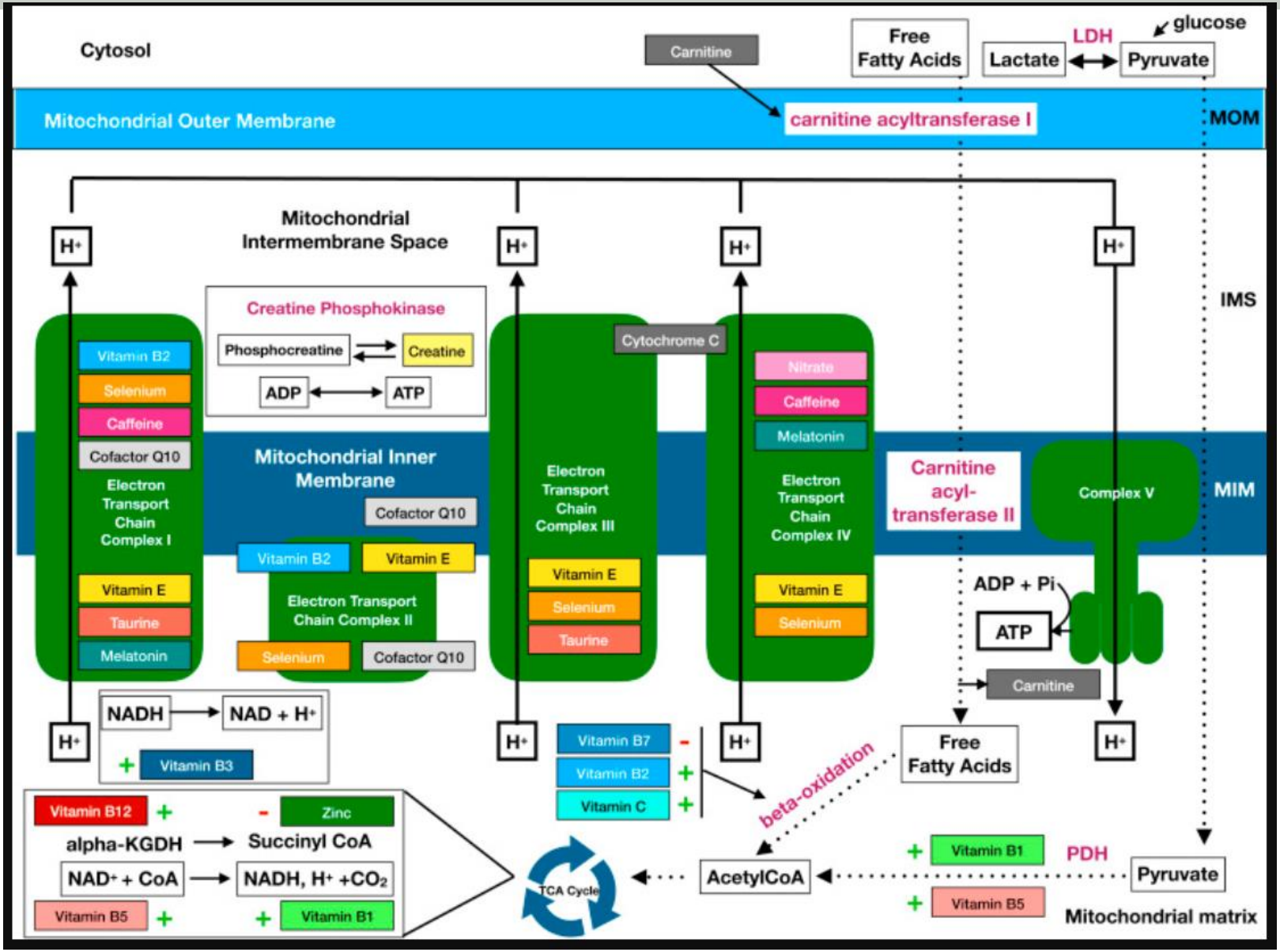
a hormone. In fact, retinol is a major hormone and regulator of the immune system. Zinc plays a role as a cofactor in the functioning of retinol in the immune system.

"Innate immunity provides the first line of host defense against invading microbial pathogens. **This defense involves retinoic acid**-inducible gene-I–like **receptors that** detect viral RNA and **activate the mitochondrial antiviral-signaling** (MAVS) **protein**, an adaptor protein, **leading to activation of the innate antiviral immune response**."[2]

Retinol hugely important for all pathways: iron dysregulation, mitochondrial, viral infections

