MITOCHONDRIAL DYSFUNCTION- THE REAL ROOT CAUSE OF CHRONIC DISEASE

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AARM
Association for the Advancement of Restorative Medicine

Overview

1. Establish that mitochondrial dysfunction is the **common denominator** in chronic disease and hormone imbalance

2. Establish that the health of the **microbiome** is intimately connected with mitochondrial function

3. Establish that the main cause of mitochondrial dysfunction is cumulative toxicity exposure from **biotoxins** (mycotoxins, dental toxins,) and **toxicants** (chemicals in personal care products, pharmaceutical drugs, pesticides, herbicides, tobacco, heavy metals, *excessive* ultraviolet light exposure) resulting in imbalance of the redox signaling pathways resulting in excessive oxidative stress which then becomes a vicious cycle resulting in mitochondrial dysfunction and death (**mitophagy**)

4. Establish that mitochondrial dysfunction is preceded by a **cell danger response (CDR)** which has become chronic

5. Establish that the chronicity of the **CDR** is a result of activation of the **nitric oxide/peroxynitrite** (NO/ONOO) cycle

6. Establish that the key to restoring health to individuals with chronic disease is to identify and eliminate the predisposing, precipitating and propagating factors of the mitochondrial dysfunction and to increase the number (biogenesis) and function of their mitochondria

Goals And Objectives

1. Define Mitochondrial Function
2. Define Mitochondrial Dysfunction (MD)
3. Review Glycolysis, Kreb's cycle and the electron transport chain (ETC)
4. Review the Cell Danger Response (CDR) in the context of MD
5. Outline the multiple causes of MD
6. Review the NO/ONOO cycle
7. Review lifestyle factors that impact mitochondrial function
8. Review the impact of the microbiome on mitochondrial function
9. Review Bioenergetics of mitochondrial dysfunction
10. Review mitochondrial dysfunction as a cause of chronic disease including chronic fatigue syndrome

The Plan

1. Part 1:
- Overview of Mitochondrial Structure & Function
- Mitochondrial Dysfunction

2. Part 2:
- Continue Mitochondrial Dysfunction, and
- Evaluation of Mitochondrial Dysfunction

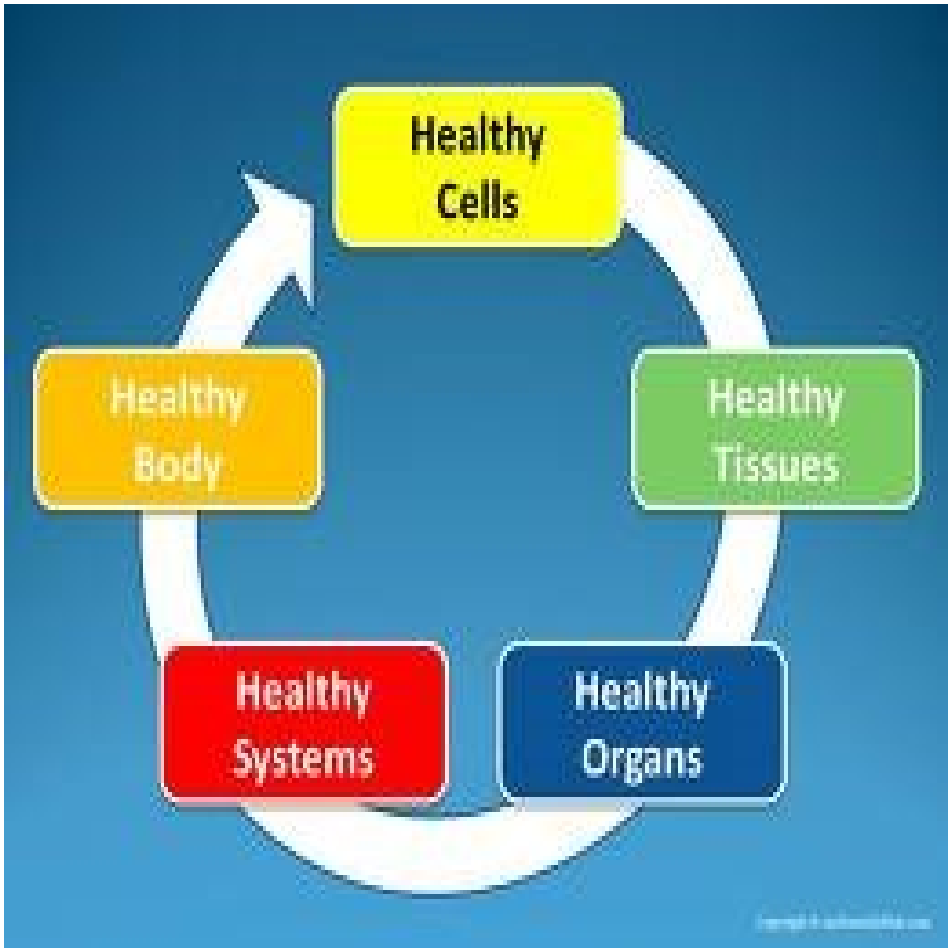
3. Part 3 :
- Restoration Of Mitochondrial Function

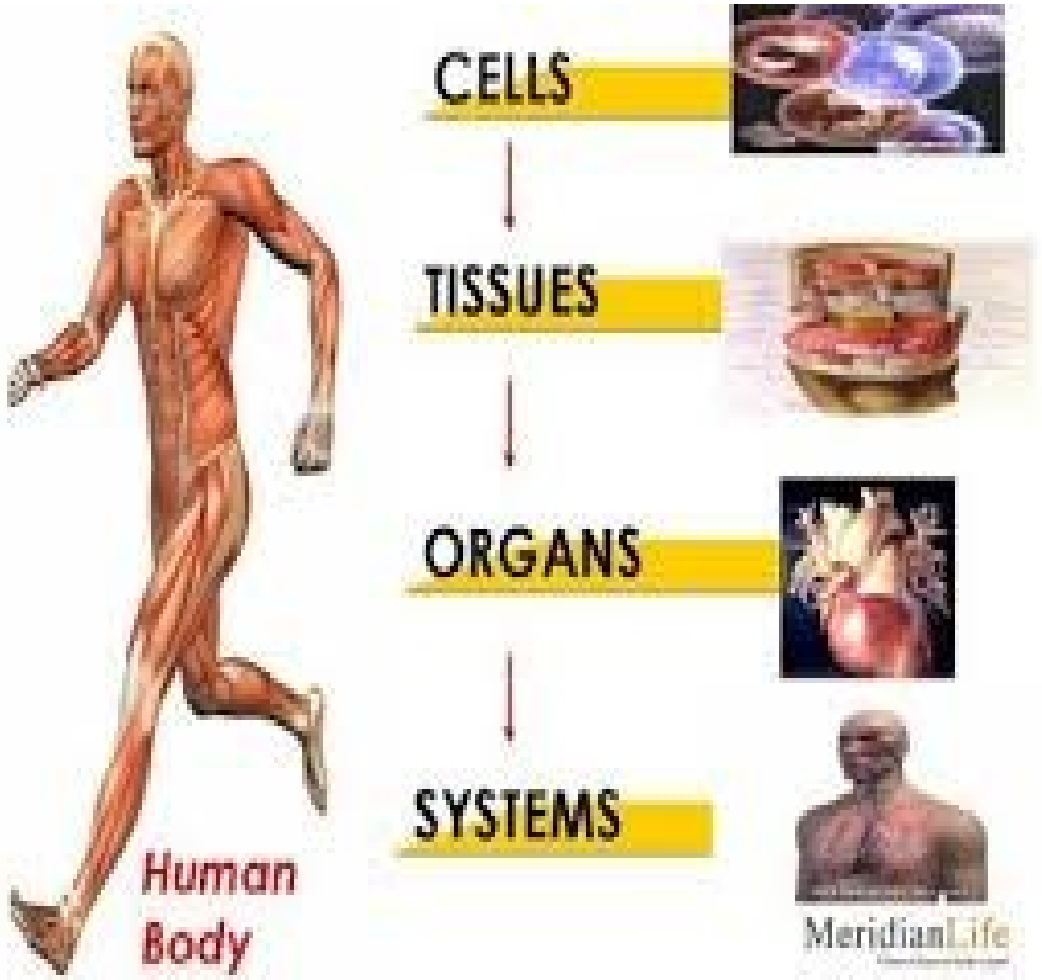
Mitochondrial Dysfunction

- The idea that mitochondrial dysfunction is implicated in the etiology of various diseases has been strengthened after several years of research. Initially, studies of mitochondrial diseases have focused on mitochondrial respiratory-chain diseases associated with mutations of mtDNA. **However, more recent evidence shows that oxidative damage is responsible for the impairment of mitochondrial function, leading to a self-induced vicious cycle that finally culminates in necrosis and apoptosis of cells and organ failure.**
- We are now starting to understand the mechanisms of a large list of ***mitochondrial-related diseases*** ***(cancer, diabetes, obesity, cardiovascular and neurodegenerative diseases, and aging); all of them seem to share the common features of disturbances of mitochondrial Ca2+, ATP, or ROS metabolism (Sheu et al., 2006)***. **Therefore, selective prevention of such phenomena should be an effective therapy in a wide range of human diseases (Smith et al., 1999; Sheu et al., 2006).**

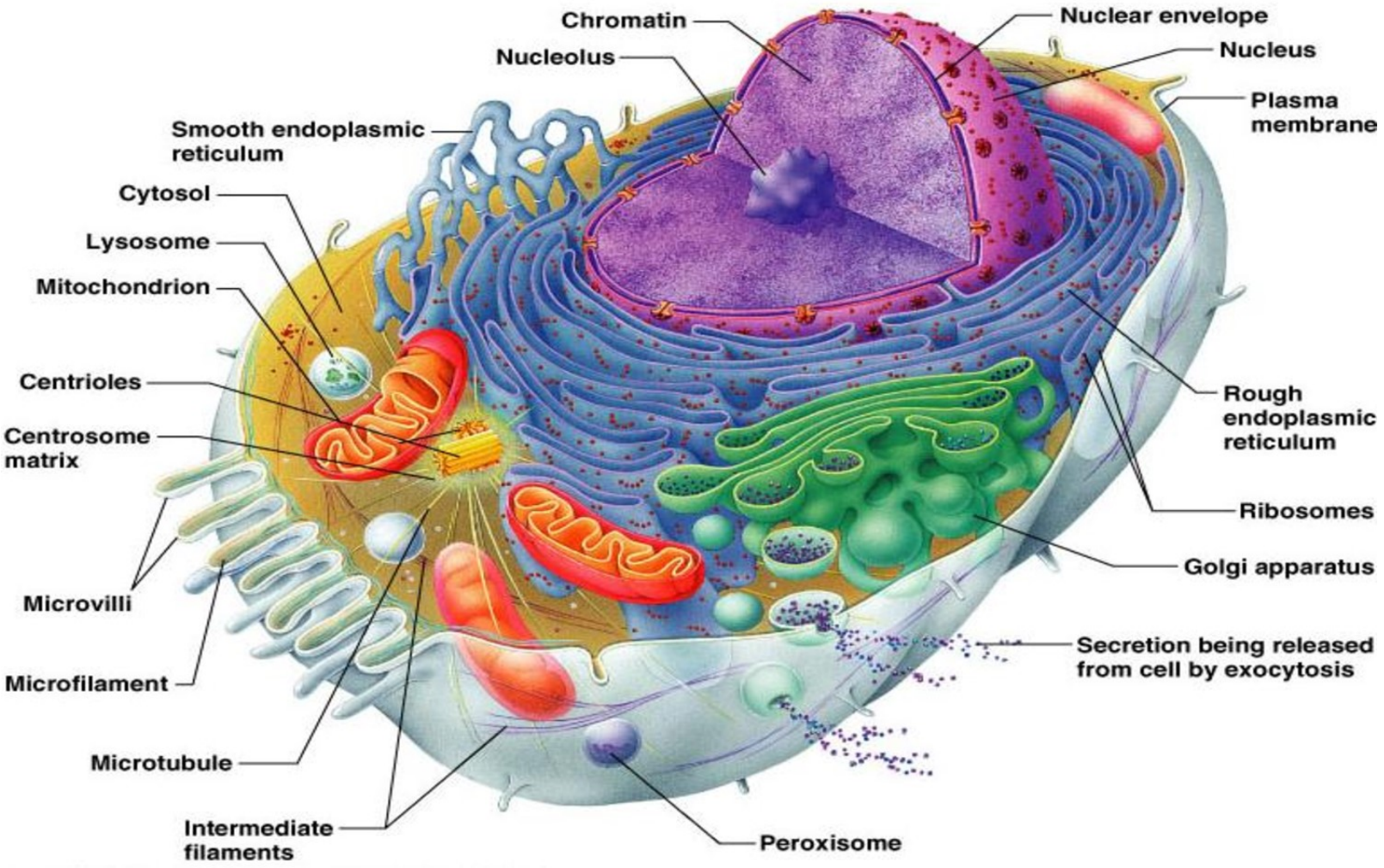
Part 1. a –Mitochondrial Structure & Function

The Big Picture




CELLS
TISSUES
ORGANS
SYSTEMS
Human Body
MeridianLife

Structure of a Generalized Cell



Root Cause

Mitochondria

Semi-autonomous organelle = complete machinery for protein synthesis:

- mitoribosomes
- tRNA
- double stranded, circular, naked DNA
- enzymes involved in transcription and translation

Note: *mtDNA* (mitochondrial DNA) codes for only *1% of the total protein required by mitochondria*

- **Most mitochondrial proteins are encoded by nuclear genes** and imported from the cytoplasm, **through one or both membranes, via transport complexes Tom and Tim.**

Structure of Mitochondria

- Mitochondria range from 0.5 to 10 micrometers in diameter.
- Mitochondria are surrounded by a double membrane system – the outer and the inner mitochondrial membrane.
- The outer membrane contains proteins called porins.
- The inner membrane has a high proportion of proteins and "double" phospholipid cardiolipin.
- The inner membrane forms numerous folds called cristae which extend into the matrix of the mitochondria.
- The matrix contains the mitochondrial genetic system as well as the enzymes responsible for the oxidative metabolism.

Basic Mitochondrial Structure

- 2 Mitochondrial Membranes

-Inner

-Outer

- 2 Mitochondrial Compartments

-Intermembrane

-Matrix

Outer Mitochondrial Membrane (OMM)

- Appears smooth
- Freely permeable to ions
- 50% lipids and has cholesterol.
- Porin proteins which form channels that allow molecules of up to 5000 Da to pass freely.
- Due to these porin proteins the concentration of intermembrane space is same as cytosol with respect to small ions.

Inner Mitochondrial Membrane (IMM)

- Many folds = cristae
- Cristae have F_1 particles = oxysomes
- Oxysomes are the site of oxidative phosphorylation and ATP synthesis
- Each crista has intracristal space
- Highly impermeable and restricts the passage of molecules and small ions [like H^+, K^+, Cl^- and OH^-]
- Freely permeable to O_2, CO_2 and H_2O

Inner Mitochondrial Membrane (IMM) cont'd

- Special membrane transporters for small molecules to enter into the matrix eg Adenine nucleotide transporter (ANT)
- Creates H^+ gradient
- Maintains a transmembrane potential, $\Delta\Psi_m$.
- Rich in proteins (nearly 76%), **cardiolipin**
- Lacks cholesterol
- Contains vitamin E
- Majority of inner membrane proteins are involved in electron transport and oxidative phosphorylation.

Permeability Transition Pore

VDAC (voltage dependent anion channel)

+

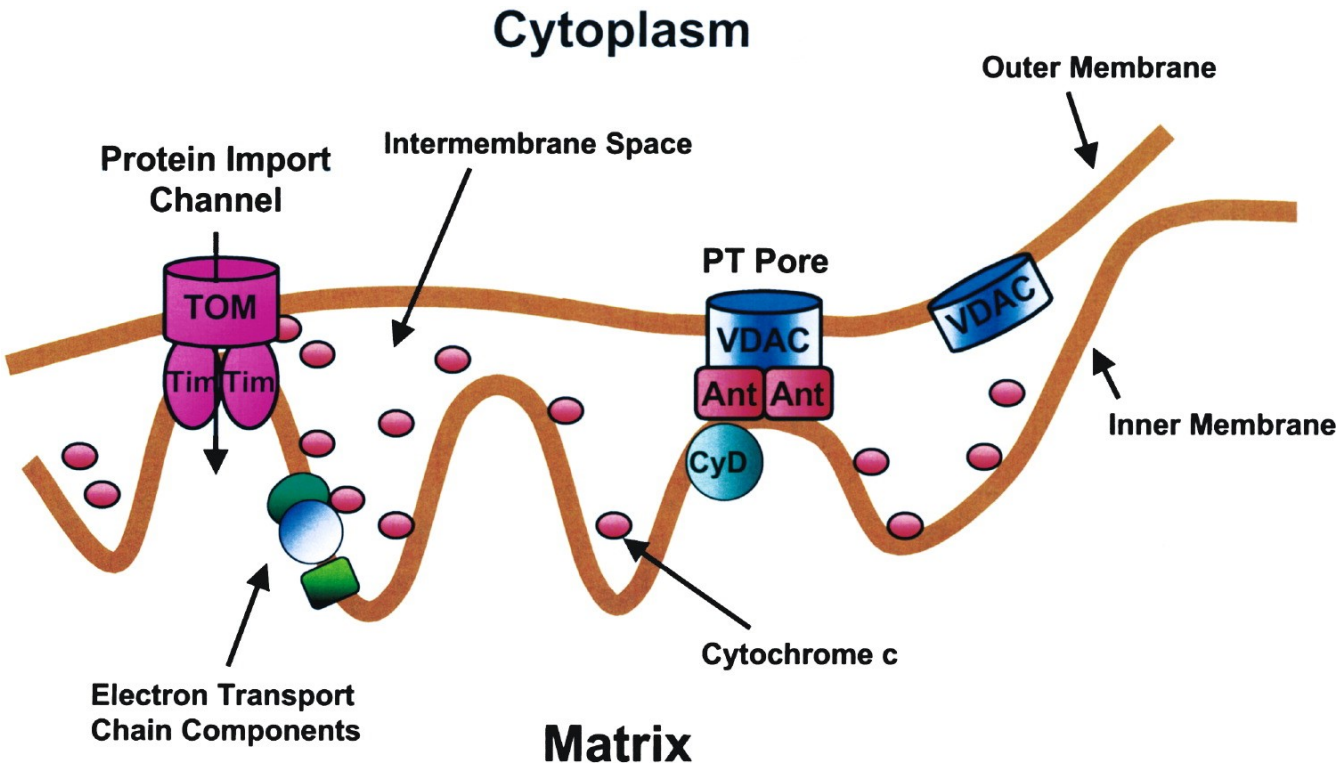
ANT (ADP/ATP translocator)

=

PT pore (permeability transition pore)

Note:

PT pore sometimes associated with loss of the inner membrane potential during apoptosis


Cytoplasm
Outer Membrane
Protein Import Channel
Intermembrane Space
PT Pore
TOM
Tim
Tim
VDAC
Ant
Ant
VDAC
CyD
Inner Membrane
Cytochrome c
Electron Transport Chain Components
Matrix

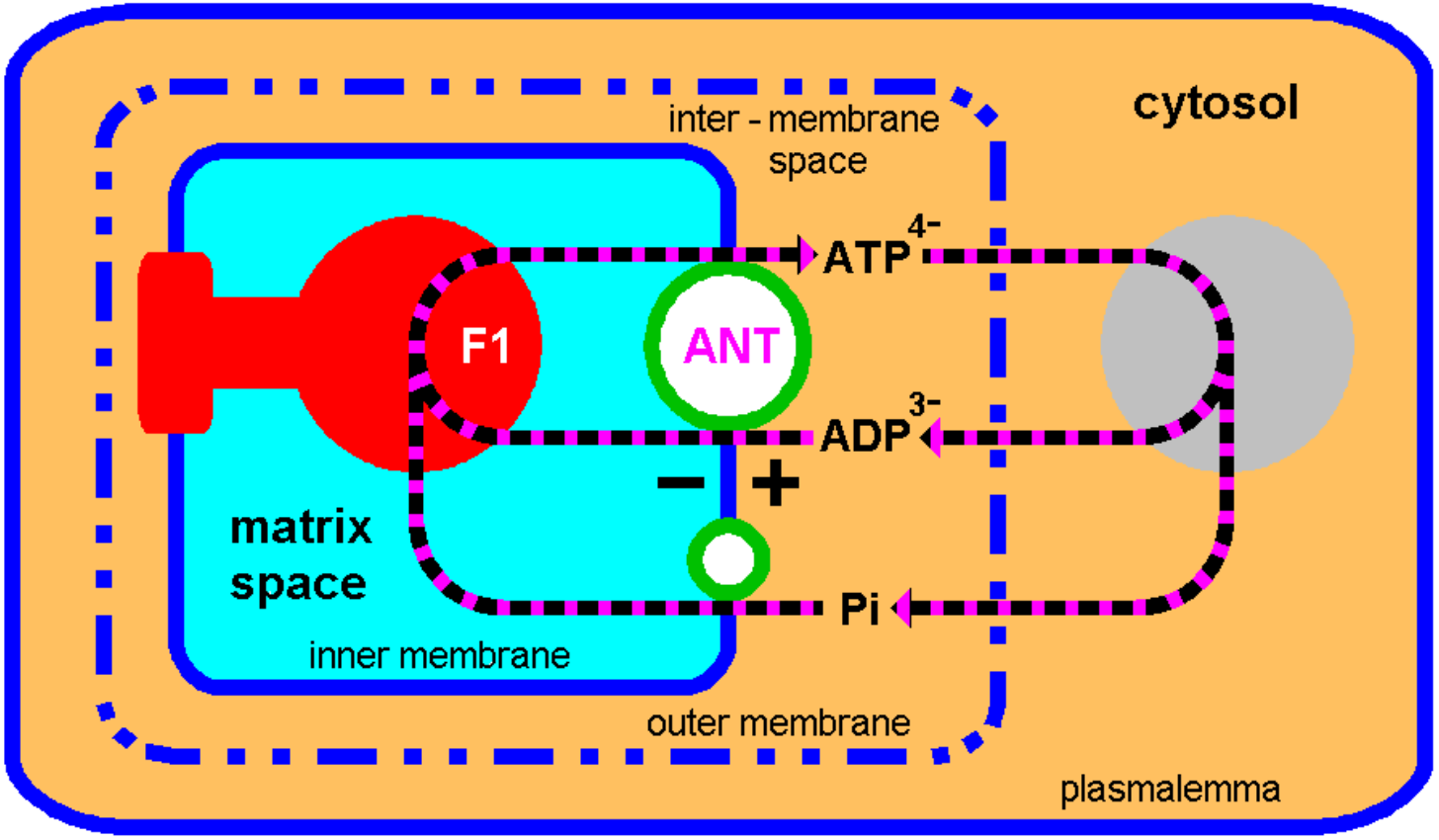
Mitochondrial Compartments

Two distinct compartments resulting from differences between the inner and outer membranes:

1. Intermembrane space

2. Mitochondrial matrix

- Double membrane structure which is the phospholipid bilayer like plasma membrane


cytosol
inter - membrane space
ATP 4-
F1
ANT
ADP 3-
matrix space
Pi
inner membrane
outer membrane
plasmalemma