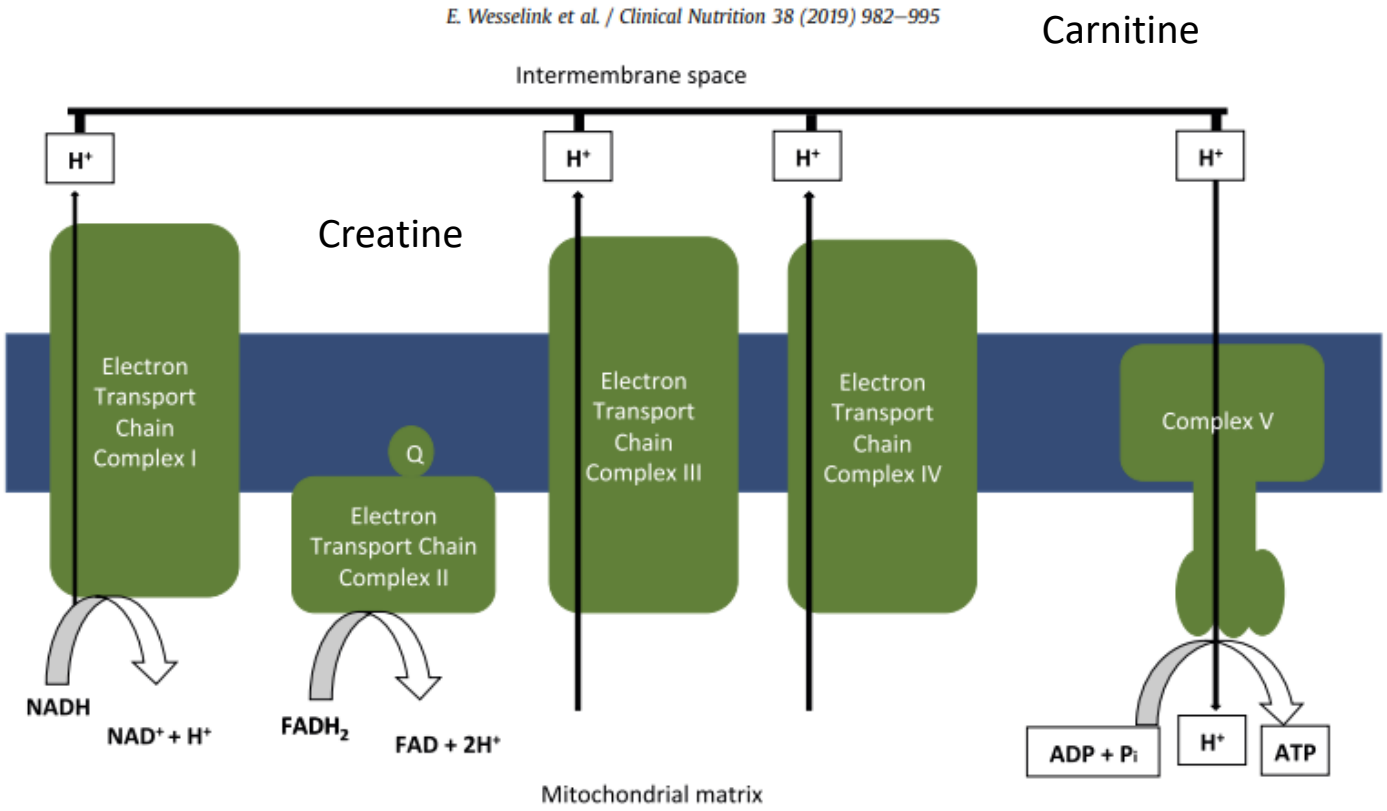
Source: Seth RB, Sun L, Ea CK, Chen ZJ. Identification and characterization of MAVS, a mitochondrial antiviral signaling protein that activates NF-kappaB and IRF 3. Cell. 2005 Sep 9;122(5):669-82; https://pubmed.ncbi.nlm.nih.gov/16125763/; https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC3099591/; https://www.nature.com/articles/s41598-017-05808-w.pdf; 2. https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC3099591/

Proton leak – blocks along the complexes?



Source: *Wesselink E, Koekkoek WAC, Grefte S, Witkamp RF, van Zanten ARH. Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence. Clin Nutr. 2019 Jun;38(3):982-995,* https://pubmed.ncbi.nlm.nih.gov/30201141/

Summary of the nutrients mentioned in Wesselink et al



Complex 1: B12, Se, CoQ10, Vit E, Taurine, melatonin, caffeine

Complex 2: B2, Vit E (α,-tocopherol), Se, CoQ10

Complex 3: Vit E, Se, Taurine

Complex 4: Melatonin, tocopherol, Se, caffeine

Complex 5: Mg

Source: *Wesselink E, Koekkoek WAC, Grefte S, Witkamp RF, van Zanten ARH. Feeding mitochondria: Potential role of nutritional components to improve critical illness convalescence. Clin Nutr. 2019 Jun;38(3):982-995; Yamanaka, R. et al. (2016). Mitochondrial Mg(2+) homeostasis decides cellular energy metabolism and vulnerability to stress. Scientific reports, 6, 30027. https://doi.org/10.1038/srep30027*

The Cu-Cp-retinol link connects with blocks along the complexes, too: most mitochondrial proteins are Cu-dependent ...