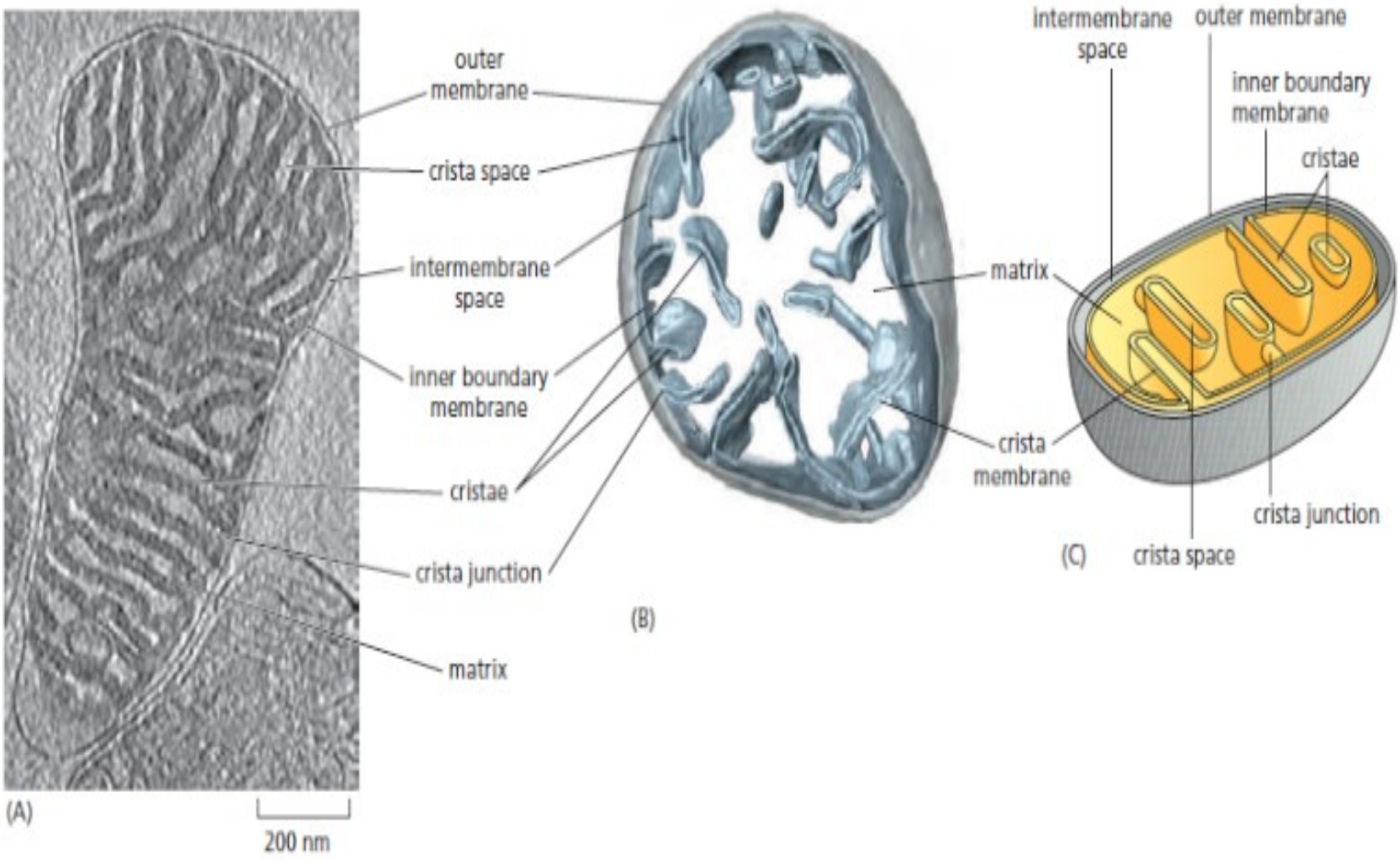
Intermembrane Space

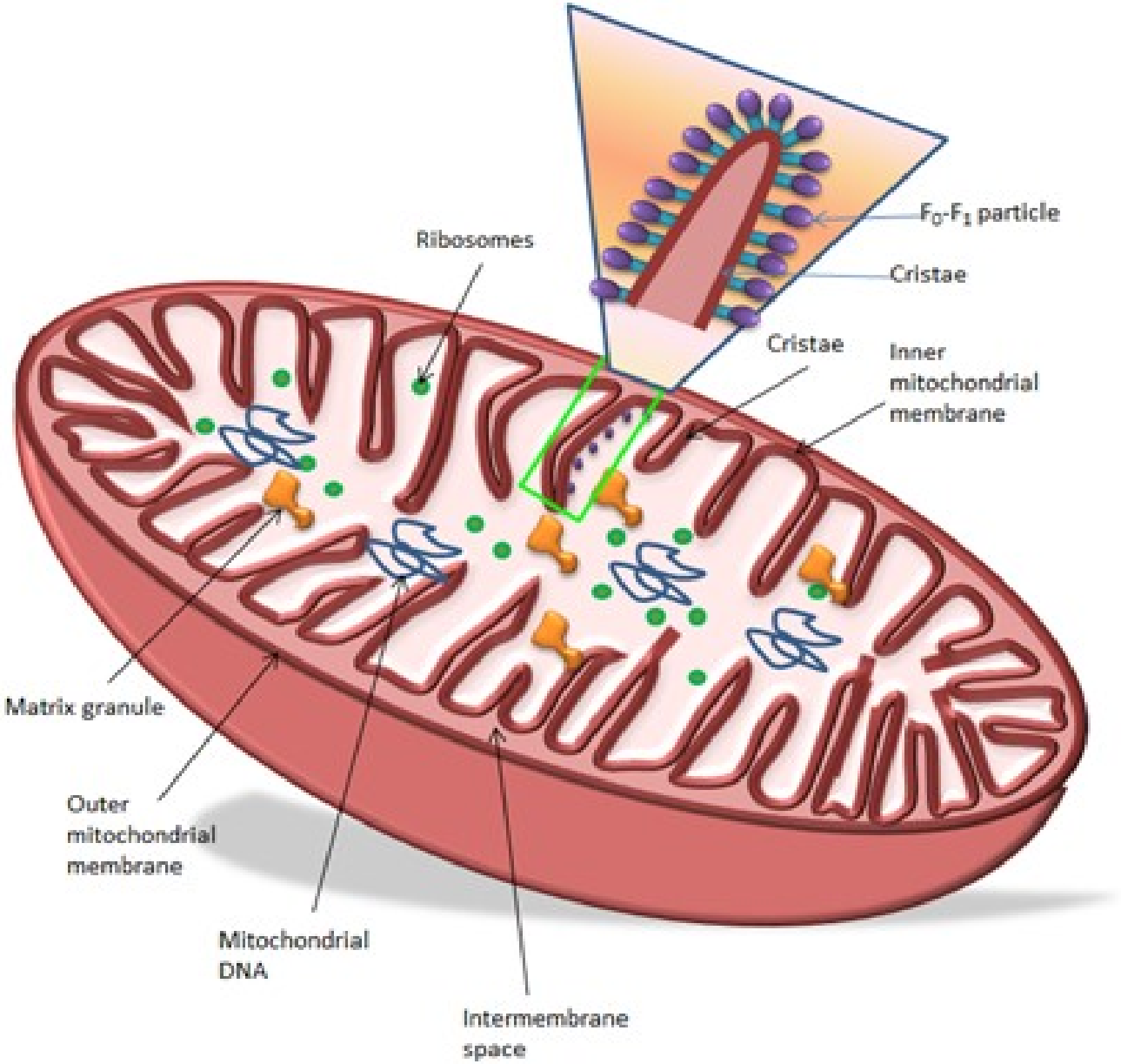
- Between the outer and inner membranes
- Pro-apoptotic proteins such as cytochrome c

Mitochondrial Matrix

- Gel-like
- Water-soluble proteins
- Enzymes for Krebs cycle, lipid oxidation and synthesis
- Ribosomes known as mitoribosomes
- mtDNA: double stranded, circular

Mitochondrial Structure




F_0-F_1 particle
Ribosomes
Cristae
Cristae
Inner
mitochondrial
membrane
Matrix granule
Outer
mitochondrial
membrane
Mitochondrial
DNA
Intermembrane
space

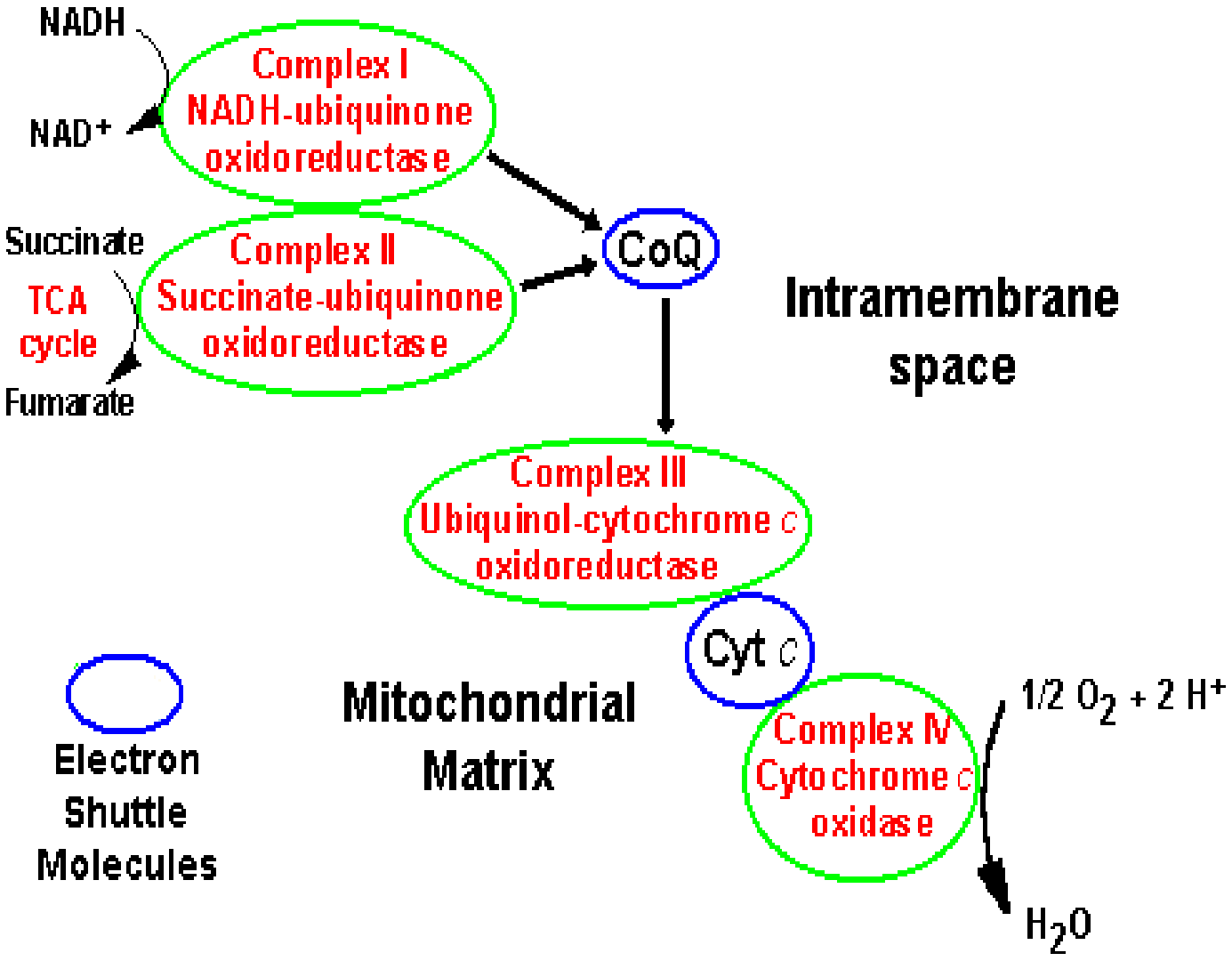
- Voltage dependent anion channel 1 (VDAC1) - primary cellular function is regulating mitochondrial metabolism
- Blocked VDAC → decrease in cellular energy →triggers the energy sensing protein=AMP-activated Protein Kinase (AMPK)

  →downregulates mTOR →

  inhibition of endothelial cell proliferation

  →decreased angiogenesis

Electron Transport Chain (ETC)



Root Cause

Mitochondrial Function

- Multiple functions which vary depending on location:
- Nuclear signaling
- Energy production (ETC)
- Reactive oxygen species
- Apoptosis regulation (cyctochrome C)
- Pyrimidine synthesis
- Steroid synthesis
- PPAR –peroxisome proliferator-activated receptor
- Microbiome cross-talk
- Sirtuins
- Calcium signaling

Mitochondrial Biogenesis Factors

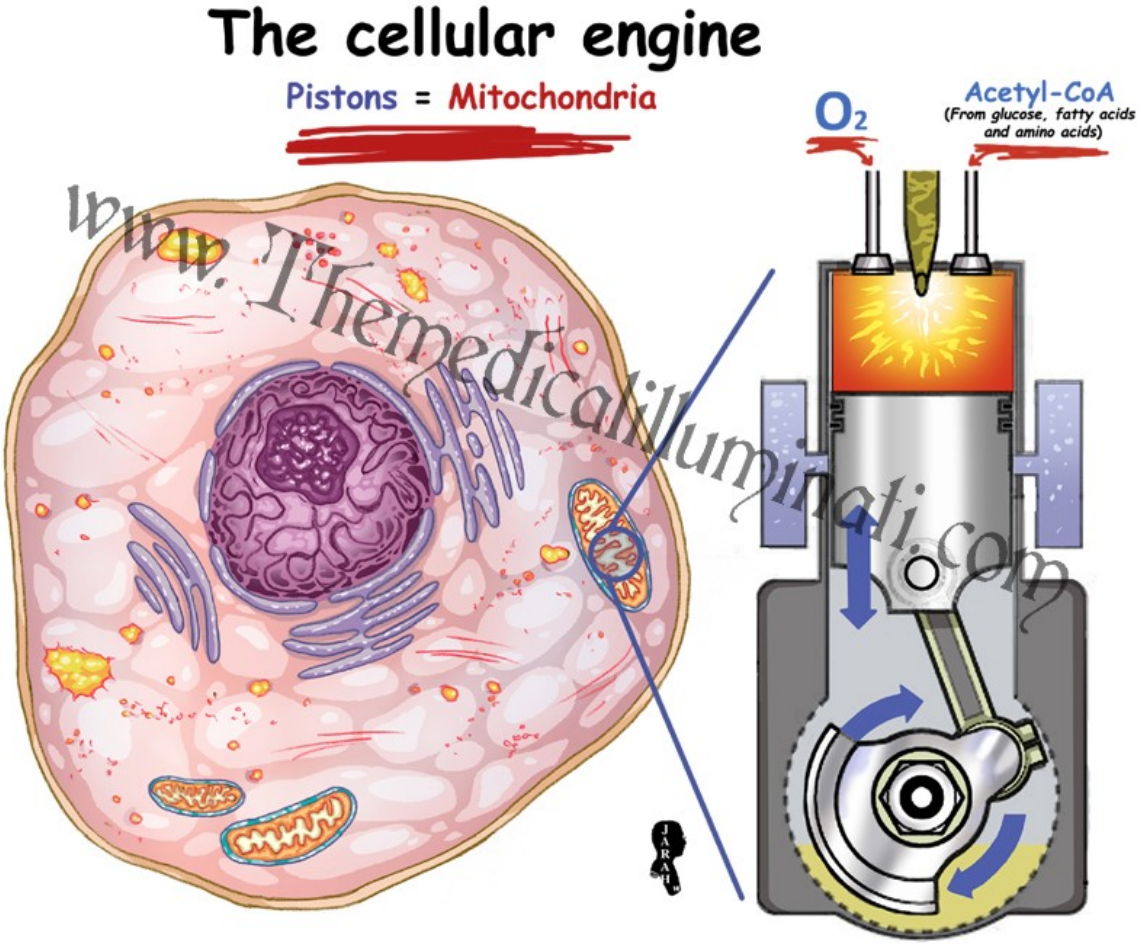
Proliferator- activated receptor-coactivator-1α,

Nuclear respiratory factor-1,

Mitochondrial transcription factor A

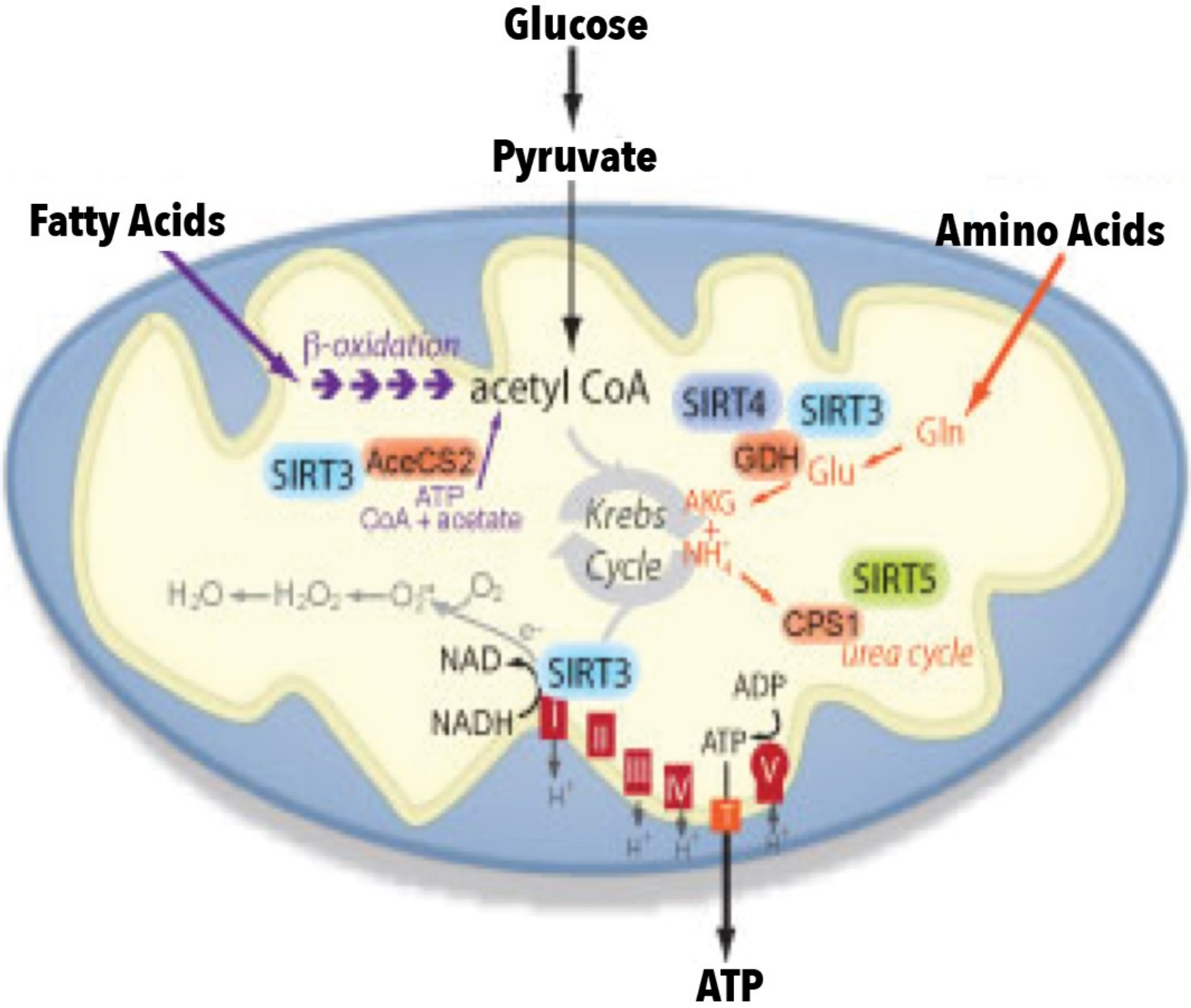
Sirtuin 1 (SIRT1) induction

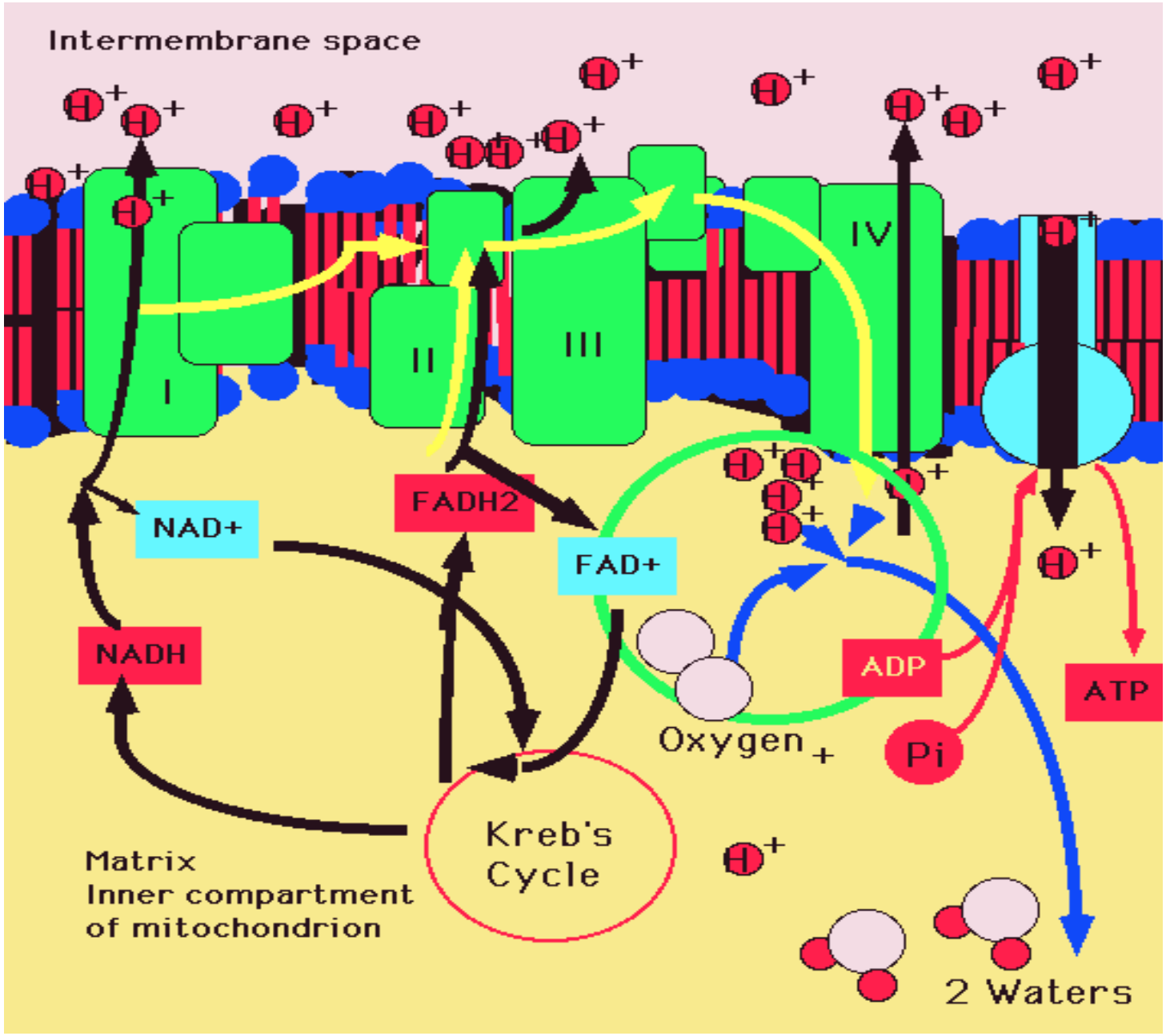
Mitochondrial Function



SIRTUINS

- NAD-dependent deacetylases
- Involved in:
- DNA repair,
- Genome stability,
- Telomere structure maintenance
- Epigenetic modifications of histones
- Elevated during caloric restriction
- Activated by curcumin and other phytonutrients

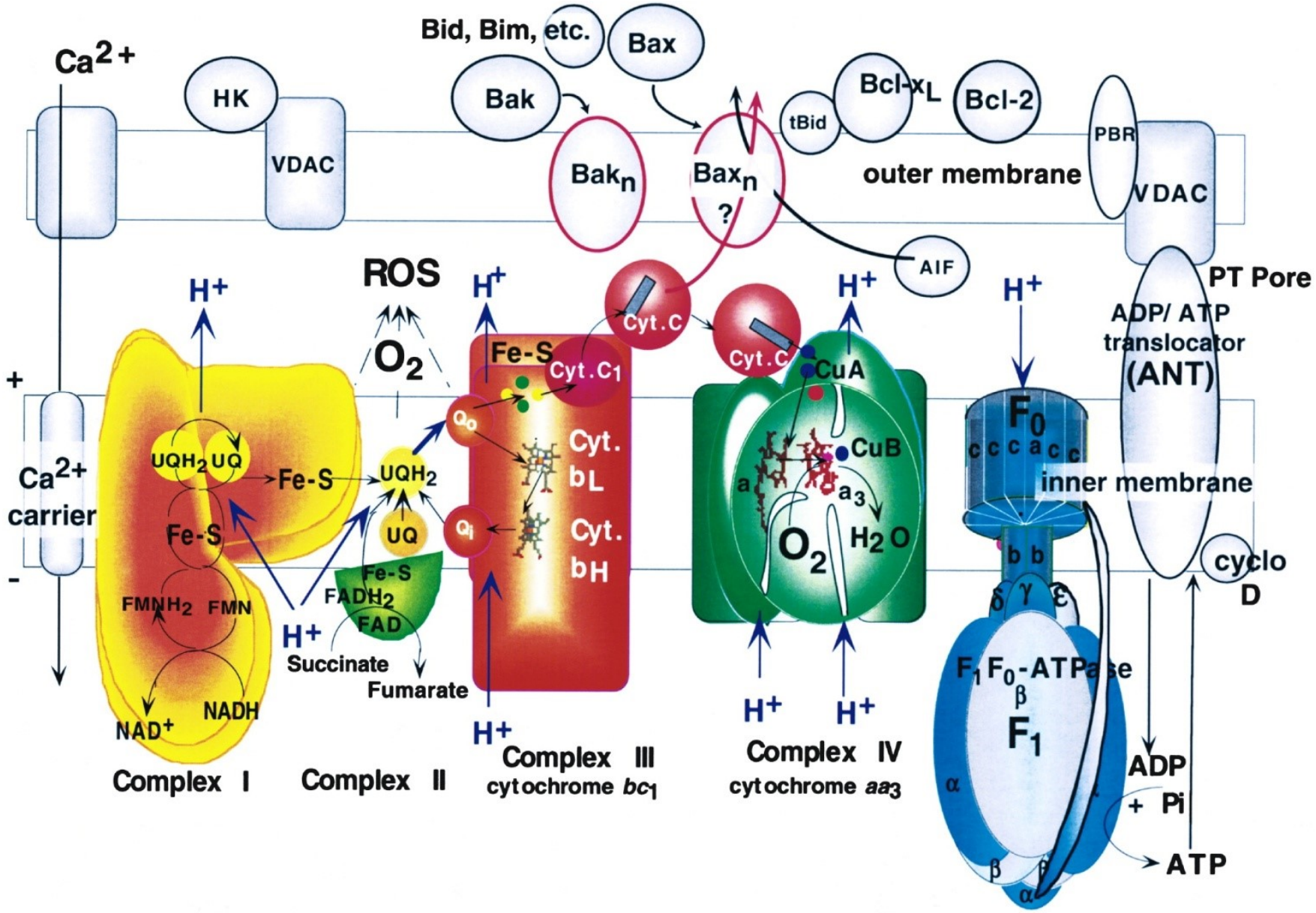

Glucose
Pyruvate
Fatty Acids
Amino Acids
β-oxidation
acetyl CoA
SIRT4
SIRT3
Gln
GDH
Glu
SIRT3
AceCS2
ATP
CoA + acetate
Krebs
Cycle
AKG
+
NH4+
SIRT5
CPS1
urea cycle
H2O ← H2O2 ← O2- O2
e-
NAD
NADH
SIRT3
ADP
ATP
I
II
III
IV
V
H+
ATP

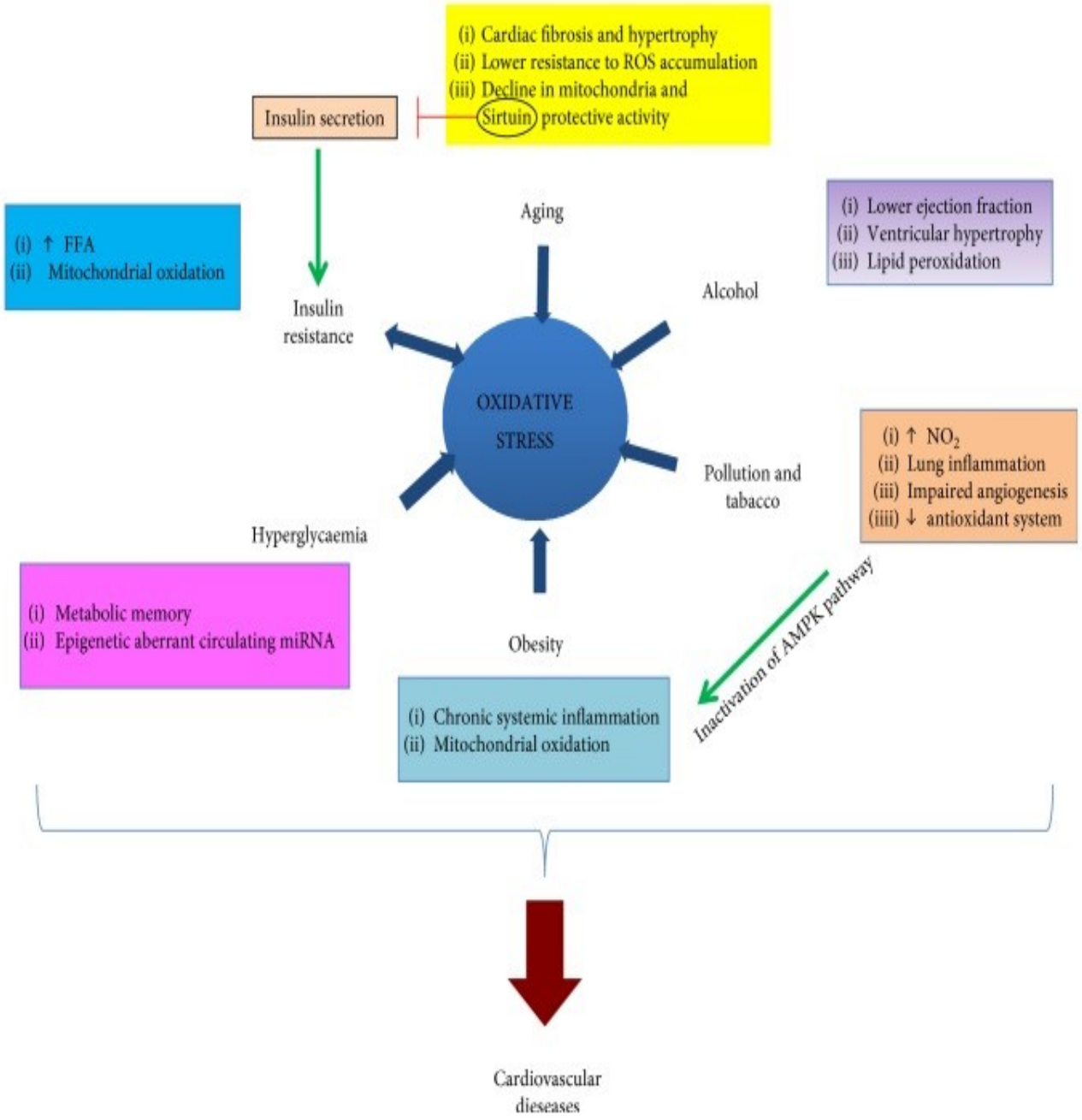

Intermembrane space
I
II
III
IV
NAD+
FADH2
FAD+
NADH
ADP
ATP
Oxygen
Pi
Kreb's Cycle
Matrix
Inner compartment
of mitochondrion
2 Waters

Succinate

- Is common to both the Krebs cycle (citric acid cycle) and the Electron transport chain

- Excellent marker of mitochondrial dysfunction


Ca2+
HK
VDAC
Bid, Bim, etc.
Bax
Bak
Bakn
Baxn
?
tBid
Bcl-xL
Bcl-2
outer membrane
PBR
VDAC
AIF
PT Pore
ADP/ ATP
translocator
(ANT)
ROS
O2
H+
Ca2+
carrier
+
-
UQH2 UQ
Fe-S
UQH2
UQ
Fe-S
FMNH2 FMN
NAD+
NADH
Fe-S
FADH2
FAD
Succinate
Fumarate
Qo
Qi
Fe-S
Cyt.C1
Cyt. bL
Cyt. bH
Cyt.C
Cyt.C
CuA
CuB
a
a3
O2
H2O
F0
c c c a c c
inner membrane
b b
δ γ ε
F1 F0-ATPase
β
F1
α
β
β
α
ADP
+ Pi
ATP
cyclo
D
Complex I
Complex II
Complex III
cytochrome bc1
Complex IV
cytochrome aa3


(i) Cardiac fibrosis and hypertrophy
(ii) Lower resistance to ROS accumulation
(iii) Decline in mitochondria and Sirtuin protective activity
Insulin secretion
(i) ↑ FFA
(ii) Mitochondrial oxidation
Insulin resistance
Aging
Alcohol
(i) Lower ejection fraction
(ii) Ventricular hypertrophy
(iii) Lipid peroxidation
OXIDATIVE STRESS
Pollution and tabacco
(i) ↑ NO_2
(ii) Lung inflammation
(iii) Impaired angiogenesis
(iiii) ↓ antioxidant system
Hyperglycaemia
(i) Metabolic memory
(ii) Epigenetic aberrant circulating miRNA
Obesity
Inactivation of AMPK pathway
(i) Chronic systemic inflammation
(ii) Mitochondrial oxidation
Cardiovascular dieseases

Magnesium and calcium-enriched deep-sea water promotes mitochondrial biogenesis by AMPK-activated signals pathway in 3T3-L1 preadipocytes.

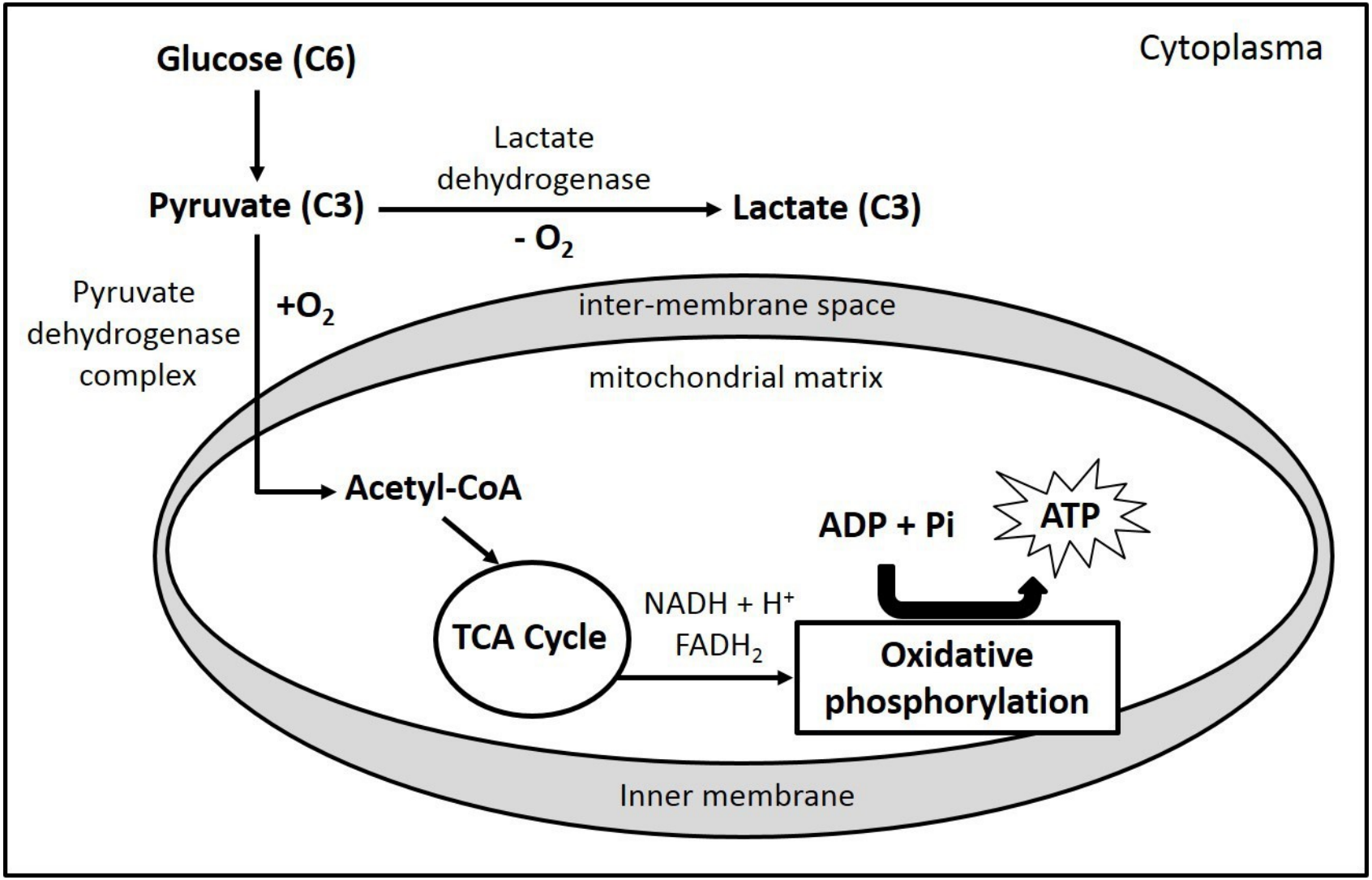
- Biomed Pharmacother. 2016 Oct;83:477-484. doi: 10.1016/j.biopha.2016.07.009. Epub 2016 Jul 18.

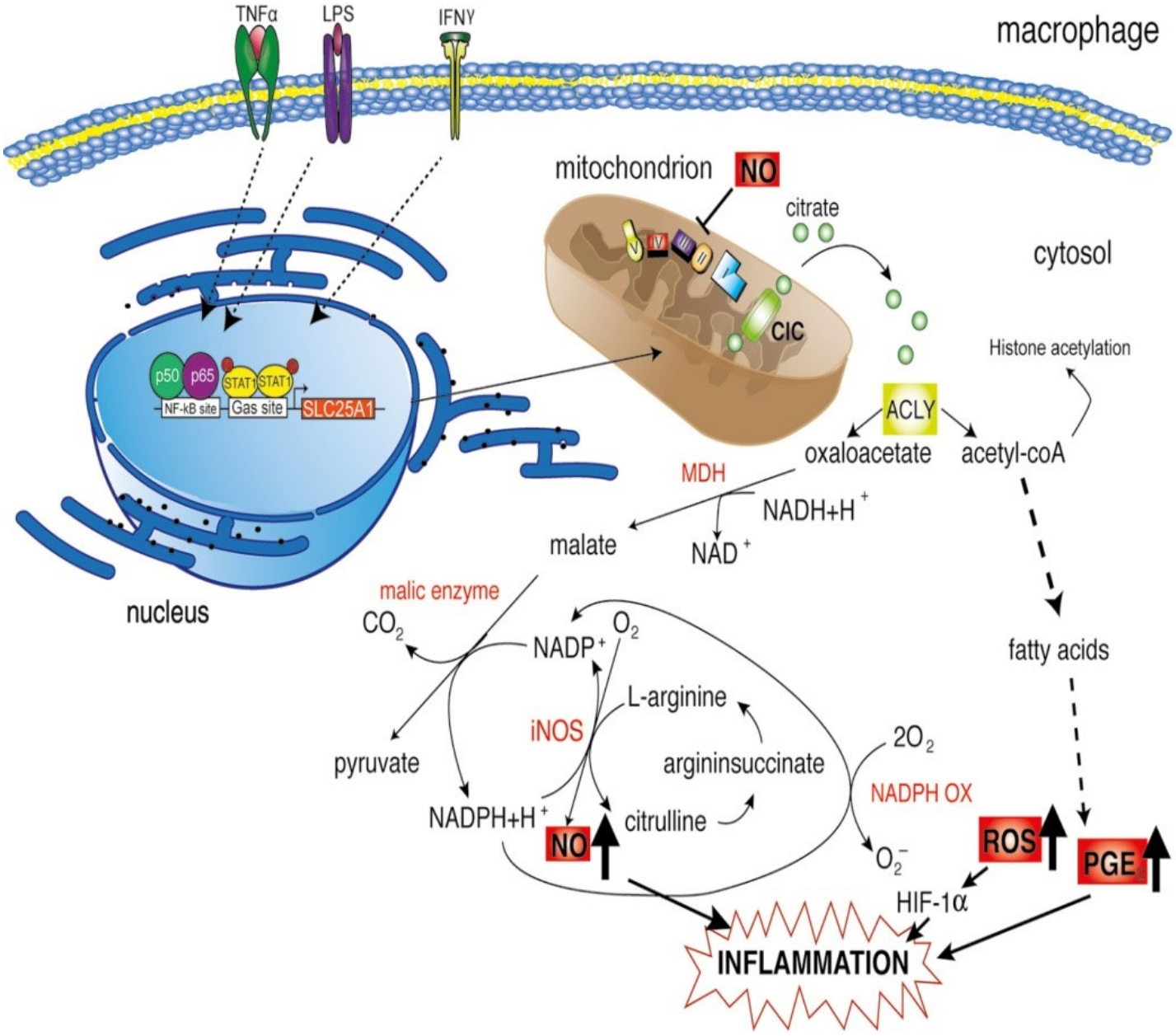
- **Magnesium and calcium-enriched deep-sea water promotes mitochondrial biogenesis by AMPK-activated signals pathway in 3T3-L1 preadipocytes.**

- Ha BG[1], Moon DS[2], Kim HJ[2], Shon YH[3].

- **Abstract**

- Recent studies showed that deficiencies of essential minerals including Mg, Ca, and K, and trace minerals including Se, Zn, and V, have implications for the development, prevention, and treatment of several chronic diseases including obesity and type 2 diabetes. Our previous studies revealed that **balanced deep-sea water (BDSW), which is composed of desalinated water enriched with Mg and Ca,** has potential as a treatment for diabetes and obesity. In this study, to determine whether BDSW regulates mitochondrial biogenesis and function, we investigated its effects on mitochondrial DNA (mtDNA) content, mitochondrial enzyme activity, expression of key transcription factors and mitochondria-specific genes, phosphorylation of signaling molecules associated with mitochondrial biogenesis, and mitochondrial function in 3T3-L1 preadipocytes. **BDSW increased mitochondrial biogenesis in a dose-dependent manner.** Quantitative real-time PCR revealed that BDSW enhances expression of PGC1-α, NRF1, and TFAM genes. Upregulation of these genes was supported by increased mitochondria staining, CytC oxidase activity, and AMPK phosphorylation. The stimulatory effect of BDSW on mitochondrial biogenesis and function suggests a novel mechanism for BDSW-induced anti-diabetic and anti-obesity action


Glucose (C6)
Cytoplasma
Lactate
dehydrogenase
Pyruvate (C3)
Lactate (C3)
- O2
Pyruvate
dehydrogenase
complex
+O2
inter-membrane space
mitochondrial matrix
Acetyl-CoA
ADP + Pi
ATP
TCA Cycle
NADH + H+
FADH2
Oxidative
phosphorylation
Inner membrane


TNFα
LPS
IFNγ
macrophage
mitochondrion
NO
citrate
cytosol
CIC
Histone acetylation
p50
p65
STAT1
STAT1
NF-kB site
Gas site
SLC25A1
ACLY
oxaloacetate
acetyl-coA
MDH
NADH+H+
NAD+
malate
nucleus
malic enzyme
CO2
NADP+
O2
fatty acids
L-arginine
iNOS
pyruvate
argininsuccinate
2O2
NADPH OX
NADPH+H+
citrulline
NO
O2−
ROS
PGE2
HIF-1α
INFLAMMATION

Part 1. b –Mitochondrial Dysfunction

Mitochondrial Dysfunction

Mitochondrial function is typically impaired in two ways:

1) Substrate or co-factor deficiency

2) Inhibition by chemicals, exogenous or endogenous

Sarah Myhill et al., Int J Clin Exp Med 2013; 6(1): 1-15

Definitions

Mitochondrial dysfunction arises from:

- Relative lack of repair pathways compared to the nucleus
- Base excision repair is present
- Nucleotide excision repair is absent (NER); many environmental toxicants cause damage to the mtDNA which then can be irreparable
- an inadequate number of mitochondria,
- an inability to provide necessary substrates to mitochondria,
- dysfunction in their electron transport and ATP-synthesis machinery

Definitions

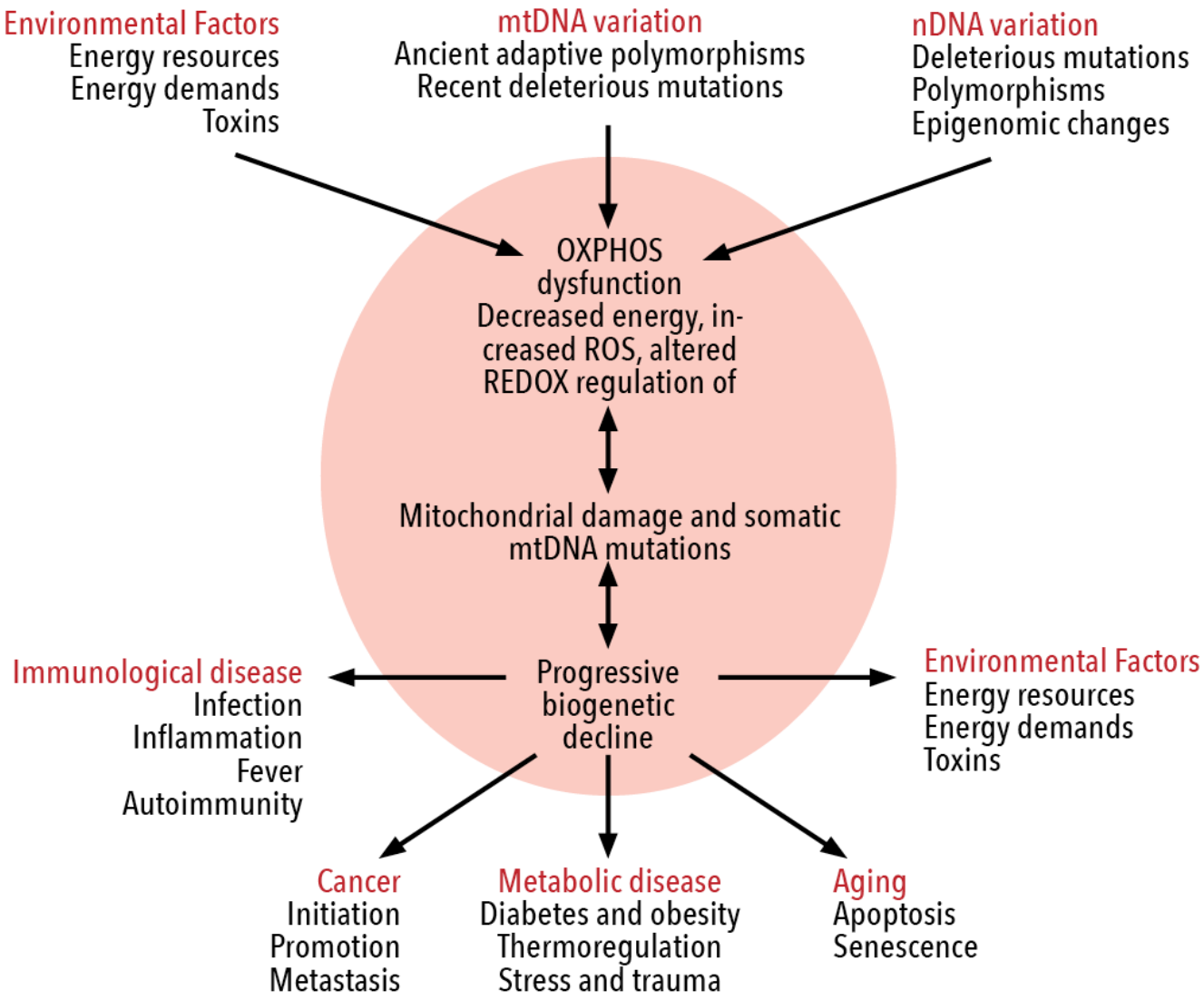
The number and functional status of mitochondria in a cell can be changed by

(1) **fusion** of partially dysfunctional mitochondria and mixing of their undamaged components to improve overall function,

(2) the generation of entirely new mitochondria (**fission**), and

(3) the selective removal and complete degradation of dysfunctional mitochondria (**mitophagy**). These events are controlled by complex cellular processes that sense (mitocheck points) the deterioration of mitochondria, such as the depolarization of mitochondrial membranes or the activation of certain transcription pathways.

Mytochondrial Dysfunction



Microbiota-mitochondria inter-talk: consequence for microbiota-host interaction

1. **Microbiota targets mitochondria to regulate its interaction with the host. Imbalance of this targeting may result in a pathogenic state as observed in numerous studies**.

Short chain fatty acids have beneficial effects on mitochondrial activity.

Pathog Dis. 2016 Feb;74(1):**Microbiota-mitochondria inter-talk: consequence for microbiota-host interaction.**
Saint-Georges-Chaumet Y[1], Edeas M[2].

Microbiome-Mitochondria Cross talk

- Correlation between microbiota quality and diversity and mitochondrial function
- Mitochondrial production of reactive oxygen species (ROS) plays an important role during the innate immune response and inflammation
- Excessive mitochondrial ROS production may affect ROS signaling induced by the microbiota to regulate the gut epithelial barrier.

Root Cause

Steps to Mitochondrial Dysfunction

1. Threat (to homeostasis)
2. Cell Danger Response (CDR)
3. Nitric oxide/peroxynitrite response (NO/ONOO)
4. Low cellular voltage

1. THREAT

1. **Threat (Homeostasis)**

- **Severe psychological stress:**
- **Radiation –diagnostic, solar**
- **Biotoxins-made by living organism [**eg mycotoxins and microbial volatile organic compounds (VOCs)]
- **Infectious agents** (viral, bacterial, fungal, parasitic)
- **Toxicants** –**A.** environmental pollutants such as organophosphate pesticides, PCBs (farmed salmon); can be **persistent or non-persistent**
- **B.** chemicals in personal care products (perfumes, cologne, lotions, antiperspirants, hair dye, make up), such as phthalates, solvents, toxic metals, pharmaceuticals,
- **Nutrient deficiency** (CoQ10, Carnitine, B2, Mn, Zn etc)
- Hormonal deficiency
- **Sleep Deprivation**
- **Abnormal Bioenergetics (EMF-electromagnetic fields, ELF-electric currents, Photoelectric-light, Semiconduction-electron donors)**

TOXICITY -THREAT

- Electro-magnetic pollution
- Endogenous toxins – autointoxication from uric acid, homocysteine, AGE- advanced glycation end products
- Exogenous toxins (mycotoxins, ciguatoxin)
- Exogenous toxicants (dietary eg aspartame, petrochemicals, toxic metals, chlorine, fluorine in tap water, pharmaceutical drugs, glyphosate)
- Exogenous natural products (tobacco, marijuana)
- Infections (virus, bacteria, fungus, parasites)
- Geopathic Stress
- Excess ultraviolet light

Threat: Severe psychological stress

Increased Plasma Levels of Circulating Cell-free mitochondrial DNA in medication-free suicide attempters-association with HPA Axis hyperactivity .

Lindqvist, Daniel; Lund University, Sweden, Malmo University, Sweden 2016

Threat: Radiation

Diagnostic : CT scans

Solar: UV radiation

Threat: Biotoxins

- Biotoxins are made by living organisms
- Mycotoxins
- Volatile organic compounds (VOCs) such as tartaric acid that is produced by invasive candida

The role of mitochondria in T-2 toxin-induced human chondrocytes apoptosis.