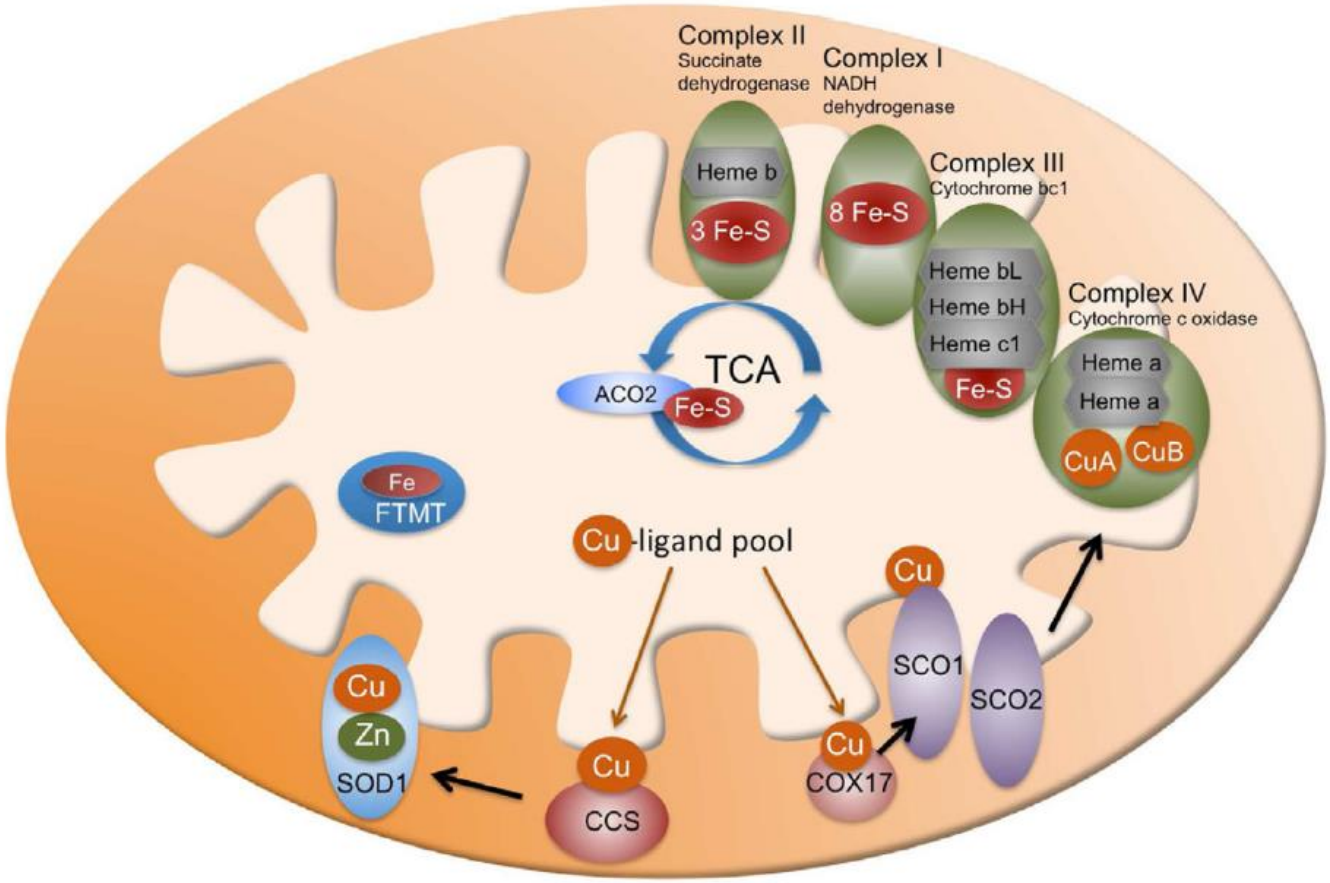


Figure 1. Mitochondrial proteins containing Fe and Cu

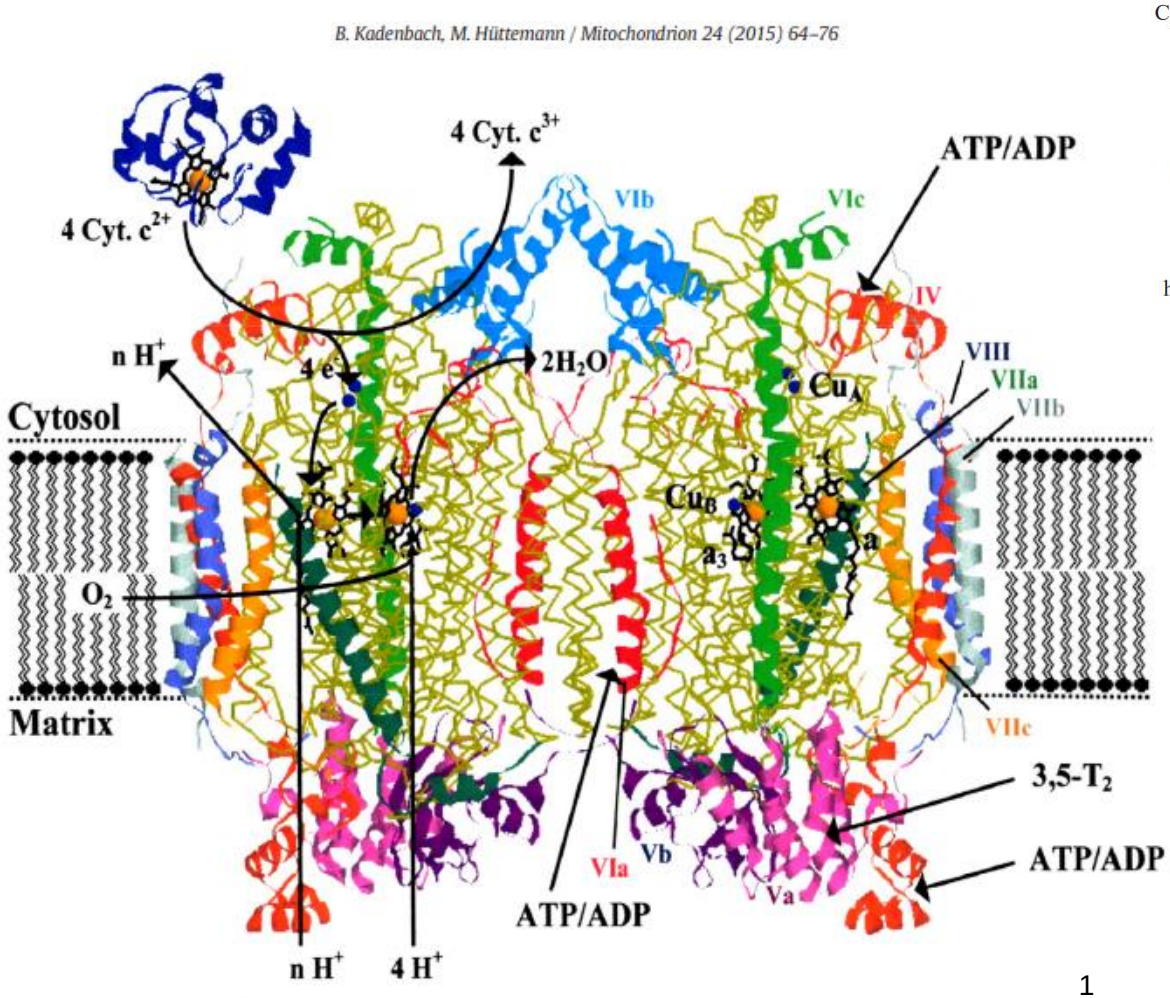
Complexes I to IV of the electron transport chain require Fe-S clusters, heme moieties and Cu centers to function. Complex II functions both in electron transport and also in the tricarboxylic acid (TCA) cycle. Complexes I, III and IV co-purify (not depicted here). Mitochondrial aconitase (ACO2), another TCA cycle enzyme, contains an Fe-S cluster. Complex IV acquires Cu from a copper-ligand pool in the mitochondrial matrix through the action of cytochrome c oxidase assembly factors COX17, SCO1 and SCO2. Cu-Zn superoxide dismutase (SOD1) contains Cu provided by the Cu chaperone CCS. Mitochondrial ferritin (FTMT) can store Fe.

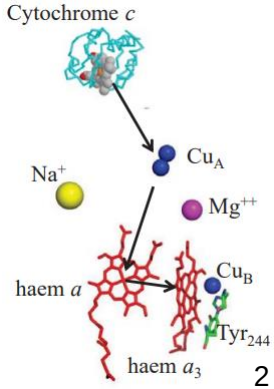
Source: Xu W, Barrientos T, Andrews NC. Iron and copper in mitochondrial diseases. Cell Metab. 2013 Mar 5;17(3):319-28.