- T-2 toxin, a mycotoxin produced by Fusarium species, has been shown to cause diverse toxic effects in animals and is also a possible pathogenic factor of Kashin-Beck disease (KBD). The role of mitochondria in KBD is recognized in our recent research. The aim of this study was to evaluate the role of mitochondria in T-2 toxin-induced human chondrocytes apoptosis to understand the pathogenesis of KBD. T-2 toxin decreased chondrocytes viabilities in concentration- and time-dependent manners. Exposure to T-2 toxin can reduce activities of mitochondrial complexes III, IV and V, ΔΨm and the cellular ATP, while intracellular ROS increased following treatment with T-2 toxin. Furthermore, mitochondrial cytochrome c release, caspase-9 and 3 activation and chondrocytes apoptosis were also obviously observed. Interestingly, Selenium (Se) can partly block T-2 toxin -induced mitochondria dysfunction, oxidative damage and chondrocytes apoptosis. These results suggest that the effect of T-2 toxin on human chondrocytes apoptosis may be mediated by a mitochondrial pathway, which is highly consistent with the chondrocytes changes in KBD.
- PLoS One. 2014 Sep 29;9(9):2014.**The role of mitochondria in T-2 toxin-induced human chondrocytes apoptosis.**Liu J

Mycotoxicoses

- Mycotoxicoses are examples of **“poisoning by natural means”** and thus are **analogous to the pathologies caused by exposure to pesticides** or **heavy metal residues**.

Mycotoxicosis-Symptoms

Symptoms depend on:

- the type of mycotoxin
- the amount and duration of the exposure
- the age, health, and sex of the exposed individual; and
- many poorly understood synergistic effects involving:
- genetics,
- dietary status, and
- interactions with other toxic insults.

Threat: Infections

- Virus
- Bacteria
- Fungus
- Parasite

Threat: Toxicants

Man-made or synthetic toxins ***and*** Natural toxins

A. environmental pollutants such as organophosphate pesticides, PCBs (farmed salmon); can be **persistent or non-persistent**

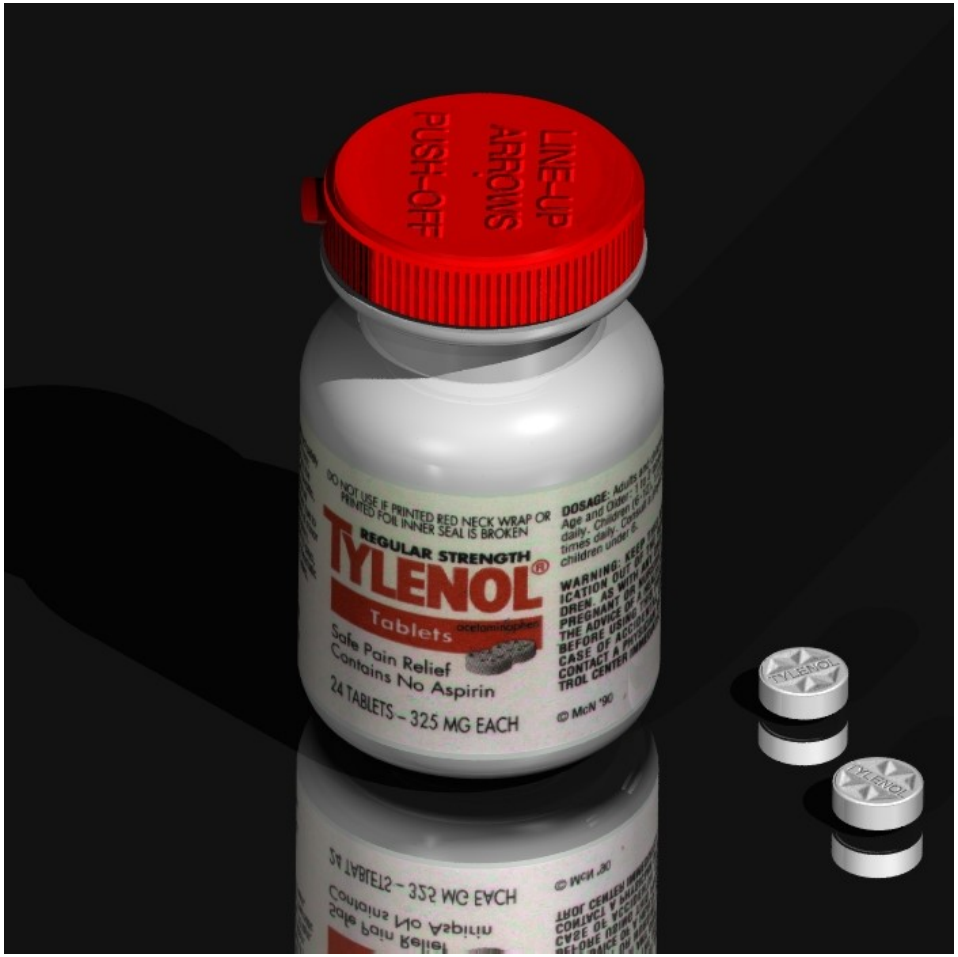
B. chemicals in personal care products (perfumes, cologne, lotions, antiperspirants, hair dye, make up), such as phthalates, solvents, toxic metals

C. pharmaceuticals

Drugs Can Cause Mitochondrial Toxicity

- Valproic acid -Inhibition of fatty acid oxidation, the citric acid cycle, and oxidative phosphorylation; carnitine depletion; complex IV inhibition (contraindicated in mitochondria depletion syndromes)
- Antiretrovirals -Impairment of mtDNA replication causing mtDNA depletion; carnitine deficiency, lactic acidosis, lipodystrophy
- Statins -CoQ10 depletion
- Aspirin Reye syndromeInhibition and uncoupling of oxidative phosphorylation
- Aminoglycoside antibiotics -Impaired mtDNA translation
- Aminoglycoside and platinum chemotherapeutics -Impaired mtDNA translation
- Acetaminophen Hepatopathy- Oxidative stress
- Metformin- Lactic acidosis Inhibition of oxidative phosphorylation, enhanced glycolysis
- Beta-blockers - Reduced exercise tolerance Oxidative stress
- Steroids Reports of deterioration in Kearns-Sayre syndrome Unknown

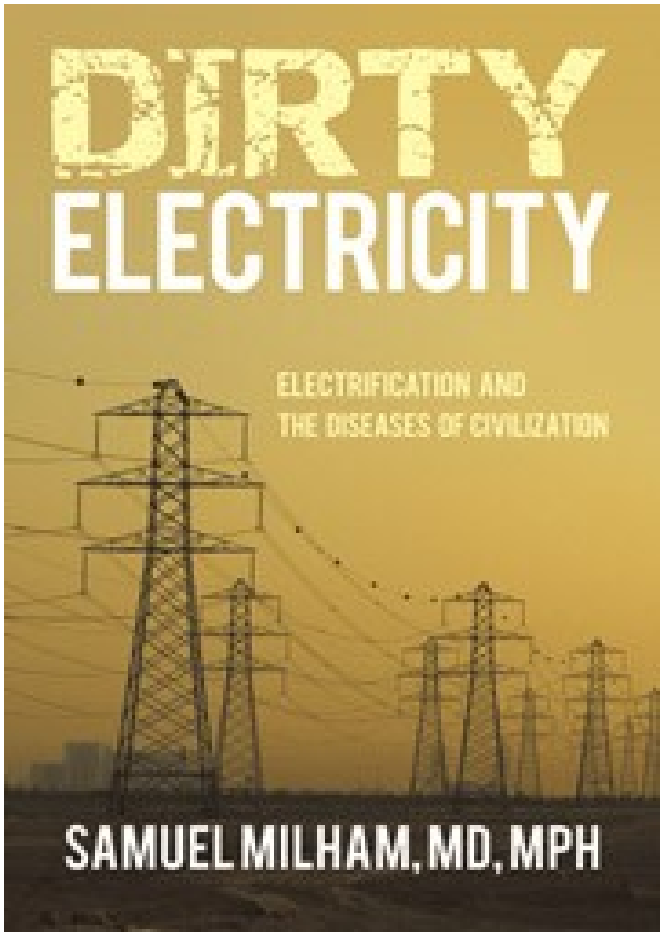
Mitotoxicant

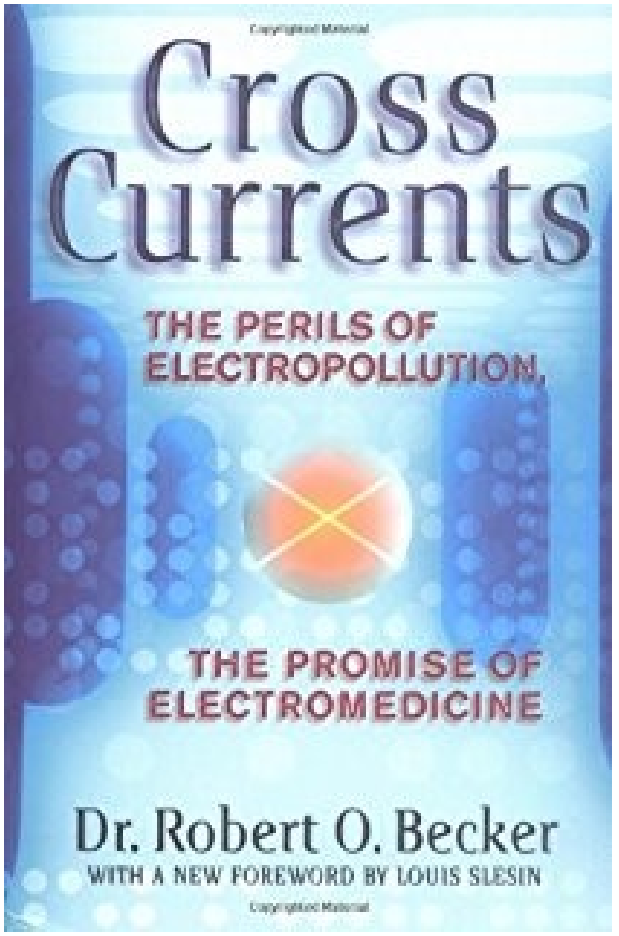


Mitotoxicant

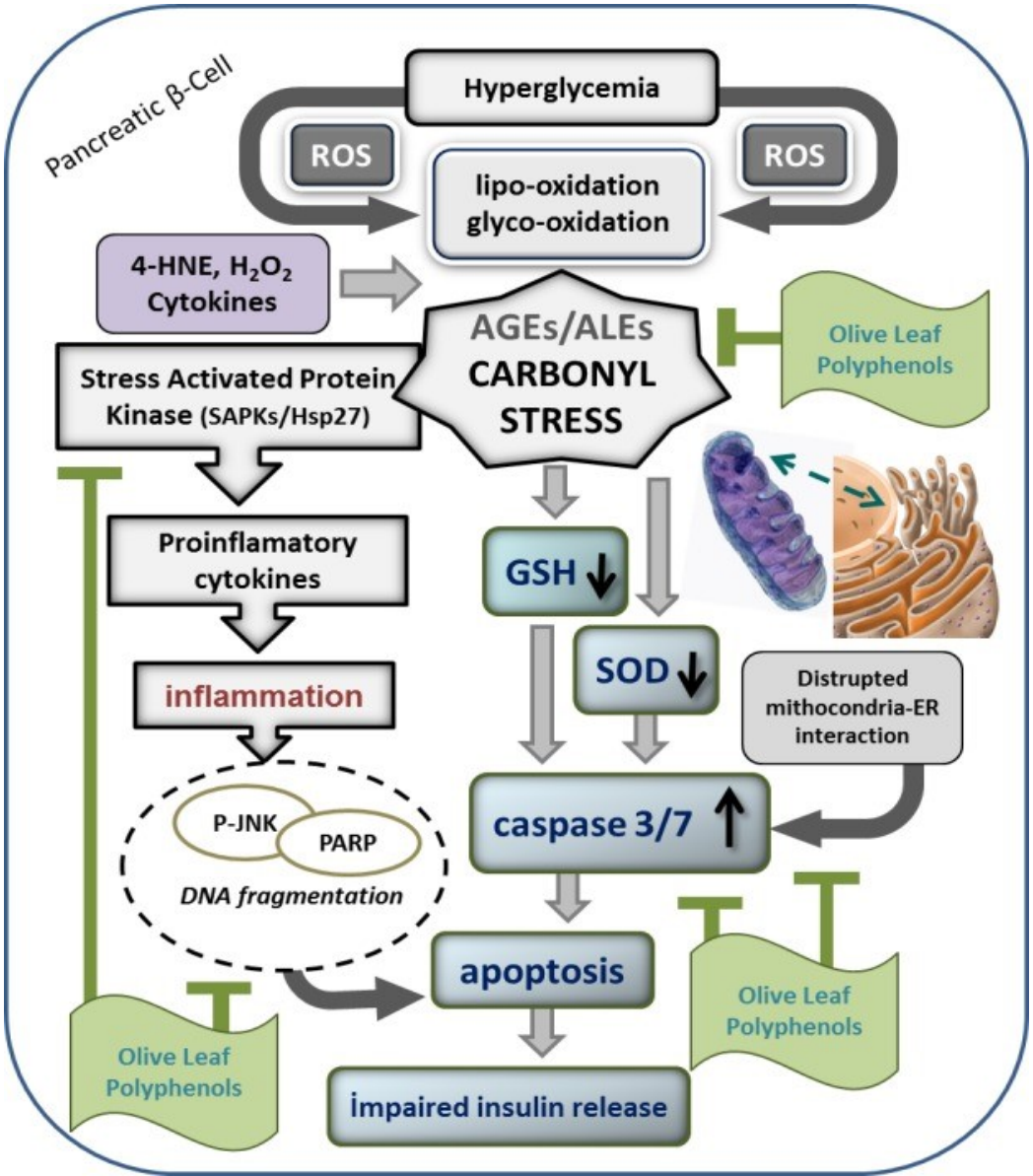
Mitotoxicant

THREAT: ELECTROMAGNETIC





ADVANCED GLYCATION END PRODUCTS- PANCREAS



Body Burden - Environmental Toxicants

Persistent Organic Pollutants

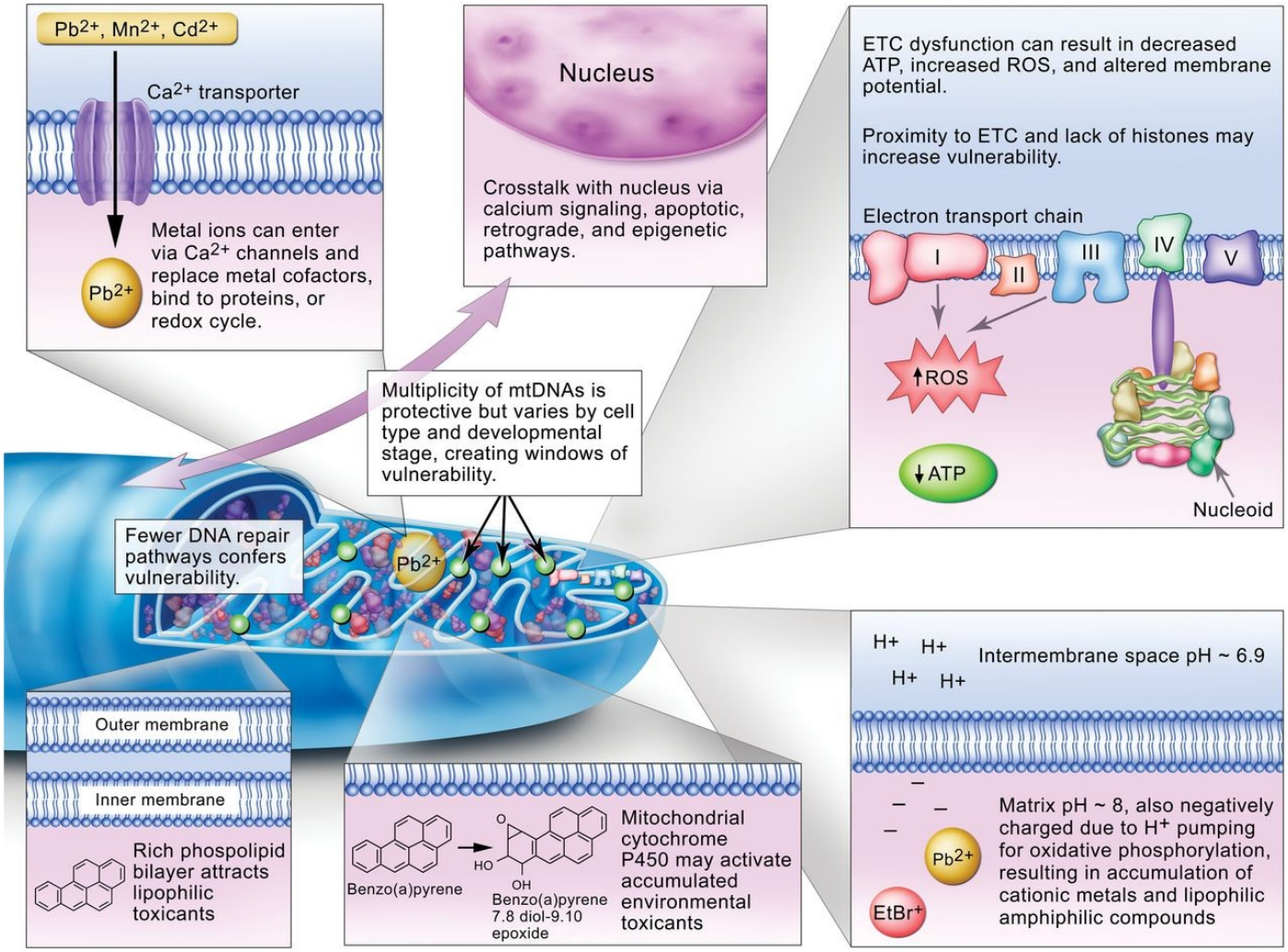
- Perfluorinated compounds (teflon, stain master, Gortex) PFO
- Chlorpyriphos
- DDE – is a metabolite of DDT that is found in all people world wide
- Polychlorinated biphenyls (**PCBs**)
- aldrin [1]
  chlordane [1]
  dichlorodiphenyl trichloroethane (DDT)[1]
  dieldrin[1]
  endrin[1]
  heptachlor[1]
  hexachlorobenzene [1,2]
  mirex[1]
  toxaphene[1]
  polychlorinated biphenyls (PCBs) [1,2], polychlorinated dibenzo-p-dioxins[2](dioxins),
  polychlorinated dibenzofurans[2] (furans)
- Heavy metals (except arsenic)

Non Persistent Toxicants –**NOT REMOVED VIA SAUNAS; MUST LOWER OR AVOID EXPOSURE**

- Pesticides (organophosphates, pyrethroid pesticide
- Solvents
- Bisphenol A (**BPA)** is an industrial chemical that has been used to make certain **plastics** and resins since the 1960s, triclosan, 4-nonoxyphenol
- Parabens
- Phthalates

Personal Care Products

Factors that affect mitochondrial vulnerability to environmental toxicants



Joel N. Meyer et al. Toxicol. Sci. 2013;toxsci.kft102

TOXICOLOGICAL SCIENCES

Threat: Circadian Rhythm Disturbance

- Circadian Clock NAD^+ Cycle Drives Mitochondrial Oxidative Metabolism in Mice

- *Science* 19 Sep 2013:**Clara Bien Peek** et al.

Impairment of the mitochondrial electron transport chain due to sleep deprivation in mice.

These results are consistent with the involvement of sleep in energy metabolism and corroborate previous experiments demonstrating the importance of the hypothalamus in sleep regulation.

- J Psychiatr Res. 2010 Sep;44(12):775-80. **Impairment of the mitochondrial electron transport chain due to sleep deprivation in mice.**

MELATONIN

Passes through all biologic barriers with ease, because of its amphiphilic properties.

Free access to all compartments of the cell, and can be especially concentrated in the nucleus and mitochondria

MELATONIN

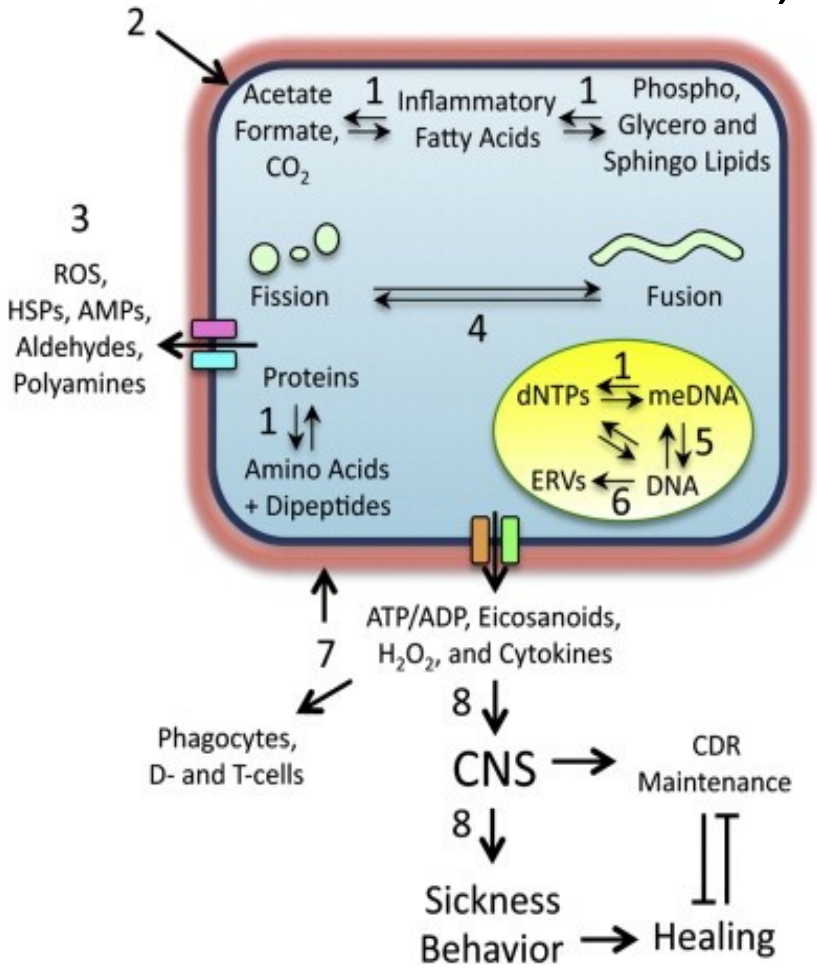
- Regulates mitochondrial homeostasis
- Free radical scavenger,
- Reduces nitric oxide (NO) generation within mitochondria
- Maintains the electron flow, efficiency of oxidative phosphorylation, ATP production and bioenergetic function of the cell **by**
- Regulating respiratory complex activities, Ca^{2+} influx, **and**
- Mitochondrial permeability transition pore opening

Metabolic features of the cell danger response (CDR)

The cell danger response (CDR) is the evolutionarily conserved metabolic response that protects cells and hosts from harm. It is **triggered by encounters with chemical, physical, or biological threats that exceed the cellular capacity for homeostasis**. The resulting metabolic mismatch between available resources and functional capacity **produces a cascade of changes in cellular electron flow, oxygen consumption, redox, membrane fluidity, lipid dynamics, bioenergetics, carbon and sulfur resource allocation, protein folding and aggregation, vitamin availability, metal homeostasis, indole, pterin, 1-carbon and polyamine metabolism, and polymer formation**. The first wave of danger signals consists of the release of metabolic intermediates like ATP and ADP, Krebs cycle intermediates, oxygen, and reactive oxygen species (ROS), and is sustained by purinergic signaling. ***After the danger has been eliminated or neutralized, a choreographed sequence of anti-inflammatory and regenerative pathways is activated to reverse the CDR and to heal*.**

- Mitochondrion. 2014 May;16:7-17. **Metabolic features of the cell danger response.** Naviaux RK[1].

Acute CDR- 8 functional changes in cell structure, physiology, metabolism, and gene expression



Abbreviations: HSPs: heat shock proteins; AMPs: antimicrobial peptides; D-cells: Dendritic Cells; ERVs: endogenous retroviruses; LINEs: long interspersed nuclear elements; meDNA: methylated DNA; dNTPs: deoxynucleoside triphosphates; CNS: central nervous system.

1) **shift cellular metabolism** from polymer to monomer synthesis to prevent the hijacking and assembly of cellular resources by intracellular pathogens,

2) **stiffen the cell membranes** to limit super-infection and pathogen egress,

3) **release antiviral and antimicrobial chemicals** into the peri-cellular environment,

4**) increase autophagy**, mitochondrial fission, and mitophagy to facilitate removal of intracellular pathogens and biogenesis centers,

5) **change DNA methylation and histone** modification to alter gene expression,

6) **mobilize endogenous retroviruses** and LINEs to produce genetic variations,

7) **warn neighboring cells and distant effector cells of the danger with extracellular nucleotides**, H2O2, eicosanoids, metabolites, and cytokines, and

8) **alter the behavior of the host** to prevent the spread of infection to kin, and sleep patterns to facilitate healing.

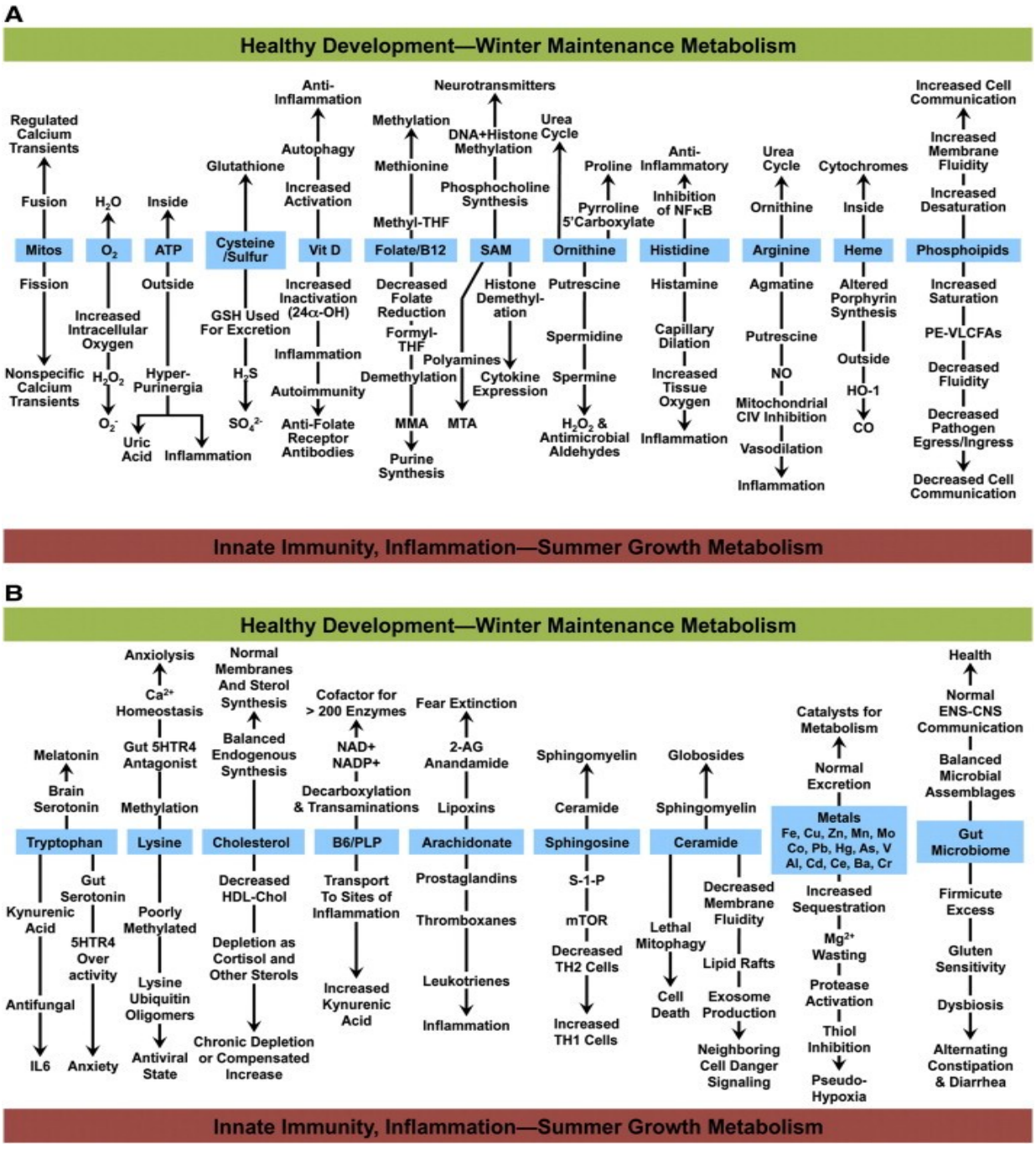
Cell Danger Response

Cell Danger Response (CDR) –initially a protective response; redox signaling via oxidants "tag" the area of insult, the insult is cleared by the oxidants and proteolytic enzymes; after the insult is cleared and the oxidative stress (excess oxidants) is normalized, new cells are made to replace the damaged cells.

- Stiffens the cell membrane to contain the insult
- **Decreased methylation** so that the invaders cannot utilize methylation for their own metabolism – **don't give methylation factors! This isn't the time to blindly treat SNPs (MTHFR)**
- **Decrease vitamin D3** due to inactivation via 24 alpha hydroxylase (upregulated)
- **Decreased glutathione** due to increased utilization
- **Relative B6 deficiency**
- Polyamine shift
- **Increase oxidants** leading to imbalance in redox signaling
- Chronic inflammatory response (CIRS) is an example of a persistent CDR –see Dr. Richie Shoemaker www.survivingmold.com

Chronic CDR

- **When the CDR persists abnormally, whole body metabolism and the gut microbiome are disturbed, the collective performance of multiple organ systems is impaired, behavior is changed, and chronic disease results.** Metabolic memory of past stress encounters is stored in the form of altered mitochondrial and cellular macromolecule content, resulting in an increase in functional reserve capacity through a process known as mitocellular hormesis. The systemic form of the CDR, and its magnified form, the purinergic life-threat response (PLTR), are under direct control by ancient pathways in the brain that are ultimately coordinated by centers in the brainstem. Chemosensory integration of whole body metabolism occurs in the brainstem and is a prerequisite for normal brain, motor, vestibular, sensory, social, and speech development. An understanding of the CDR permits us to reframe old concepts of pathogenesis for a broad array of chronic, developmental, autoimmune, and degenerative disorders. These disorders include autism spectrum disorders (ASD), attention deficit hyperactivity disorder (ADHD), asthma, atopy, gluten and many other food and chemical sensitivity syndromes, emphysema, Tourette's syndrome, bipolar disorder, schizophrenia, post-traumatic stress disorder (PTSD), chronic traumatic encephalopathy (CTE), traumatic brain injury (TBI), epilepsy, suicidal ideation, organ transplant biology, diabetes, kidney, liver, and heart disease, cancer, Alzheimer and Parkinson disease, and autoimmune disorders like lupus, rheumatoid arthritis, multiple sclerosis, and primary sclerosing cholangitis.


A
Healthy Development—Winter Maintenance Metabolism
Regulated Calcium Transients
Fusion
Mitos
Fission
Nonspecific Calcium Transients
H_2O
O_2
Increased Intracellular Oxygen
H_2O_2
O_2^-
Inside
ATP
Outside
Hyper-Purinergia
Uric Acid
Inflammation
Glutathione
Cysteine /Sulfur
GSH Used For Excretion
H_2S
SO_4^{2-}
Anti-Inflammation
Autophagy
Increased Activation
Vit D
Increased Inactivation (24α-OH)
Inflammation
Autoimmunity
Anti-Folate Receptor Antibodies
Methylation
Methionine
Methyl-THF
Folate/B12
Decreased Folate Reduction
Formyl-THF
Demethylation
MMA
Purine Synthesis
Neurotransmitters
DNA+Histone Methylation
Phosphocholine Synthesis
SAM
Histone Demethyl-ation
Polyamines
Cytokine Expression
MTA
Urea Cycle
Proline
Pyrroline 5'Carboxylate
Ornithine
Putrescine
Spermidine
Spermine
H_2O_2 & Antimicrobial Aldehydes
Anti-Inflammatory
Inhibition of NFκB
Histidine
Histamine
Capillary Dilation
Increased Tissue Oxygen
Inflammation
Urea Cycle
Ornithine
Arginine
Agmatine
Putrescine
NO
Mitochondrial CIV Inhibition
Vasodilation
Inflammation
Cytochromes
Inside
Heme
Altered Porphyrin Synthesis
Outside
HO-1
CO
Increased Cell Communication
Increased Membrane Fluidity
Increased Desaturation
Phosphoipids
Increased Saturation
PE-VLCFAs
Decreased Fluidity
Decreased Pathogen Egress/Ingress
Decreased Cell Communication
Innate Immunity, Inflammation—Summer Growth Metabolism
B
Healthy Development—Winter Maintenance Metabolism
Melatonin
Brain Serotonin
Tryptophan
Kynurenic Acid
Antifungal
IL6
Gut Serotonin
5HTR4 Over activity
Anxiety
Anxiolysis
Ca^{2+} Homeostasis
Gut 5HTR4 Antagonist
Methylation
Lysine
Poorly Methylated
Lysine Ubiquitin Oligomers
Antiviral State
Normal Membranes And Sterol Synthesis
Balanced Endogenous Synthesis
Cholesterol
Decreased HDL-Chol
Depletion as Cortisol and Other Sterols
Chronic Depletion or Compensated Increase
Cofactor for > 200 Enzymes
NAD+ NADP+
Decarboxylation & Transaminations
B6/PLP
Transport To Sites of Inflammation
Increased Kynurenic Acid
Fear Extinction
2-AG Anandamide
Lipoxins
Arachidonate
Prostaglandins
Thromboxanes
Leukotrienes
Inflammation
Sphingomyelin
Ceramide
Sphingosine
S-1-P
mTOR
Decreased TH2 Cells
Increased TH1 Cells
Globosides
Sphingomyelin
Ceramide
Lethal Mitophagy
Cell Death
Decreased Membrane Fluidity
Lipid Rafts
Exosome Production
Neighboring Cell Danger Signaling
Catalysts for Metabolism
Normal Excretion
Metals
Fe, Cu, Zn, Mn, Mo
Co, Pb, Hg, As, V
Al, Cd, Ce, Ba, Cr
Increased Sequestration
Mg^{2+} Wasting
Protease Activation
Thiol Inhibition
Pseudo-Hypoxia
Health
Normal ENS-CNS Communication
Balanced Microbial Assemblages
Gut Microbiome
Firmicute Excess
Gluten Sensitivity
Dysbiosis
Alternating Constipation & Diarrhea
Innate Immunity, Inflammation—Summer Growth Metabolism

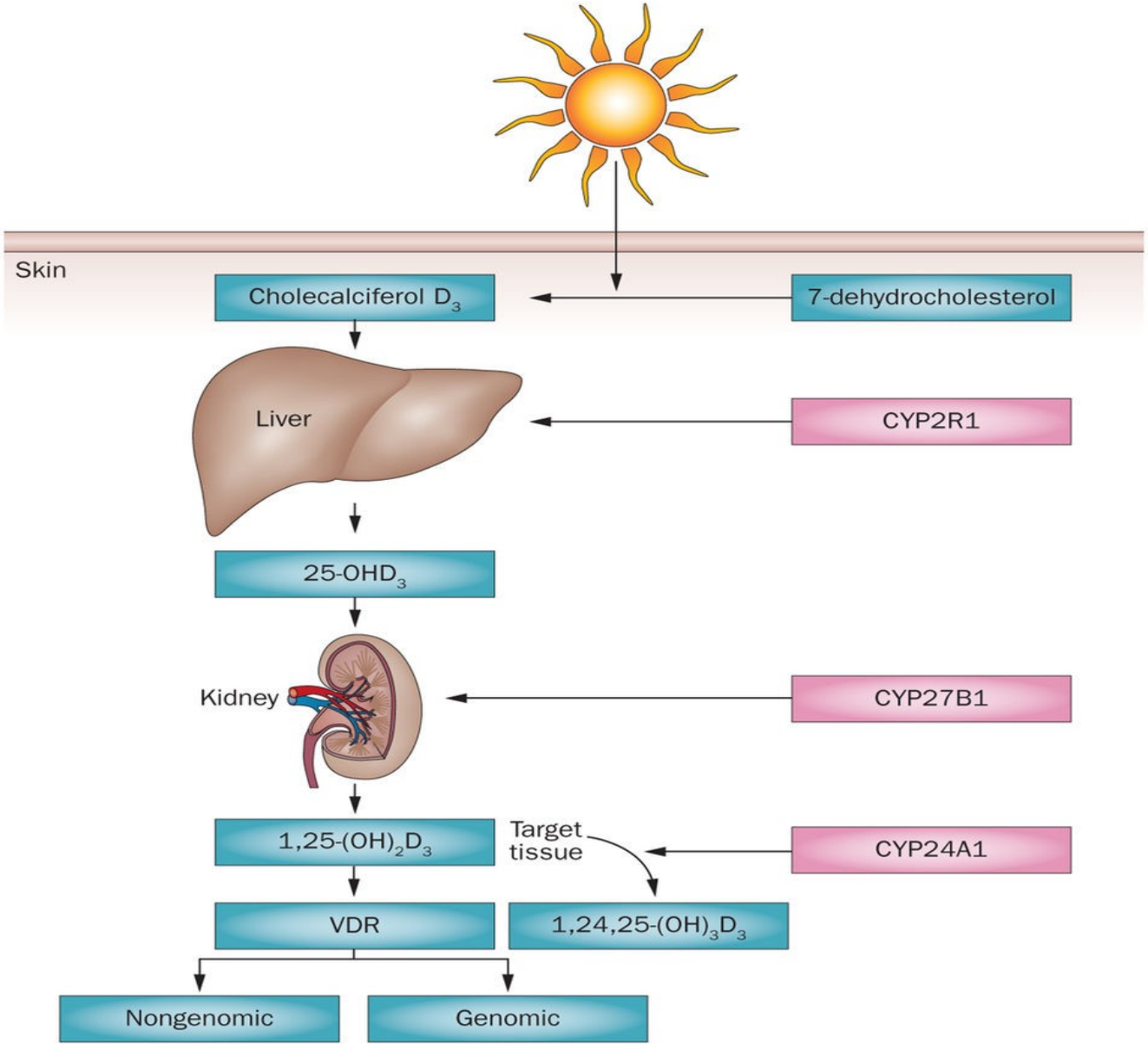
Metabolic features of the cell danger response.

- A. Twelve branch-point metabolites from mitochondria to phospholipids. Each of the metabolites and effectors indicated can be metabolized in two or more alternative pathways. The pathways indicated in the upward direction in the figure are characteristic of healthy development. They are also active during conditions of caloric restriction, such as those that occurred historically during the winter, during which the maintenance and preservation of limiting resources and energy is essential. The metabolic pathways indicated in the bottom half of the Figure are active during periods of unrestricted nutrient and resource availability, as is characteristic of the abundance of summer. When cell division can occur, healthy growth without inflammation results. However, when cell division cannot occur readily, as is the case in many differentiated tissues like the brain, and physical exercise is limited, innate immune disease and chronic inflammation result.

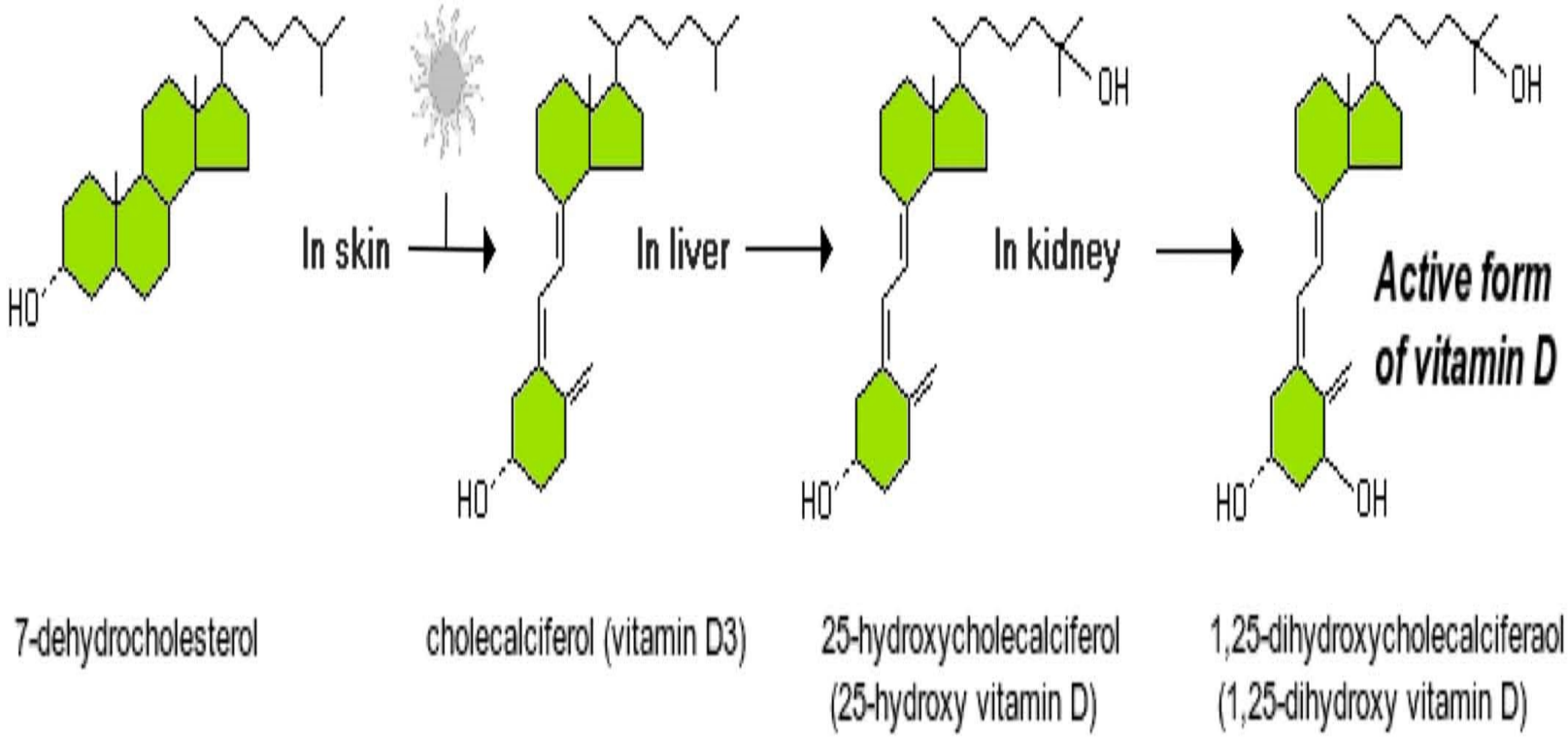
Metabolic features of the cell danger response.

- B. Nine branch-point metabolites and effectors from tryptophan to the gut microbiome. The reactions illustrated in the bottom half of the Figure are characteristic of the CDR. The list of CDR metabolites and their metabolic fates illustrated in panels A and B is not intended to be complete. Other metabolites, effectors, and metabolic fates also exist and are coordinately regulated with those indicated, and tailored by metabolic memory to help defend the cell during danger. When the CDR persists pathologically, chronic disease results.

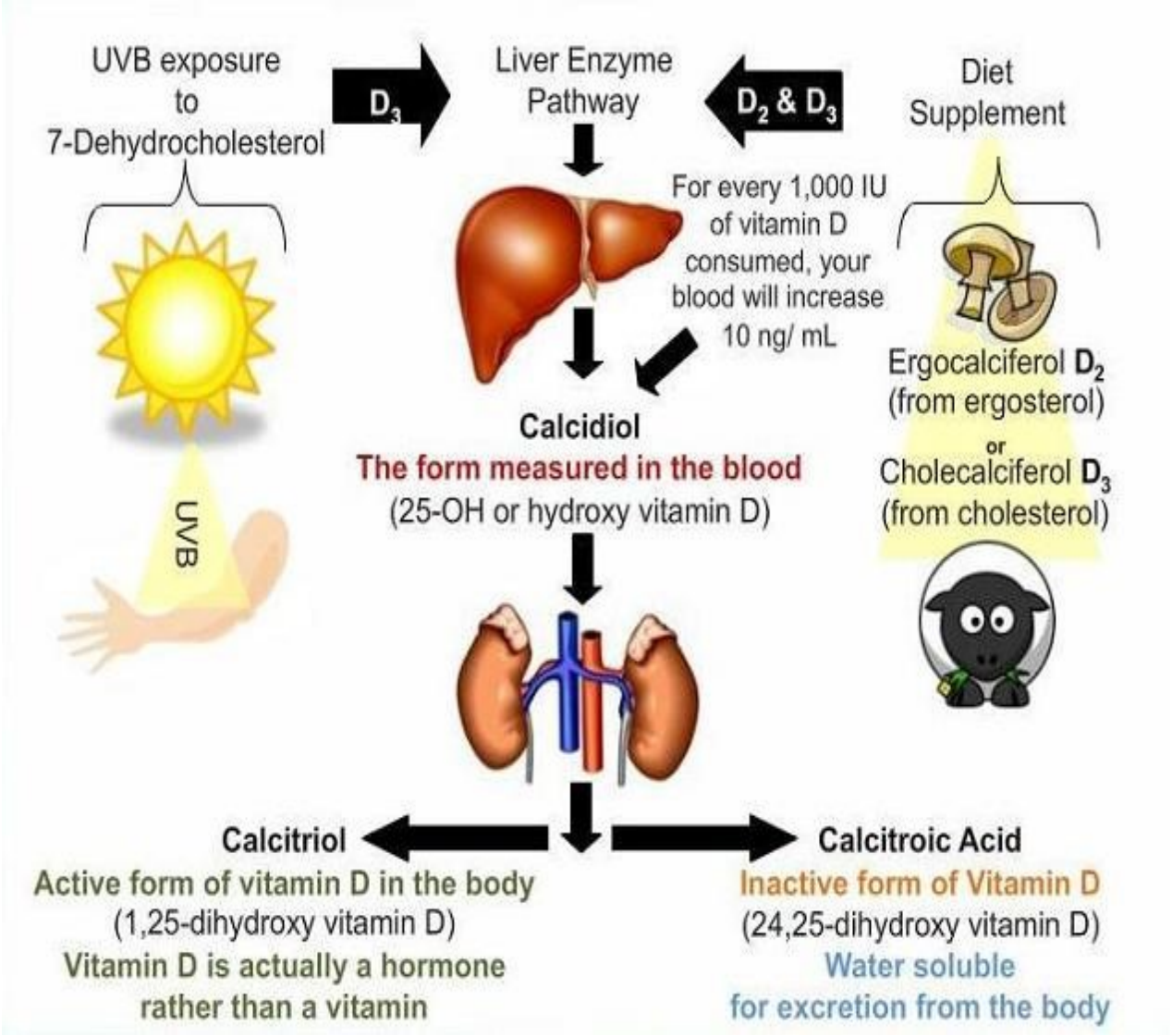
Vitamin D Metabolism



Vitamin D Metabolism

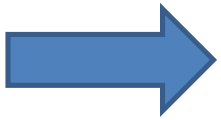


Vitamin D Metabolism



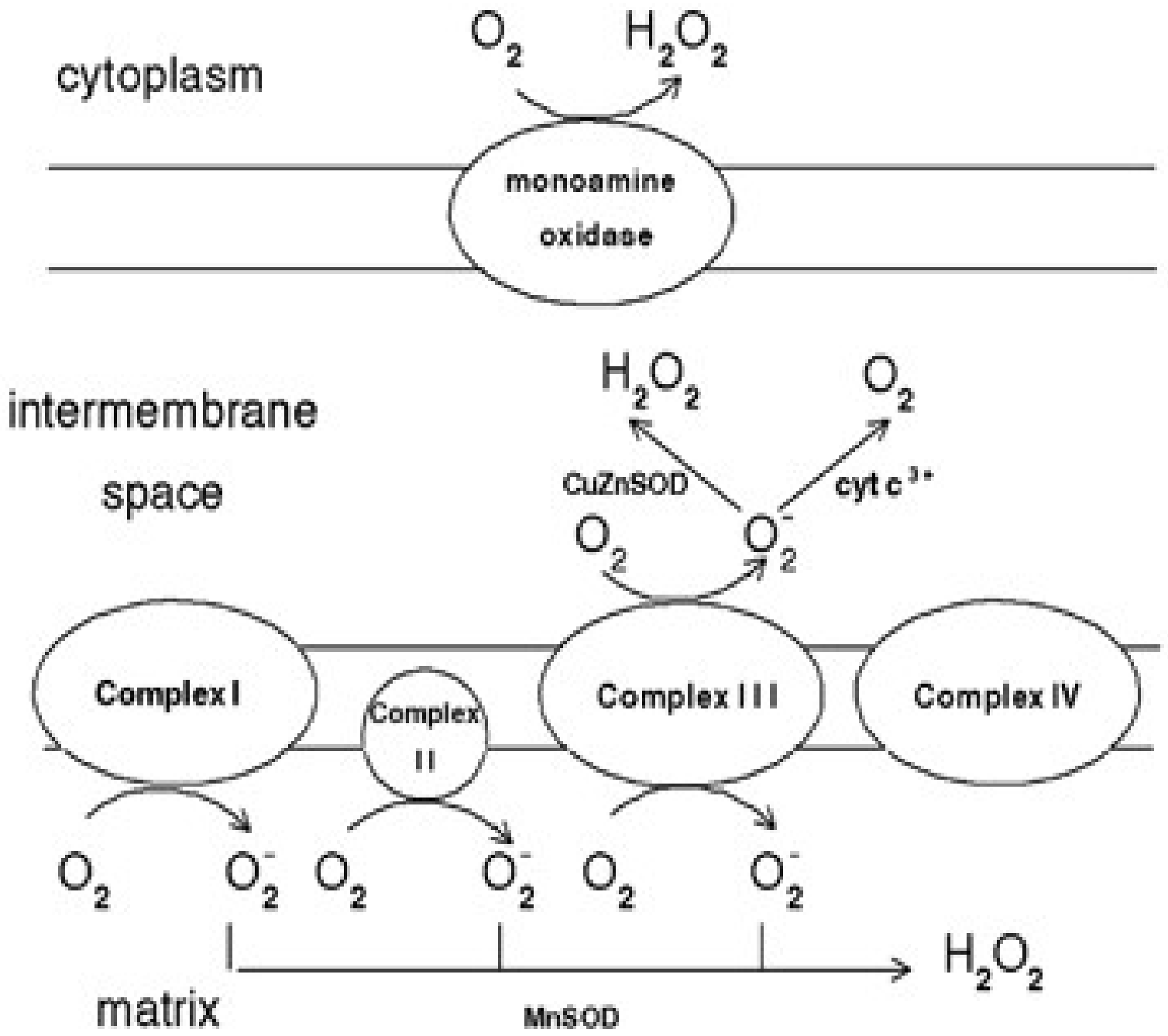
- Think CDR if both 25 OH vitamin and 1, 25 OH Vitamin D are low.
- Lysine helps stop the response