Copper subunits in Complex 4 are key to its function, too

The copper-dependent enzyme, cytochrome *c* oxidase, plays a critical role in cellular energy production.
By catalyzing the reduction of molecular oxygen (O_2) to water (H_2O), cytochrome *c* oxidase generates an electrical gradient used by the mitochondria to create the vital energy-storing molecule, ATP

Linus Pauling Institute
https://lpi.oregonstate.edu/mic/minerals/copper





2

The rate of **haem synthesis** correlates with cytochrome oxidase activity, too [2]

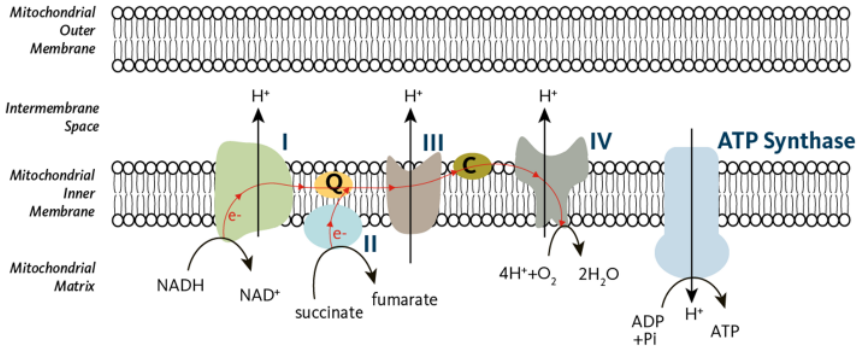
1

Heme–copper oxidases (HCuOs) terminate the respiratory chain in mitochondria **and most bacteria**. [3]

Fig. 2. Crystal structure of dimeric COX from bovine heart (Tsukihara et al., 1996). The nuclear-coded subunits are in color, the mitochondrial-coded subunit I, II and III are in yellow. Indicated are schematically on the left monomer the electron transport pathways from cytochrome *c* (Cyt. c) to oxygen accompanied by uptake of protons from the matrix for water formation and pumped protons (nH^+). On the right monomer binding sites for 3,5-diiodothyronine (T_2) and ATP or ADP are indicated. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Source: *1. Kadenbach B, Hüttemann M. The subunit composition and function of mammalian cytochrome c oxidase. Mitochondrion. 2015 Sep;24:64-76; 2; Rich PR. Mitochondrial cytochrome c oxidase: catalysis, coupling and controversies. Biochem Soc Trans. 2017 Jun 15; 45(3):813-829; 3. https://www.sciencedirect.com/science/article/pii/S0005272811002398; www.rcp123.org*

The miracle of CoQ10



Coenzyme Q_{10} is a lipid-soluble component of the mitochondrial inner membrane that is critical to electron transport (in red) in the mitochondrial respiratory chain. Coenzyme Q_{10} carries electrons from complexes I and II to complex III, thus participating in ATP production. *C, cytochrome C; e-, electron; H+, proton; Q, coenzyme Q_{10}*

CoQ10 has often been termed "the hub around which life processes revolve in the human body." Coenzyme Q (also called ubiquinone) is the first electron carrier in the electron transport chains of our mitochondria, the powerhouses of ATP synthesis in our cells. The benzoquinone head group of coenzyme Q10 has been called nature's favourite electron acceptor: it takes up electrons from reducing equivalents generated during both glucose and fatty acid metabolism and ferries them to electron acceptors. Without CoQ10 there would be no aerobic energy production: mammalian life would ultimately cease to exist. It is also the only lipid-soluble antioxidant produced by humans and localises to almost every membrane preventing lipid peroxidation, regenerating the reduced state of antioxidants such as a-tocopherol and ascorbic acid. Other functions of CoQ10 in cell membranes include metabolic regulation, cell signalling and cell growth through local regulation of cytosolic redox intermediates such as NAD(P)H.

The "10" in CoQ10's name comes from its polyisoprene tail consisting of 10 isoprene subunits. The ring structure of quinone (the "Q" in coenzyme Q) is synthesised from tyrosine, while the isoprene sidechain is derived from the mevalonate pathway that also produces cholesterol. This is a very complex process and any defects in the enzymes, cofactors, or dietary nutrient deficiencies can impair its biosynthesis.

Studies have shown that CoQ10 provides both protection against and vital support in the case of a host of illnesses, from ME and fibromyalgia to Alzheimer's, Parkinson's and even amyotrophic lateral sclerosis. Any deficiency in CoQ10 can clearly have an impact on energy metabolism as well as contributing to dysfunction/disease of every

spinach and cauliflower - but not in high enough levels that food sources could cover our entire needs. It is synthesised endogenously in every cell of the body, but its concentrations decline gradually with age.

More pernicious threats impair our supplies of CoQ10 too. E. coli bacteria synthesise a molecule called chorismate, an essential precursor for the biosynthesis of the quinone nucleus of coenzyme Q. For this, E coli (and all other bacteria) need the "Shikimate" pathway - and it is exactly this that is specifically disrupted by glyphosate, the world's most prevalent herbicide. So, our access to endogenous CoQ10 is being throttled by the increasing use of this ubiquitous chemical. Statins are another threat: statins block the mevalonate pathway, but it is here that the isoprenoid side chains of CoQ10 are biosynthesised.

Ubiquinone or ubiquinol - does it matter?

Ubiquinol is the reduced form of ubiquinone. Much has been made of the need to take the reduced form over recent years, but how much does it actually matter? Both ubiquinone and ubiquinol are lipid soluble due to the presence of the 10-unit isoprene tail. They act as a redox pair where the conversion of one form to the other can be readily achieved depending on when and where [illegible] are needed in the body [illegible] tissues that involve high ae[illegible] ontain more of the oxidised [illegible] ne) than the reduced form[illegible] n, around 95% of Co[illegible] e ubiquinol form. Ex[illegible] absorbed in the sm[illegible] nters the circulation via [illegible] em. Before absorption, [illegible] d to the reduced for[illegible] enterocytes.

So, when taken [illegible] reat

Source: https://lpi.oregonstate.edu/mic/dietary-factors/coenzyme-Q10; *https://www.sciencedirect.com/science/article/pii/S0005272816300573*

A supplement supplier that has dedicated itself to the mitochondria for over two decades

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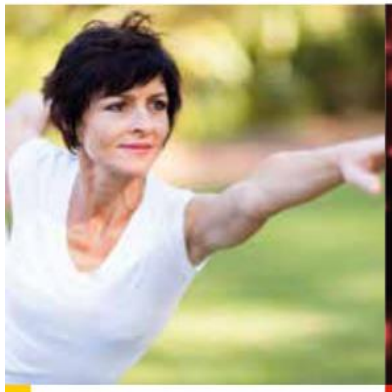

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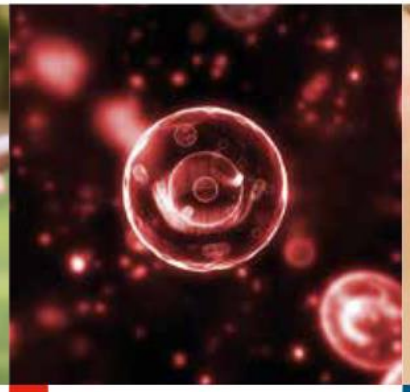

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Unique spectrum of products to restore mitochondrial function, without any additives/excipients

Study conducted by MMD Lab analysed the capacity of a range of the products for mitobiogenesis, ATP generation and mitochondrial metabolism

Professor B. König, Leipzig | Ralf Meyer, Naturopath, Pirmasens, Germany

Mitochondrial analysis Part 1

Activating mitochondrial biogenesis (1), mitochondrial ATP generation (2) and mitochondrial metabolism (1) from peripheral leukocytes (1) and isolated mitochondria (2) using micro- and macronutrient supplements

KEYWORDS

In vitro mitochondrial analysis on isolated human peripheral blood mononuclear cells (PBMC)/mitochondria, stimulation of mitochondrial biogenesis, PGC-1alpha, aerobic mitochondrial ATP – stimulation, activation of mitochondrial metabolism, simple blind testing of the activation of the above parameters, giving micro-/macronutrient supplements in varying doses and with differing incubation times.

SUMMARY

Both the functional as well as the structural integrity of the mitochondria play a key role in the development of numerous disorders.

Part 1 of this publication presents the results of the analyses into whether the parameters measured in cells or isolated mitochondria can be influenced by micro-/macronutrient supplements.

Peripheral blood mononuclear cells (PBMCs) were isolated from the blood of four patients (three female and one male) with differing pathologies, and various parameters of mitochondrial integrity and functionality were determined in the absence (as a control) and presence of various concentrations of therapeutic substances with differing incubation times (4 hours, 16 -24 hours, 72 hours, and 96 hours).

The mitochondria needed to be isolated from the PBMCs to determine mitochondrial ATP generation.

It could be demonstrated in vitro that, compared to the controls:

- The factor responsible for mitobiogenesis, PGC-1alpha, rose by up to 5,400%,
- Mitochondrial ATP generation increased by up to 550%, and
- Mitochondrial metabolism went increased by up to 590%.

All the measurements were conducted blinded. The clinic of Ralf Meyer sent the substances to be tested to Professor König with the designations "Supplement 1 to 10," without indicating the name or contents.

Increase in mitobiogenesis by up to 5400%, ATP generation by up to 500%, mitochondrial metabolism by up to 590%

Mitochondrial ATP generation, mitochondrial metabolism, mitobiogenesis (PGC-1alpha)

The increase in percent of the stimulation of mitochondrial biogenesis measured in isolated PMBCs/mitochondria, percentage increase in aerobic ATP generation (measured in isolated mitochondria from PMBCs) and mitochondrial metabolism (MTT, measured in isolated mitochondria from PMBCs) via optimal dosage of the following supplements with Patient 1.

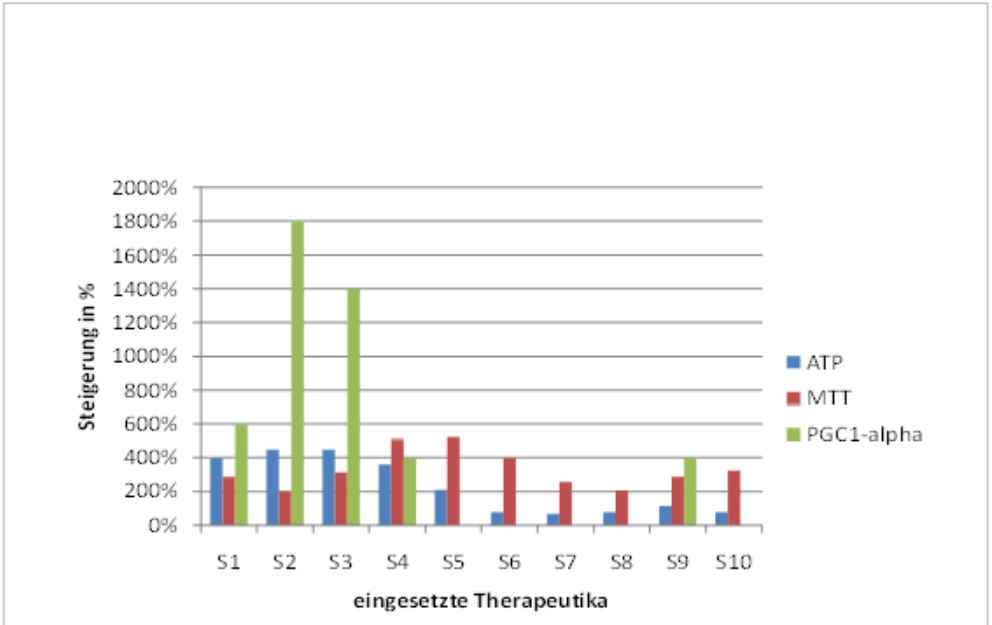
		Mitobiogenesis (generation of PGC-1alpha) Increase, %	ATP generation Increase, %	Mitochondrial metabolism Increase, %
S1	Pro EM san	2800 %	500 %	310 %
S2	Pro Dialvit44	4200 %	550 %	240 %
S3	Colostral product	5400 %	550 %	380 %
S4	Pro Curmin Complete II	3400 %	450 %	530 %
S5	Pro Sanatox	2000 %	300 %	590 %
S6	Pro Basan Complete		150 %	420 %
S7	Pro Osteo Complete		120 %	290 %
S8	Omega 3 product		150 %	250 %
S9	Pro Sirtusan	3200 %	220 %	350 %
S10	Pro Krypto Balance		160 %	340 %