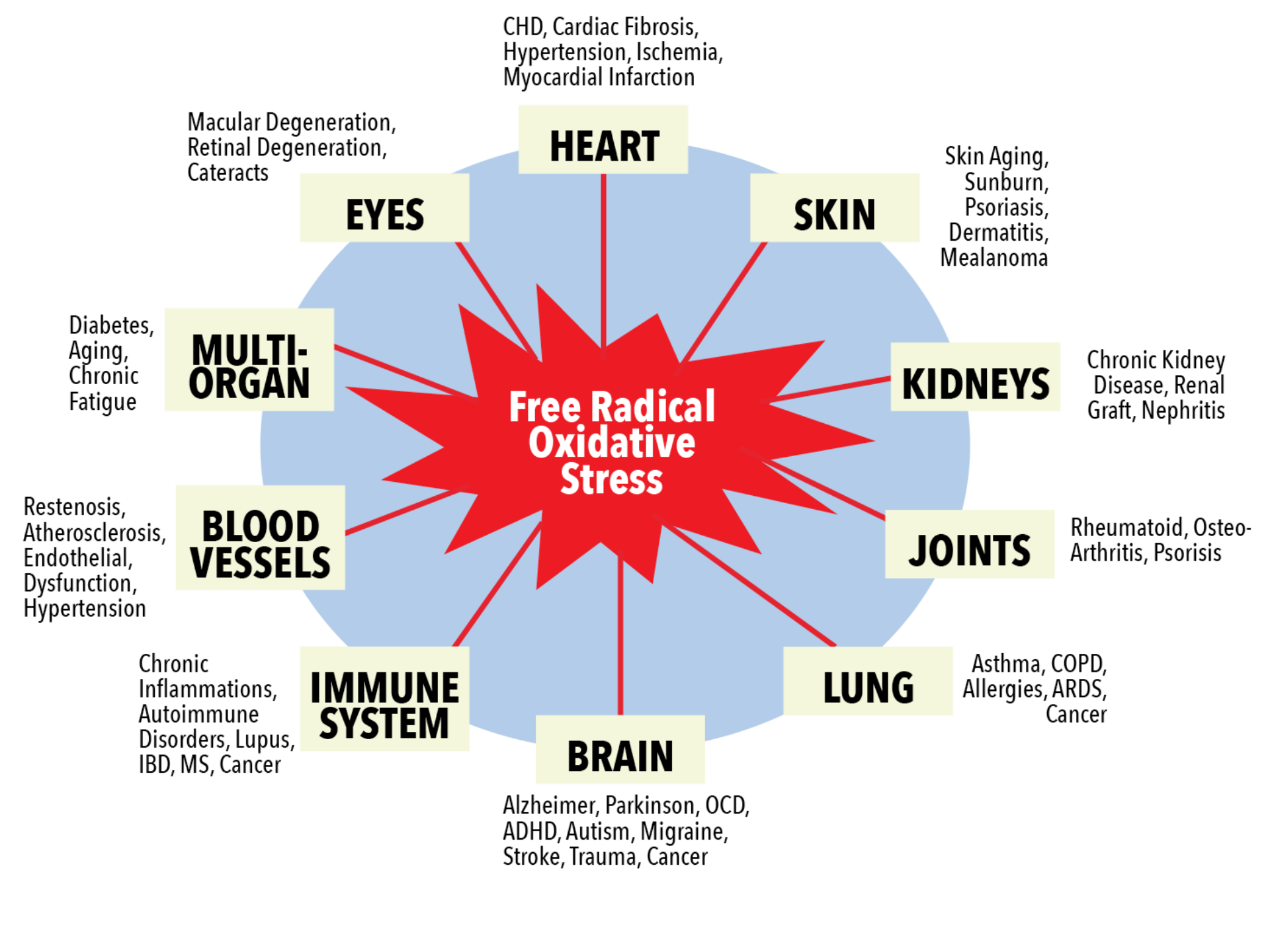
Goldilocks principle= Homeostasis

- Need a little oxidative stress but not excessive oxidative stress 
- Mitochondrial Hormesis

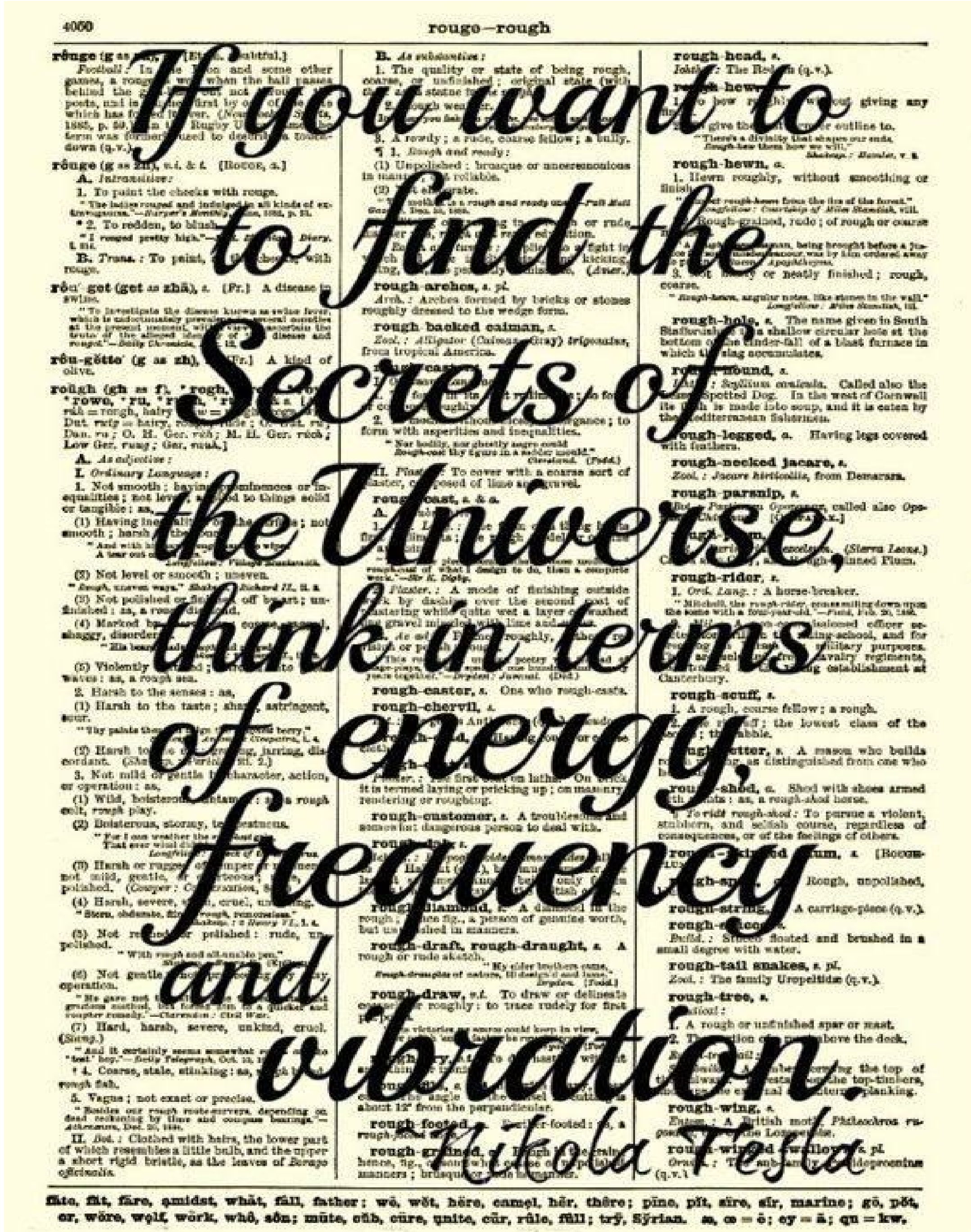
3. NO/ONOO Cycle

Preceding short-term stressors **[**infection (viral or bacterial) →inflammatory cytokines; tbi-->NMDA stimulation; severe psychological stress; pesticides; volatile organic solvents; **]** →Elevation of iNOS (inducible nitric oxide synthase) → Elevation of NO (nitric oxide) → combines with OO- (superoxide)→ ONOO-(Peroxynitrite)= potent OXIDANT→ OXIDATIVE STRESS= imbalance between oxidants and Reductants→ stimulate NF-kB→ stimulate 5 inflammatory Genes=IL-1B, IL-6, IL-8, TNFa, INFg→ act locally→ iNOS→NO→ vicious cycle →


cytoplasm
O_2
H_2O_2
monoamine oxidase
intermembrane space
H_2O_2
O_2
CuZnSOD
cyt c $^{3+}$
O_2
O_2^-
Complex I
Complex II
Complex III
Complex IV
O_2
O_2^-
O_2
O_2^-
O_2
O_2^-
H_2O_2
matrix
MnSOD


CHD, Cardiac Fibrosis, Hypertension, Ischemia, Myocardial Infarction
HEART
Macular Degeneration, Retinal Degeneration, Cateracts
EYES
SKIN
Skin Aging, Sunburn, Psoriasis, Dermatitis, Mealanoma
Diabetes, Aging, Chronic Fatigue
MULTI-ORGAN
Free Radical Oxidative Stress
KIDNEYS
Chronic Kidney Disease, Renal Graft, Nephritis
Restenosis, Atherosclerosis, Endothelial, Dysfunction, Hypertension
BLOOD VESSELS
JOINTS
Rheumatoid, Osteo-Arthritis, Psorisis
Chronic Inflammations, Autoimmune Disorders, Lupus, IBD, MS, Cancer
IMMUNE SYSTEM
LUNG
Asthma, COPD, Allergies, ARDS, Cancer
BRAIN
Alzheimer, Parkinson, OCD, ADHD, Autism, Migraine, Stroke, Trauma, Cancer

LIFESTYLE CAUSES OF CHRONIC INFLAMMATION


If you want to
to find the
Secrets of
the Universe,
think in terms
of energy,
frequency
and
vibration.
-Nikola Tesla

Cellular Voltage

1. The body needs a constant supply of energy or voltage
2. The majority of the energy supply comes from the environment:

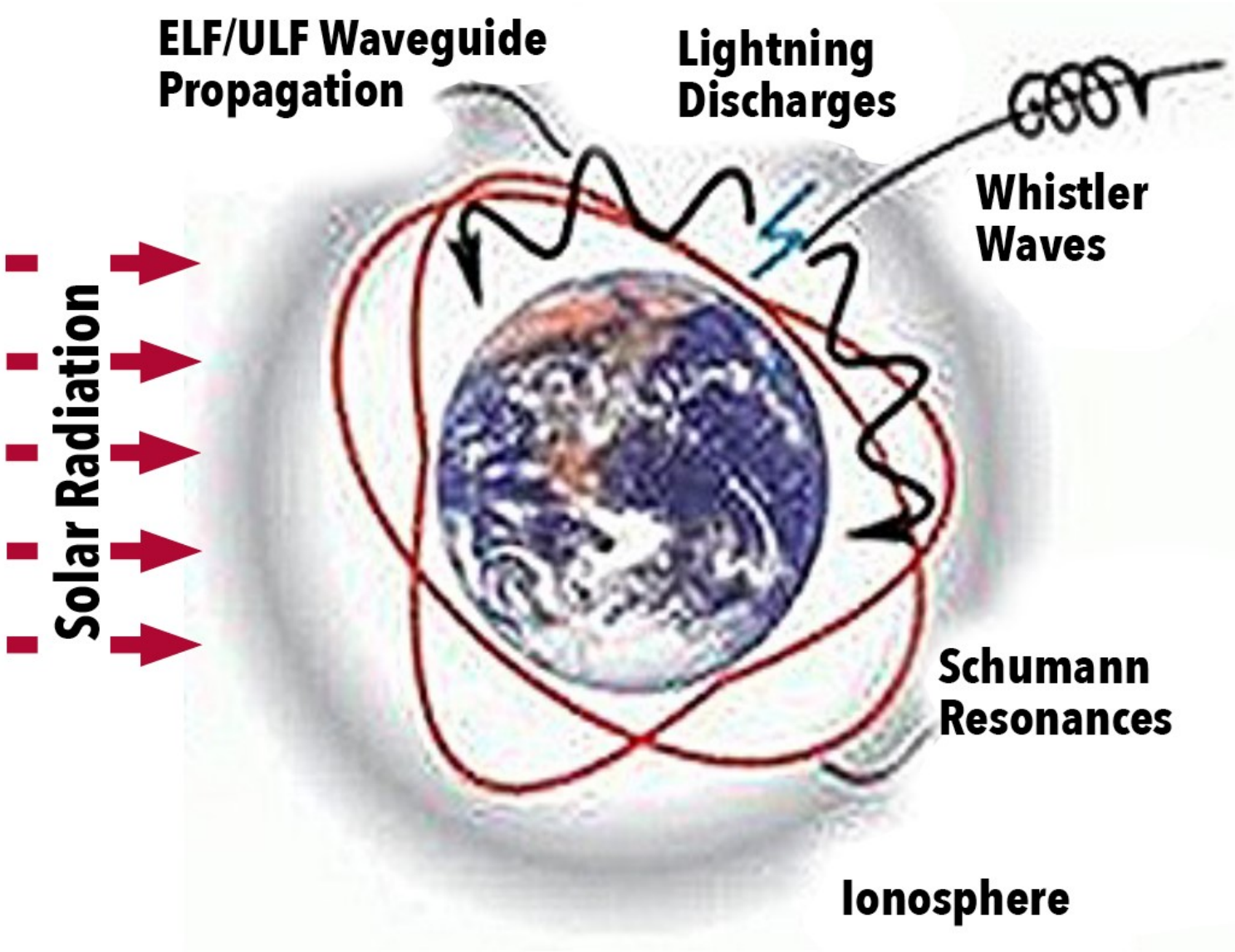
- EMF- Electromagnetic Fields
- ELF-Electric Fields
- Photoelectric-Light
- Semi-conduction- Electron donation
- Water – 4th Phase
- Oxygen
- Nutrients

Electromagnetic Fields

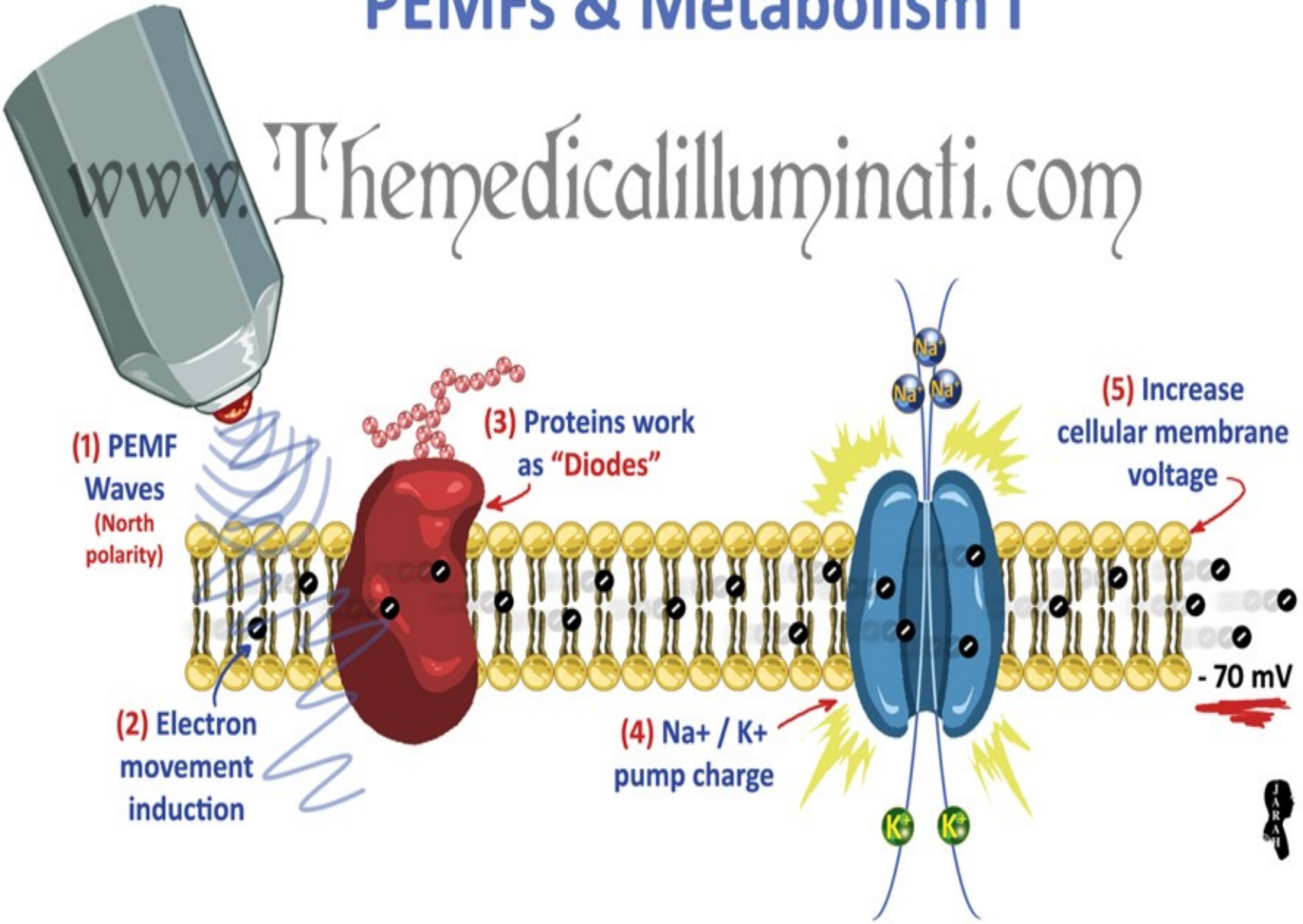
- The earth generates a magnetic field discovered in 1935 by Carl Gauss

- Used to be 5 Gauss, but now is 0.6 gauss and continuing to fall

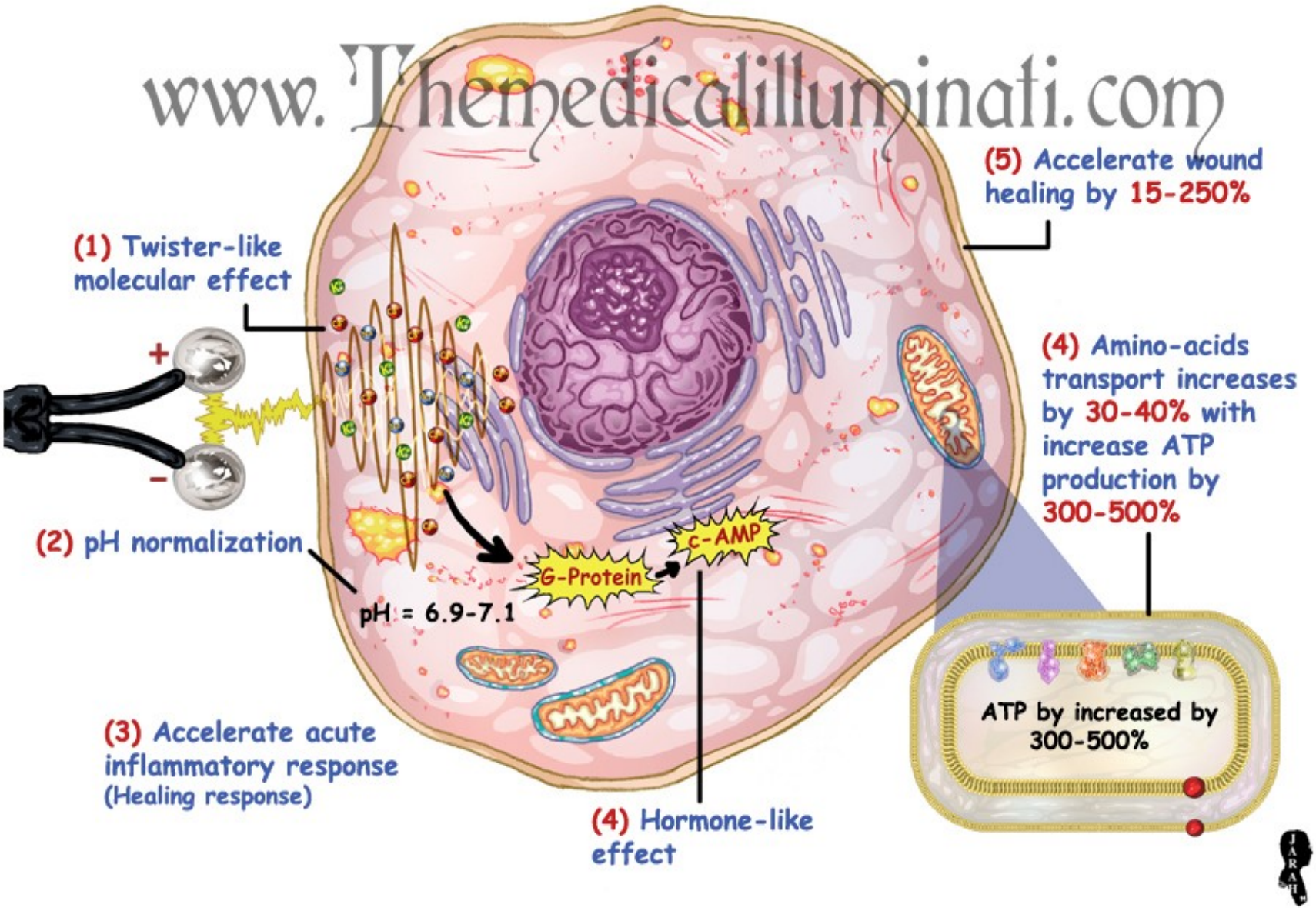
Electric Fields-ELF


ELF/ULF Waveguide Propagation
Lightning Discharges
Whistler Waves
Solar Radiation
Schumann Resonances
Ionosphere

PEMFs & Metabolism I



Microcurrent Therapy Effects

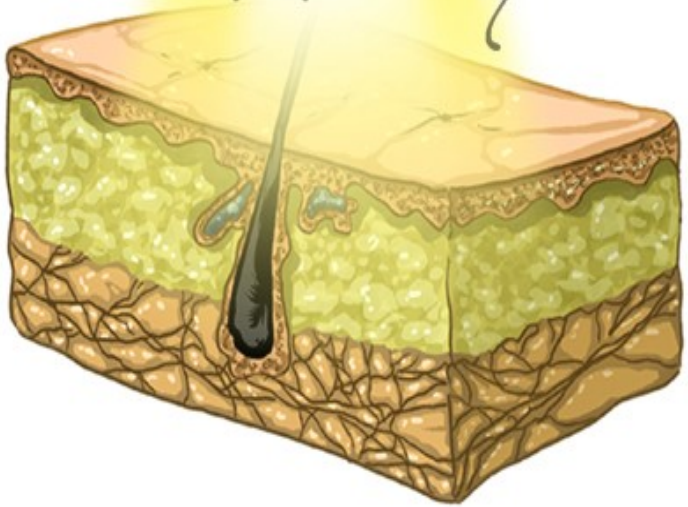


Human Photosynthesis

(According to Dr. Herrara)