Table: Supplements tested on Patient 1

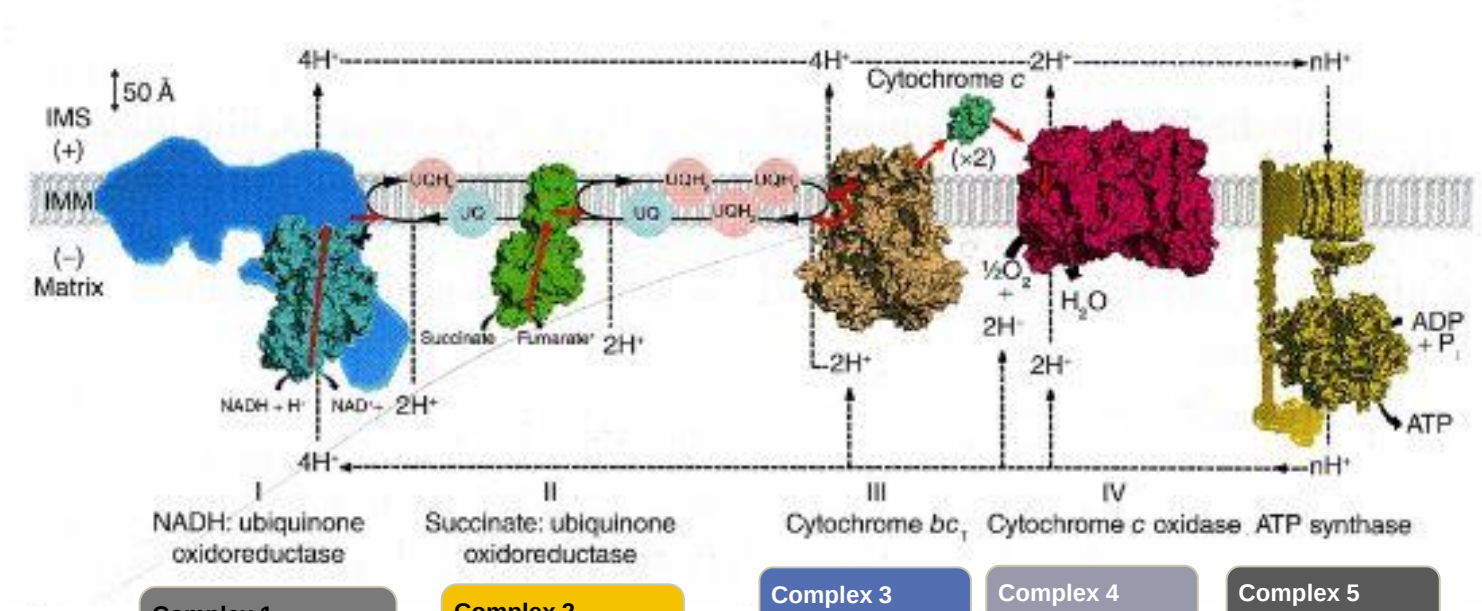
Demonstrated in vitro that all the supplements can influence mitochondrial function/integrity positively to varying degrees

		Mitobiogenesis Increase, %	ATP generation Increase, %	Mitochondrial metabolism Increase, %
S1	Pro EM san	600 %	500 %	310 %
S2	Pro Dialvit44	1800 %	550 %	240 %
S3	Colostral product	1400 %	550 %	380 %
S4	ProCurmin Complete II	400 %	450 %	530 %
S5	Pro Sanatox		300 %	590 %
S6	Pro Basan Complete		150 %	420 %
S7	Pro Osteo Complete		120 %	290%
S8	Omega 3 product		150 %	250 %
S9	Pro Sirtusan	400 %	220 %	350 %
S10	Pro Krypto Balance		160 %	340 %

Table: Supplements tested on Patient 2



Pro Dialvit 44: A multinutrient complex for the mitochondria



Complex 1

NADH

- **FMN from B2**
- **Iron**
- **Sulphur**
- **NADH from B3**
- **CoQ**

Complex 2

Succinate Dehydrogenase

- **FAD from B2**
- **Iron**
- **Sulphur**
- **CoQ**
- **Hydroxocobalamin to activate succinate/heme synthesis**
- **DHA to form cardiolipin**

Complex 3

Cytochrome reductase

- **Sulphur**
- **Iron**
- **CoQ**
- **B1 to form Coenzyme A**

Complex 4

Cytochrome oxidase

- **Copper**
- **Iron in cytochrome A**

Complex 5

ATP synthase

- **Mg**

Source: Rich, R.P., Marechal, A., "The mitochondrial chain", in "Essays in Biochemistry: Mitochondrial Function", by Brown, G.C. et al., Portland Press Ltd., 2010, London, with permission; Vasquez, A., Mitochondrial nutrition and mitochondrial medicine for primary care conditions

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- **Glutathione** (GSH) key intracellular nutrient, formed from **L-cysteine, L-glutamine and L-glycine**
- **Alpha lipoic acid, lecithin, selenium, ellagic acid and grape seed extract** all contribute to glutathione synthesis and neutralise free radicals
- **Mn, Cr and Q10** are vital for the resynthesis and reactivation of GSH, and electron transfer along the ETC

Source: Multiple references available evidencing the benefits of these nutrients on the pathways described; please contact AONM

Mitochondrial Triad | Pro Sirtusan

PGC1-α a marker for this

To stimulate and strengthen

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- Mitochondrial biogenesis via sirtuin enzyme activation,
- Anti-inflammatory mitochondrial function,
- Regeneration of the electron transport chain,
- Antioxidative capacity,
- Strengthens the liver/gallbladder, kidneys, heart, nervous system, GIT, immune system.

Recommended dose:

2 x 1 capsules daily.

Ingredients	per daily dose
Resveratrol extract from knotweed	400 mg
Quercetin	100 mg
Rhodiola rosea	40 mg
Amla berry extract	80 mg
Astaxanthin	10 mg
Cranberry extract	60 mg
Genistein from soya	60 mg
Ginkgo biloba leaf powder	40 mg
Green tea extract	30 mg
Ginger	40 mg
Cabbage extract	40 mg
Wheat grass extract	100 mg

Mitochondrial Triad | Pro Curmin Complete

ProCurmin Complete II

- Synergy of polyphenol extracts such as curcumin, piperin and quercetin, combined with Agaricus, molybdenum, carnitine

ProCurmin Forte

Up to 40 times higher bioavailability than conventional curcumin, as well as equally bioactive tumerosaccharides, with added Vitamin C and other valuable polyphenols

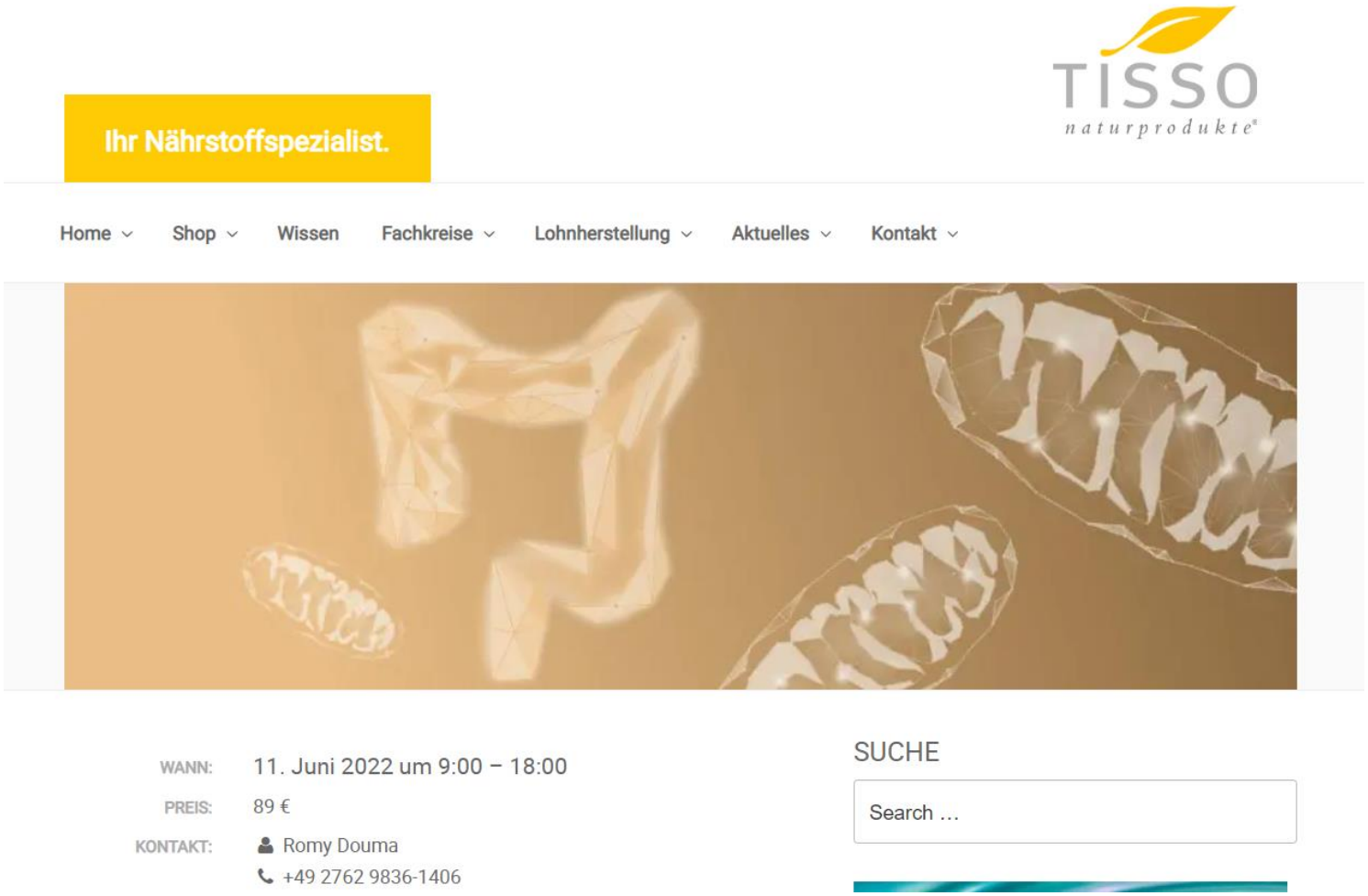
Supports and regulates:

- Systemic mitochondrial function of all cells, helps restore cells' ability to undergo apoptosis
- Immune performance (antiallergic, antiviral, antibacterial , as well as antimycotic)
- Cellular respiration and activity
- Rheumatic disorders, anti-inflammatory
- Blood pressure and liver metabolism

Recomm. dose:
2 x 1 caps. daily

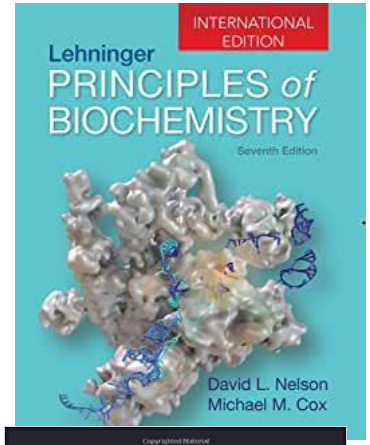
Recomm. dose:
2 x 3 caps. daily

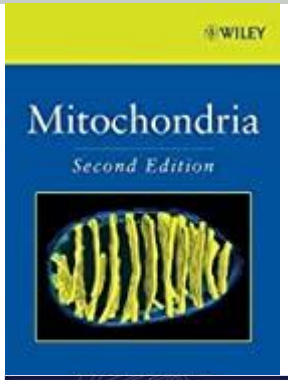
Educational online seminar on the “MitoBiom“ concept on June 11th in English – a few free places available