Sun light

Sun light



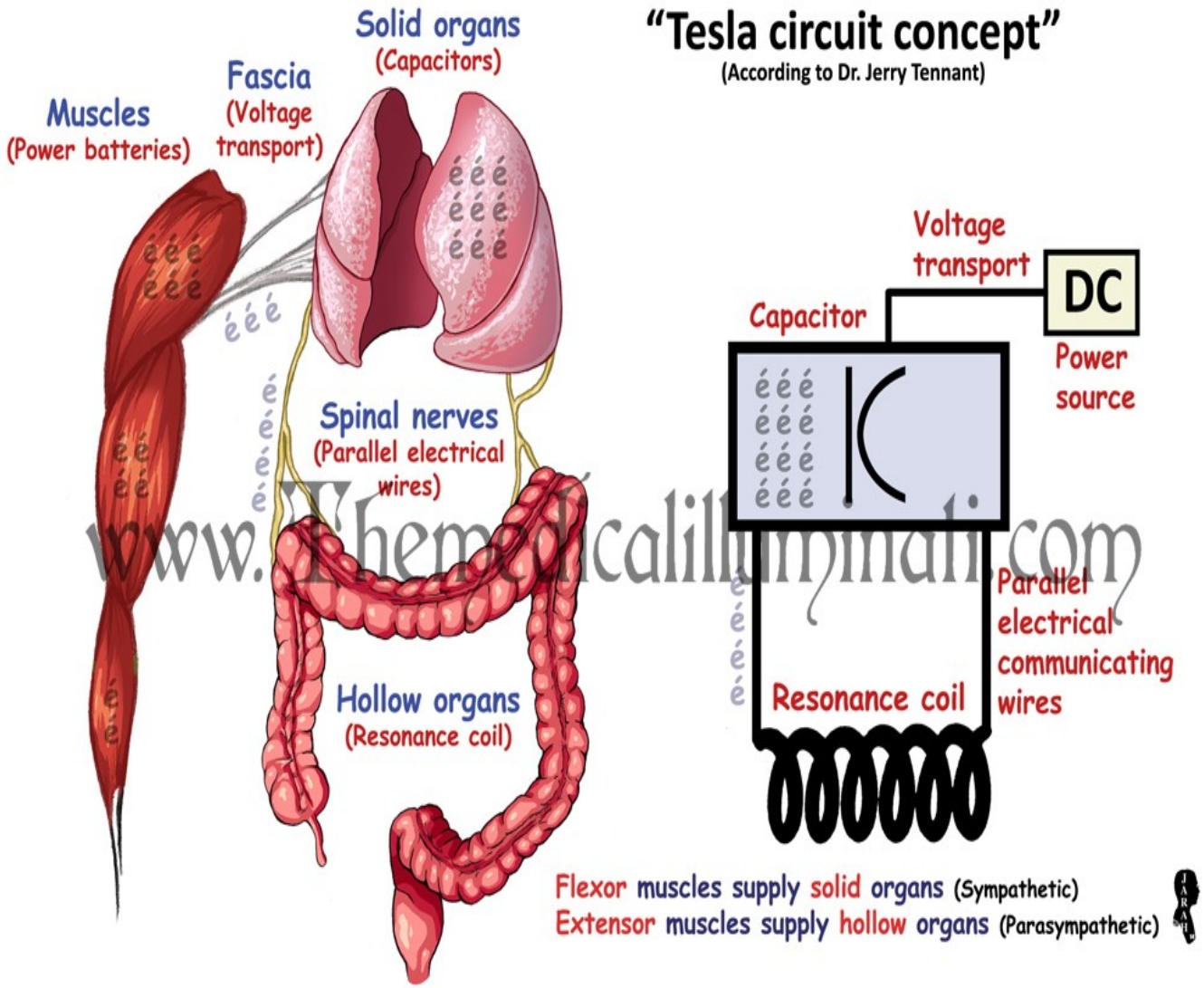
Light Energy + Human pigment (Melatonin & Hemoglobin) + $H_2O = 4H^+ + O_2 + 4é$ (To mitochondria to produce ATP)

Up to 33% of the body's energy is produced through human photosynthesis

The body's electrical wiring system

"Tesla circuit concept"

(According to Dr. Jerry Tennant)

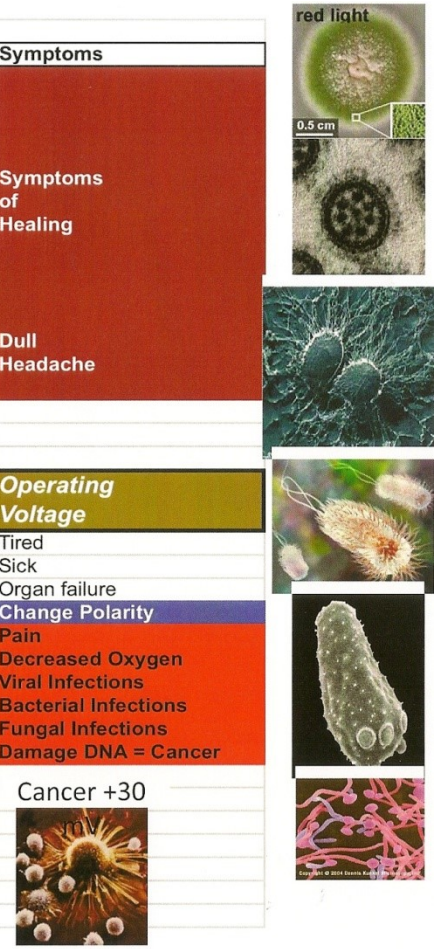


				Values are Approximate		
Nakatani	Cell Voltage	Cell pH	Salivary pH	Cell pH	Cell Voltage	Symptoms
210	-105	8.84	8.04	Viruses	-105	
200	-100	8.75	7.95	Bacteria	-100	
190	-95	8.66	7.86	Fungus	-95	
180	-90	8.58	7.78	Cancer Cells	-90	Symptoms
170	-85	8.49	7.69	Die at 7.8-8.8	-85	of
160	-80	8.40	7.60		-80	Healing
150	-75	8.31	7.51		-75	
140	**-70**	**8.23**	**7.43**		**-70**	
130	-65	8.14	7.34		-65	
120	-60	8.05	7.25		-60	
110	-55	7.96	7.16		-55	Dull
100	**-50**	**7.88**	**7.08**	**Normal**	**-50**	**Headache**
90	-45	7.79	6.99	**Healing**	-45	
80	-40	7.70	6.90		-40	
70	-35	7.61	6.81		-35	
60	-30	7.53	6.73		-30	
50	-25	7.44	6.64		-25	***Operating***
40	**-20**	**7.35**	**6.55**		**-20**	***Voltage***
30	-15	7.26	6.46		-15	Tired
20	-10	7.18	6.38		10	Sick
10	-5	7.09	6.29		-5	Organ failure
0	0	7.00	6.20		0	**Change Polarity**
	5	6.91	6.11		5	**Pain**
	10	6.83	6.03		10	**Decreased Oxygen**
	15	6.74	5.94		15	**Viral Infections**
	20	6.65	5.85		20	**Bacterial Infections**
	25	6.56	5.76		25	**Fungal Infections**
	30	6.48	5.68		30	**Damage DNA = Cancer**
	35	6.39	5.59		35	
	40	6.30	5.50		40	
	45	6.21	5.41		45	
	50	6.13	5.33		50	
	55	6.04	5.24		55	
	60	5.95	5.15		60	
	65	5.86	5.06		65	

Electron Donor

Electron Stealer

Cancer +30



The Biophoton Theory

- All living cells are able to "**absorb**" light energy by their DNA, and "**re-emit**" the absorbed light energy as biophotons (**Fritz-Albert Popp theory**)
- Human cellular interactions are driven by "**Bio-photons**", also known as "**Ultra-weak photon emission**", according to **Dr. Fritz-Albert Popp**
- ***Light is stored in the DNA molecules of the nuclei*** -
- Dynamic web of light constantly released and absorbed by the DNA may connect cell organelles, cells, tissues, and organs within the body and **serve as the organism's main communication network and as the principal regulating instance of all life processes**.

The Biophoton Theory

- **Molecular activation**: when a photon is absorbed by a molecule, its electrons will change position between the orbits at the atomic level, resulting in high energy state known as "**Singlet state**". This molecular excited singlet state behaves differently than the same molecule in its normal state, and can cause "**Electron transfer**" to its neighbor molecule, resulting in tissue excitation. When this occurs in the mitochondria (*via cytochrome oxidase c*), the electron transport chain reaction is activated **10** times its normal rate, resulting in more ATP production

Photo-biology

- Non-ionizing radiation:

1. Infrared (**1000-800** nm)
2. Visible (**800-400** nm)- ROYGBIV
3. Ultraviolet (**< 400** nm); subdivided into: **UV-A** (***Long UV***): (**400-315** nm); **UV-B** (***Near UV***): (**315-280** nm); **UV-C** (***Middle UV***): (**280-100** nm)

Chromophores

Definition: Living cells that absorb light

- Molecules absorb non-ionizing photons
- Capture the energy from photons
- Utilize that energy in chemical reactions.

Examples:

- *Chlorophyll*
- *Hemoglobin*
- *Porphyrin*
- *Bilirubin*
- *Cytochromes*
- *Catalases*
- *Melatonin*

The Biophoton Theory

Alexander Gruwitsch (**1922**):

Coherent light wave in a **UV frequency** … emitted from living cells (*Animals and plants*)=“**Biophotons**”.

Coherent means that the emitted biophotons are **ordered** and ***NOT*** randomly emitted like normal light photons.

UV-light (UV-A & UV-C light) **200-800**

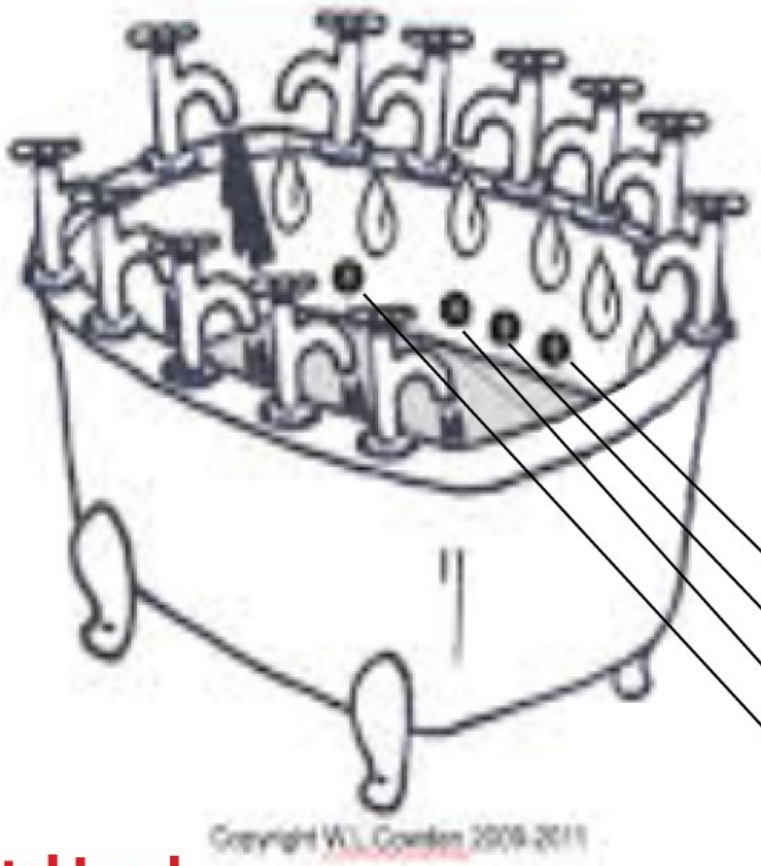
Mitochondrial Dysfunction Evaluation

- YOU HAVE TO LOOK AT EVERYTHING!
- COMPREHENSIVE & HOLISTIC VIEW
- Comprehensive history –eg: FMLogics, Living Matrix

Health Is Like A Bathtub

"DIRTY WATER" FAUCETS =
Nutrient depleted foods
Electromagnetic fields
Radiation pollution
Toxic relationships
Toxic emotions
Tissue acidity
Heavy metals
Polluted air
Antibiotics
Pesticides
Biotoxins
Hypoxia
Allergens

"CLEAN WATER" FAUCETS =
Health foods & nutrients
Purpose & will to live
Sunshine & exercise
Good relationships
Peace, joy & love
Great attitude
Restful sleep
Pure water
Fresh air



"DRAINS" =
Bowel
Liver
Kidneys
Lymphatics

Disease is a bathtub full of DIRTY WATER = High Total Load

Mitochondrial Dysfunction Evaluation

Look for evidence of:

1. Decrease ATP production
2. Increase in reactive oxygen species (ROS) – imbalance in redox signaling
3. Altered membrane potential –VDAC (voltage dependent anion channel found in the outer mitochondrial membrane)

Why assess mitochondrial function?

- Establish the baseline
- Monitoring and surveillance
- Need to show that the therapeutic program is working
- Important for patient compliance

Work up

- Comprehensive history
- Comprehensive exam
- Labs
- Computerized Regulation Thermometry (AlfaSight)

Mitochondrial Function Profile

- Blood test which combines several tests which together assess mitochondrial function and identify where the problem areas with energy production are. It is exceptionally useful for chronic fatigue sufferers as it gives clear indications for a treatment regime.

Made up of the following individual tests:

- ATP profiles;
- NAD (functional B3);
- SODase;
- L-carnitine;
- Cell-free DNA;
- Glutathione Peroxidase

- All the above tests are performed at Acumen Laboratory
- Co-enzyme Q10 - this test is performed at Biolab Medical Unit
- **About "ATP profiles"**
- The most significant test in the Mitochondrial function profile is called "ATP profiles". It was developed by Dr John McLaren-Howard. The result is made up of three elements. First of all, it **measures the rate at which ATP is recycled** in cells. Because production of ATP is highly dependent on **magnesium status** so the first part of the test studies this aspect.
- The second part of the test measures **the efficiency with which ATP is made from ADP**. If this is abnormal, then this could be as a result of magnesium deficiency, and/or low levels of Co-enzyme Q10, and/or low levels of vitamin B3 (NAD) and/or low levels of acetyl L-carnitine.
- The third possibility is that **the protein which transports ATP and ADP across mitochondrial membranes is impaired** and this is also measured

Assessment of Mitochondrial Dysfunction

Markers of oxidative stress (F2-Isoprostanes, 8 OH dG)

Organic Acid testing

Mitochondrial Health Package (NeuroScience):

- Plasma peroxidases
- Mitochondrial Membrane Potential (MMP)
- Mitochondrial Challenge test

RBC Magnesium or Exatest

Melatonin levels (D.U.T.C.H)

Steroid Hormones (D.U.T.C.H) & Thyroid hormones

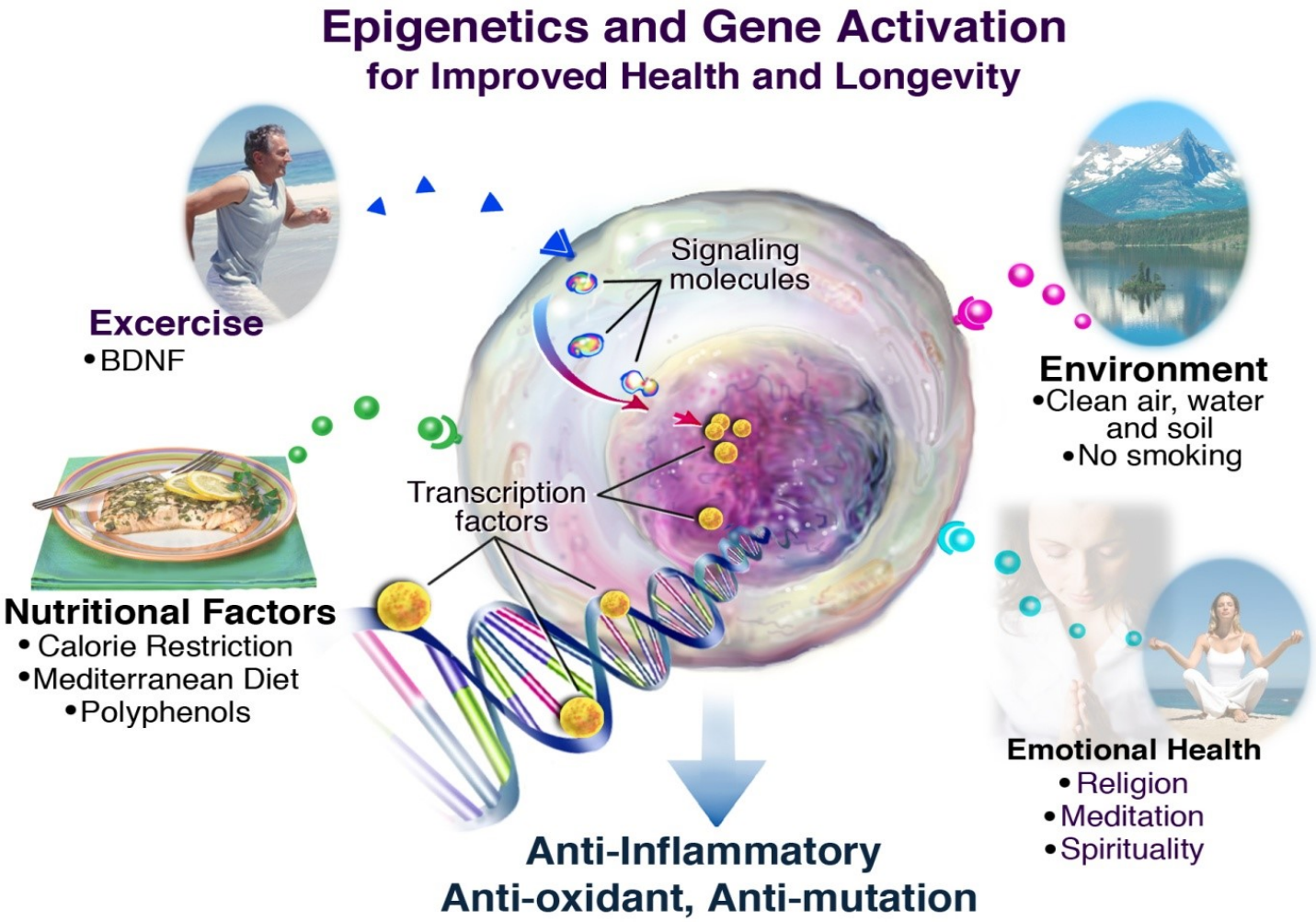
Genomic testing- methylation and/or PON1 SNPs decrease the ability to detoxify pesticides

Voltage

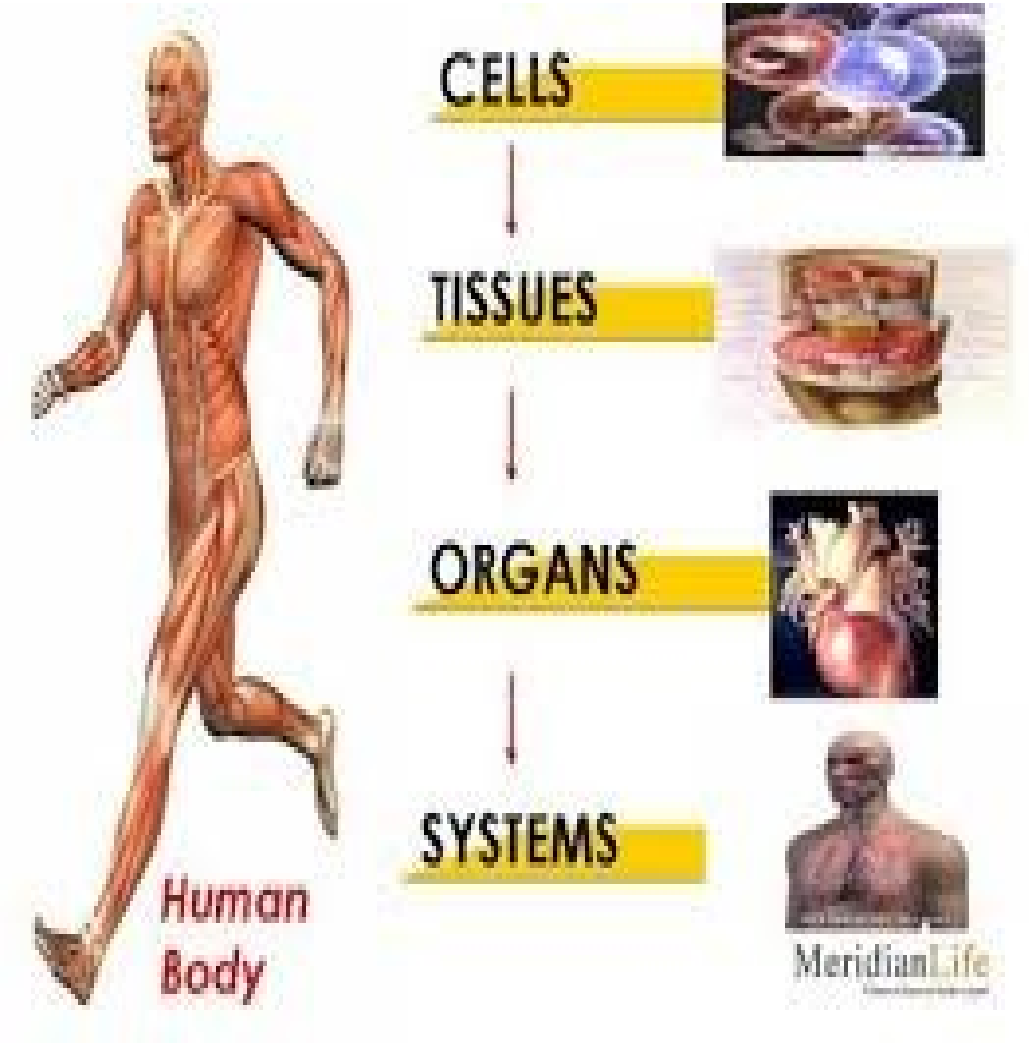
Part 3 –Mitochondrial Restoration

MITOCHONDRIAL RESCUE & RESTORATION

MITOCHONDRIAL RESCUE & RESTORATION



MITOCHONDRIAL RESTORATION



MITOCHONDRIAL RESCUE & RESTORATION

It is all about the cells

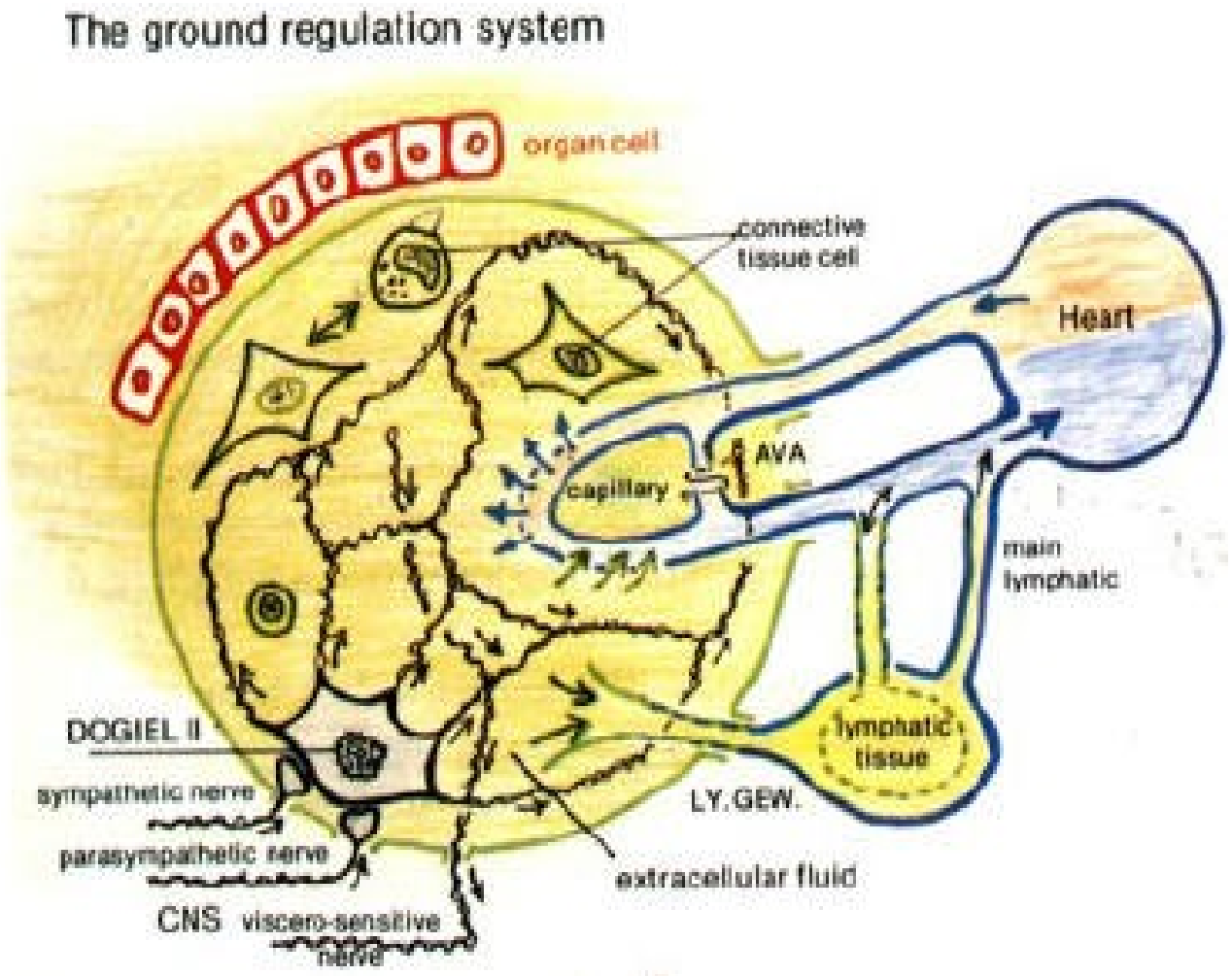
What does a cell need to stay healthy ?

1. **PEMF** – Significantly increases the cells electrical charge & magnetic energy, allowing it to repair & regenerate.
2. **H2O** – Drink half your body weight in ounces.
3. **Good Quality Macro Nutrients** - Carbohydrates (sugars), Lipids (fats), Proteins.
4. **Micro Nutrients** (Vitamins & Minerals) – Organic, Non GMO, Natural Supplementation & Good Quality Salt.
5. **Oxygen** – Exercise / Movement
   This increases your O2 levels

~70 millivolts
Measurable
charge

~20 millivolts
Measurable
charge

Pischinger's Ground System



Healthy ECM aka Terrain aka Biological soil

MITOCHONDRIAL RESCUE & RESTORATION

1. RESTORE FUNCTION

2. MAKE NEW MITOCHONDRIA aka **BIOGENESIS**

BIOGENESIS

- The **health of mitochondria** is in part **regulated** by their **biogenesis** and **peroxisome proliferator-activated receptor gamma-coactivator-alpha (PGC-1α)** is regarded as the **key regulator**

  Mitochondrial transcription factor A (**TFAM**) is responsible for the transcriptional control of **mtDNA** and its **translocation to the mitochondria is important to initiate mtDNA transcription and replication**

Magnesium and calcium-enriched deep-sea water promotes mitochondrial biogenesis by AMPK-activated signals pathway in 3T3-L1 preadipocytes.