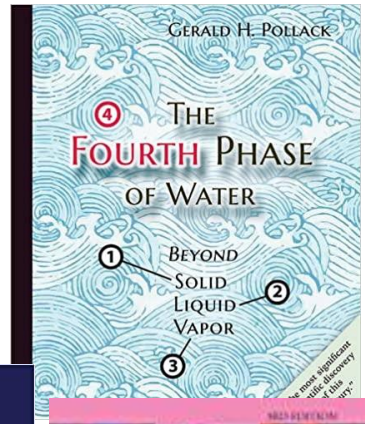


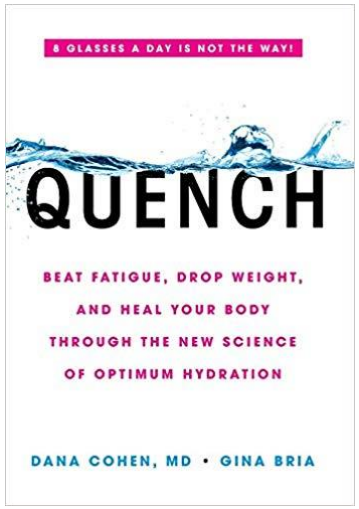
https://www.tisso.de/Veranstaltung/live-stream-seminar-mitobiom-concept-module-i/

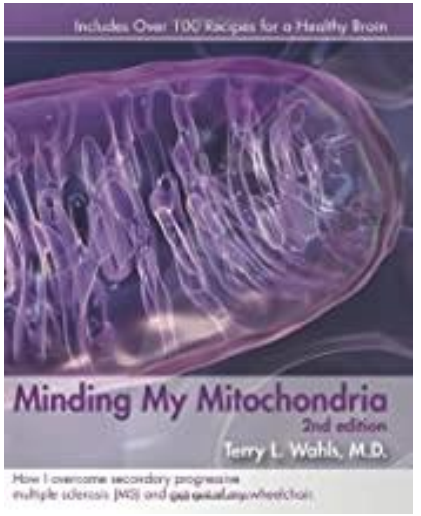
Many resources available on these amazing orchestrators of our cells

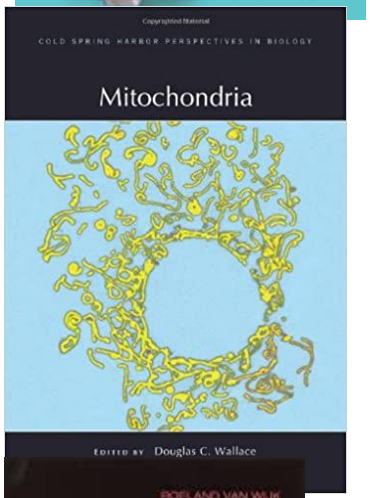


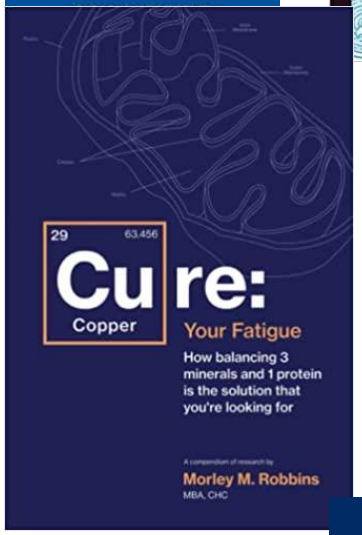


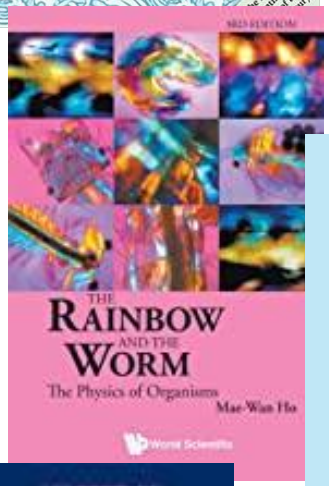


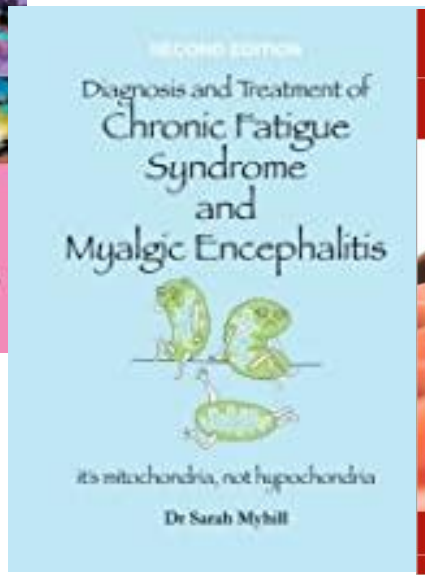


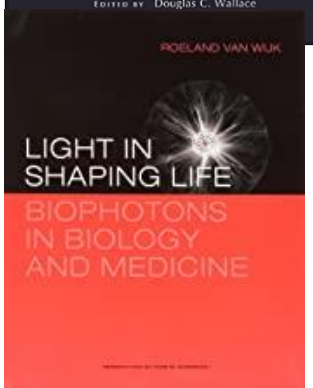


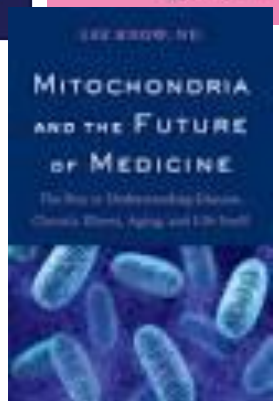












AONM May 12th 2022 Awareness Day Special

WEBINAR May 12th, 2022 | 6.00 pm (BST)

Dr. Sarah Myhill, MBBS

AONM May 12th 2022 Awareness Day Special How is mitochondrial dysfunction linked to chronic disease, and what can we do about it?

In 1992 Thomas Hennessy Jr. founded International Awareness Day for Chronic Immunological and Neurological Diseases.

To commemorate Awareness Day 2022 we are delighted to have Dr. Sarah Myhill speaking about the role of the mitochondria in disorders such as long-COVID, ME, Fibromyalgia, Lyme Disease, EDS, PANS/PANDAS, Autism, MCS, MCAS. She will also be discussing ways in which we can improve the function of our mitochondria

Thanks very much for your attention!

gilian@aonm.org