- Biomed Pharmacother. 2016 Oct;83:477-484. doi: 10.1016/j.biopha.2016.07.009. Epub 2016 Jul 18.

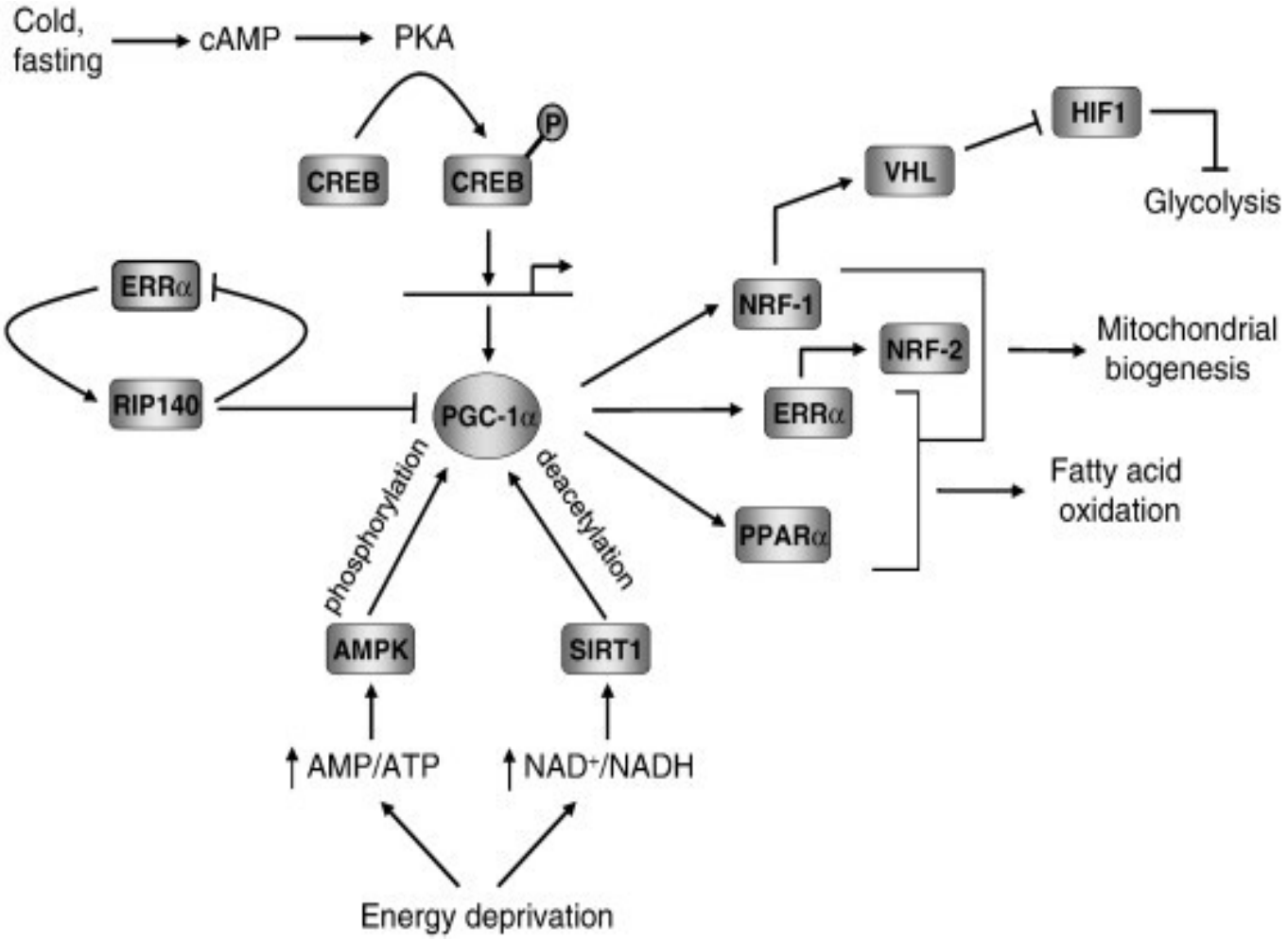
- **Magnesium and calcium-enriched deep-sea water promotes mitochondrial biogenesis by AMPK-activated signals pathway in 3T3-L1 preadipocytes.**

- Ha BG[1], Moon DS[2], Kim HJ[2], Shon YH[3].

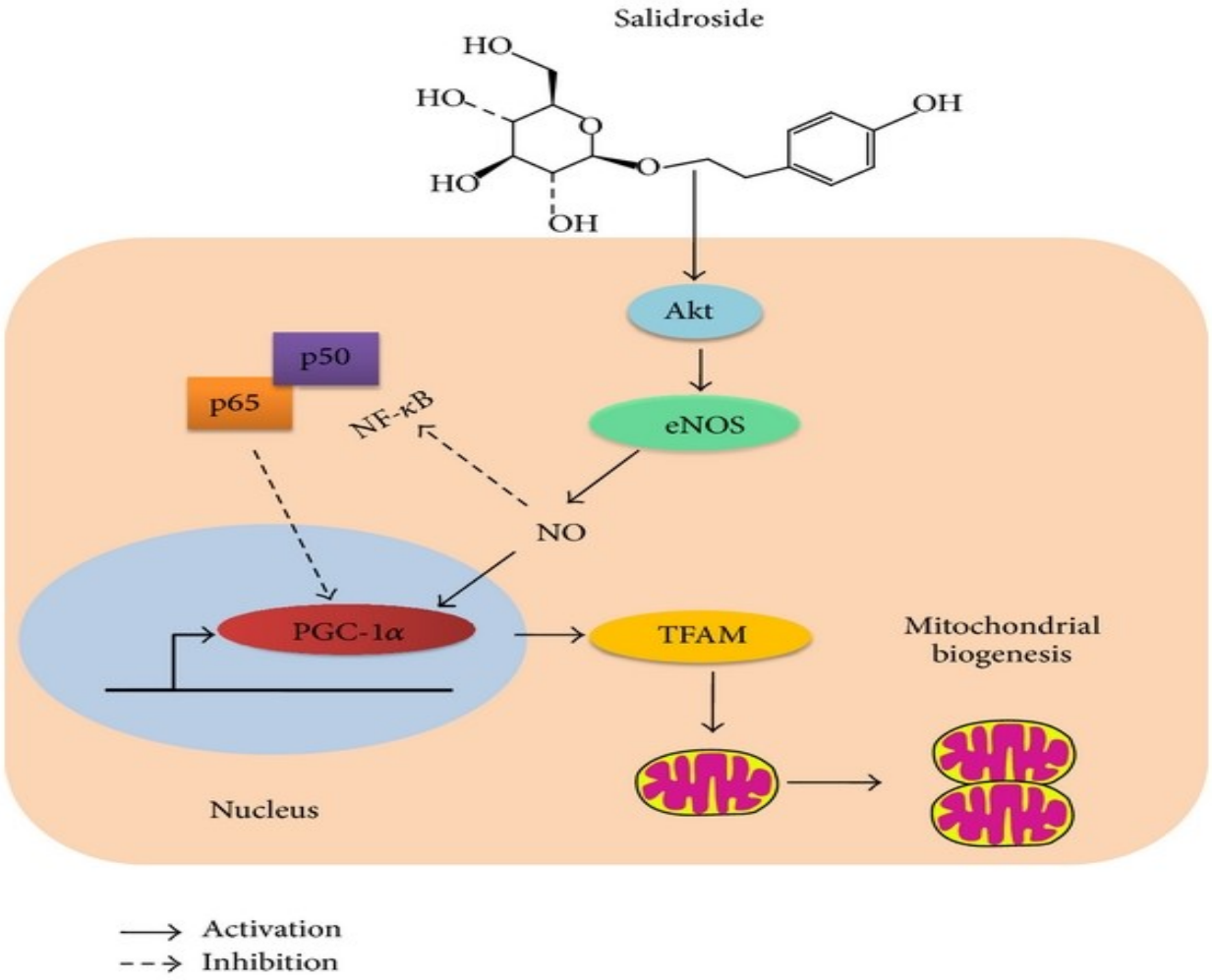
- **Abstract**

- Recent studies showed that deficiencies of essential minerals including Mg, Ca, and K, and trace minerals including Se, Zn, and V, have implications for the development, prevention, and treatment of several chronic diseases including obesity and type 2 diabetes. Our previous studies revealed that **balanced deep-sea water (BDSW), which is composed of desalinated water enriched with Mg and Ca,** has potential as a treatment for diabetes and obesity. In this study, to determine whether BDSW regulates mitochondrial biogenesis and function, we investigated its effects on mitochondrial DNA (mtDNA) content, mitochondrial enzyme activity, expression of key transcription factors and mitochondria-specific genes, phosphorylation of signaling molecules associated with mitochondrial biogenesis, and mitochondrial function in 3T3-L1 preadipocytes. **BDSW increased mitochondrial biogenesis in a dose-dependent manner.** Quantitative real-time PCR revealed that **BDSW enhances expression of PGC1-α, NRF1, and TFAM genes.** Upregulation of these genes was supported by increased mitochondria staining, CytC oxidase activity, and AMPK phosphorylation. The stimulatory effect of BDSW on mitochondrial biogenesis and function suggests a novel mechanism for BDSW-induced anti-diabetic and anti-obesity action

PGC-1 family coactivators play a key role in modulating mitochondrial function and energy homeostasis in a number of physiological settings


Cold, fasting
cAMP
PKA
CREB
CREB
P
ERRα
RIP140
PGC-1α
NRF-1
NRF-2
ERRα
PPARα
VHL
HIF1
Glycolysis
Mitochondrial biogenesis
Fatty acid oxidation
phosphorylation
deacetylation
AMPK
SIRT1
AMP/ATP
NAD+/NADH
Energy deprivation

Salidroside Stimulates Mitochondrial Biogenesis and Protects against H_2O_2-Induced Endothelial Dysfunction



RHODIOLA ROSEA

Active constituents include:

- Rosavin
- Rosin
- Salidroside
- Proanthocyanidins
- Quercetin
- Tyrosol

RHODIOLA ROSEA

The naturally occurring ratio of rosavins to salidrosides in *R. rosea* is approximately 3:1

Dosages in studies for physical performance and fatigue range from 100 mg to 680 mg

PYRROLOQUINOLINE QUINONE

Pyrroloquinoline quinone stimulates mitochondrial biogenesis through cAMP response element-binding protein phosphorylation and increased PGC-1alpha expression.

Cannabidiol

- *Cell Death and Disease* (2013) **4**, e949; doi:10.1038/cddis.2013.471
  Published online 5 December 2013
- Direct modulation of the outer mitochondrial membrane channel, **voltage-dependent anion channel 1 (VDAC1)** by cannabidiol: a novel mechanism for cannabinoid-induced cell death

VDAC1 as a new molecular target for CBD

Our study suggests that CBD-induced cell death may occur through the inhibition of VDAC1 conductance and that this interaction may be responsible for the anticancer and immunosuppressive properties of CBD. However, we cannot rule out the possibility that the interaction of VDAC1 with CBD leads to cell death indirectly, for example by increasing the concentration of CBD in the mitochondria, thus leading to the increased formation of ROS and mitochondrial membrane permeability. **We hypothesize that cancer and immune cells are more susceptible to CBD-induced cell death compared with other cell types due to their high proliferative rate, metabolic rate, and VDAC1 activity.**

Treatment of Mitochondrial Dysfunction

1. Identify predisposing factors such as source of moisture in the case of fungal infections and mycotoxins:

- Leaking roof
- High humidity (>60%)
- Humidifiers
- Plants with standing water
- Flooding
- Water fountain
- Fish tank
- Pipe leaks

2. Identify trigger or precipitating factors

3. Identify propagating or maintenance factors

Basic Treatment Regime

1) Eating the evolutionary correct stone-age diet,

2) Ensuring optimum hours of good quality sleep,

3) Taking a standard package of nutritional supplements, and

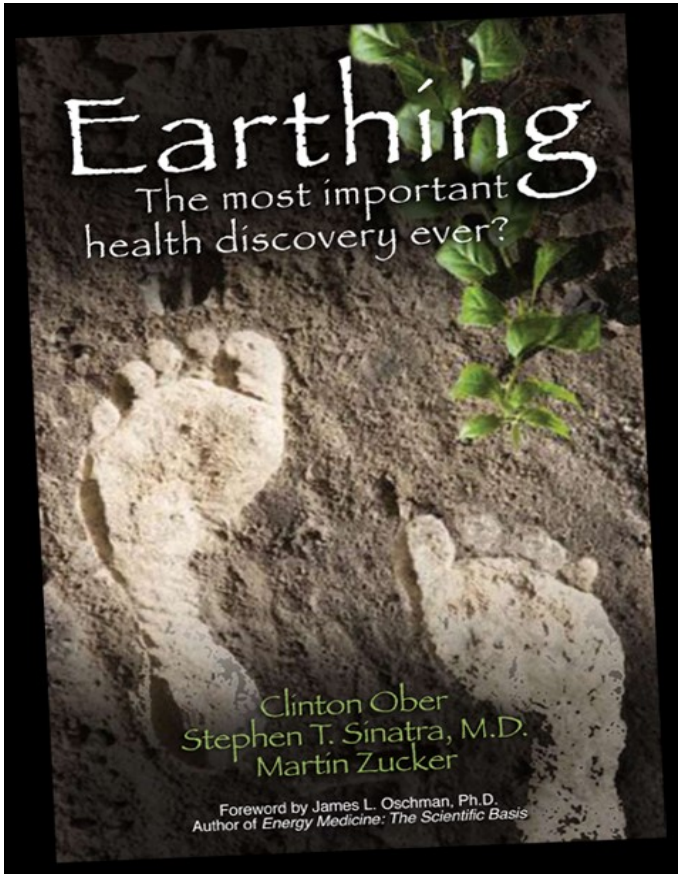
4) Getting the right balance between work and rest.

Additions to the basic regime were

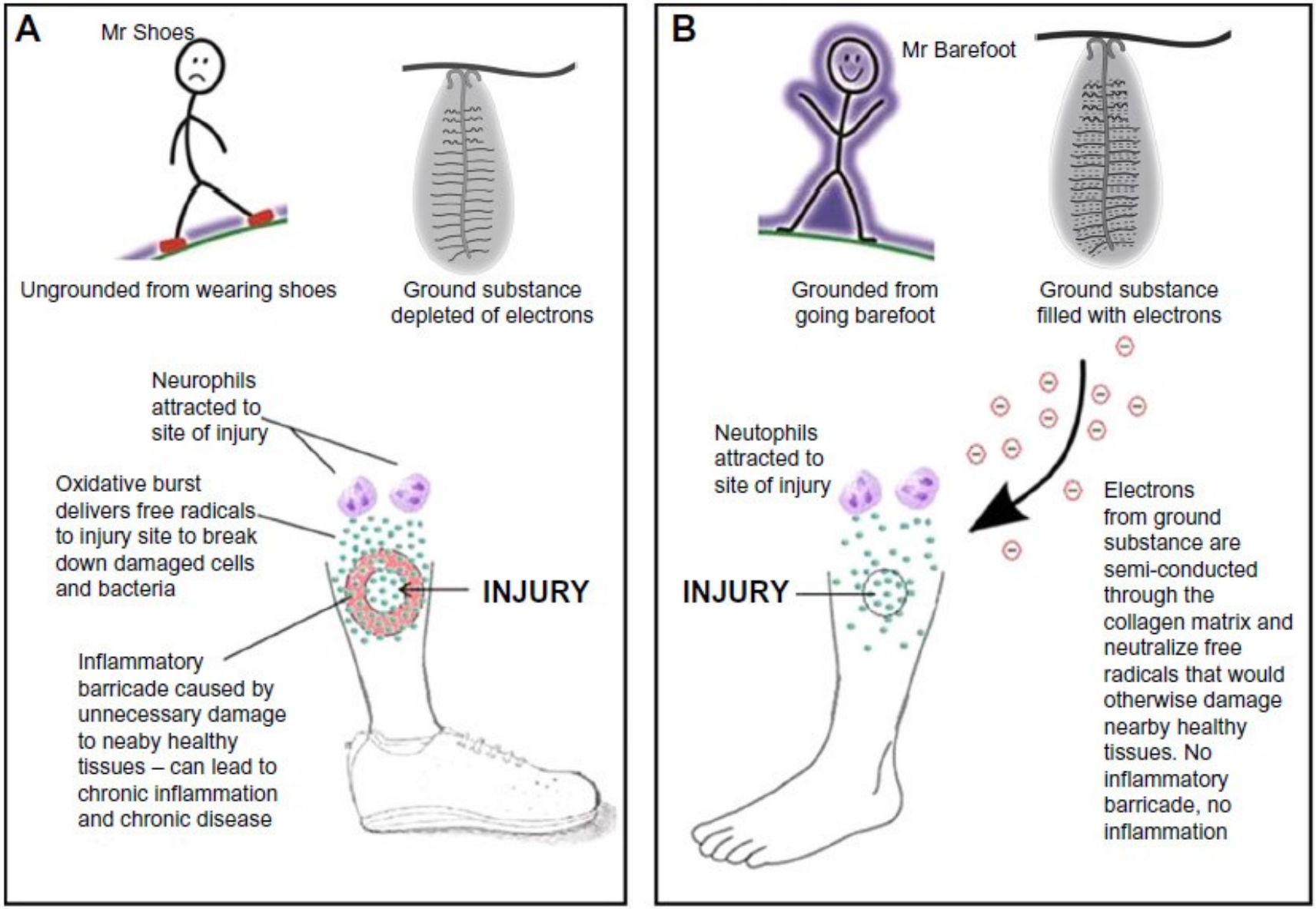
5) additional supplements tailored for each patient according to the results of the ATP Profile and additional nutritional tests and clues from the clinical history.

Sarah Myhill et al., Int J Clin Exp Med 2013; 6(1): 1-15

Earthing


Earthing
The most important health discovery ever?
Clinton Ober
Stephen T. Sinatra, M.D.
Martin Zucker
Foreword by James L. Oschman, Ph.D.
Author of Energy Medicine: The Scientific Basis

Electrons


A
Mr Shoes
Ungrounded from wearing shoes
Ground substance depleted of electrons
Neurophils attracted to site of injury
Oxidative burst delivers free radicals to injury site to break down damaged cells and bacteria
INJURY
Inflammatory barricade caused by unnecessary damage to neaby healthy tissues – can lead to chronic inflammation and chronic disease
B
Mr Barefoot
Grounded from going barefoot
Ground substance filled with electrons
Neutophils attracted to site of injury
INJURY
Electrons from ground substance are semi-conducted through the collagen matrix and neutralize free radicals that would otherwise damage nearby healthy tissues. No inflammatory barricade, no inflammation

Mitochondrial Dysfunction and Chronic Disease: Treatment With Natural Supplements (credit: Garth L. Nicolson, PhD)

- Loss of function in mitochondria, the key organelle responsible for cellular energy production, can result in the excess fatigue and other symptoms that are common complaints in almost every chronic disease. At the molecular level, a **reduction in mitochondrial function occurs as a *result of the following changes*:**

  (1) a loss of maintenance of the electrical and chemical transmembrane potential of the inner mitochondrial membrane,

  (2) alterations in the function of the electron transport chain, or

  (3) a reduction in the transport of critical metabolites into mitochondria. In turn, **these changes result in a reduced efficiency of oxidative phosphorylation and a reduction in production of adenosine-5'-triphosphate (ATP).** Several components of this system require routine replacement, and this need can **be facilitated with natural supplements.** Clinical trials have shown the utility of using oral replacement supplements, such as L-carnitine, alpha-lipoic acid (α-lipoic acid [1,2-dithiolane-3-pentanoic acid]), coenzyme Q_{10} (CoQ_{10} [ubiquinone]), reduced nicotinamide adenine dinucleotide (NADH), membrane phospholipids, and other supplements. **Combinations of these supplements can reduce significantly the fatigue and other symptoms associated with chronic disease and can naturally restore mitochondrial function, even in long-term patients with intractable fatigue.**

- Integr Med (Encinitas). 2014 Aug; 13(4): 35–43. **Mitochondrial Dysfunction and Chronic Disease: Treatment With Natural Supplements** Garth L. Nicolson, PhD

MITOCHONDRIAL RESCUE & RESTORATION

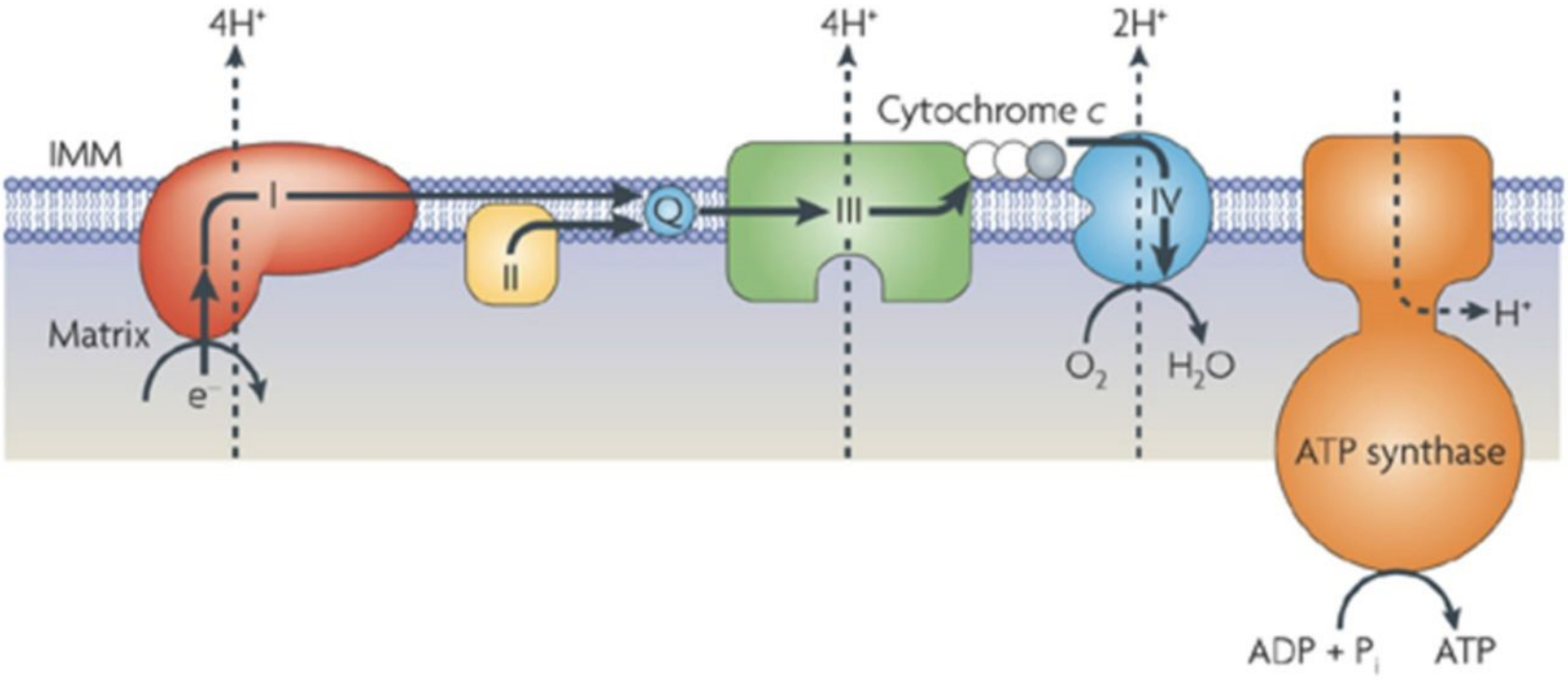
- **Vitamins**: C, D and E, thiamine, riboflavin
- **Minerals**: Magnesium, calcium, phosphate
- **Lipids**: Membrane phospholipids, unsaturated fatty acids
- **Metabolites**: Creatine, pyruvate
- **Cofactors**: CoQ_{10}, α-lipoic acid, NADH, nicotinic acid
- **Transporters**: L-Carnitine, membrane phospholipids
- **Antioxidants:** CoQ_{10}, α-lipoic acid, NADH, glutathione
- **Enzyme inhibitors**: α-Lipoic acid, dichloroacetate
- **Herbs**: Curcumin, schisandrin

Kerr DS. Treatment of mitochondrial electron transport chain disorders: a review of clinical trials over the past decade. Mol Genet Metab. 2010;99(3):246–255

Membrane Restoration

- Healthy fats
- Avoid damaged processed fats (margarine etc)
- Phosphatidyl choline (liposomal preparations)
- Parent Essential fatty acids
- Seed oils

Role of coenzyme Q10 (CoQ10) in the electron transport chain.



Abhinav Sharma et al. Circ Heart Fail. 2016;9:e002639

MICRONUTRIENT RESTORATION

- CoQ10 (ubiquinol)-300 mg – a good place to start; check lab tests to determine therapeutic efficacy
- Alpha Lipoic acid (increases glutathione) 200–600 mg/d
- NADH – oral stabilized, micro encapsulated
- Membrane phospholipids
- ALCAR- 2000 mg once daily
- Melatonin- 3 mg good starting point
- Molecular H2- 1-2 tabs daily in water

L-Carnitine

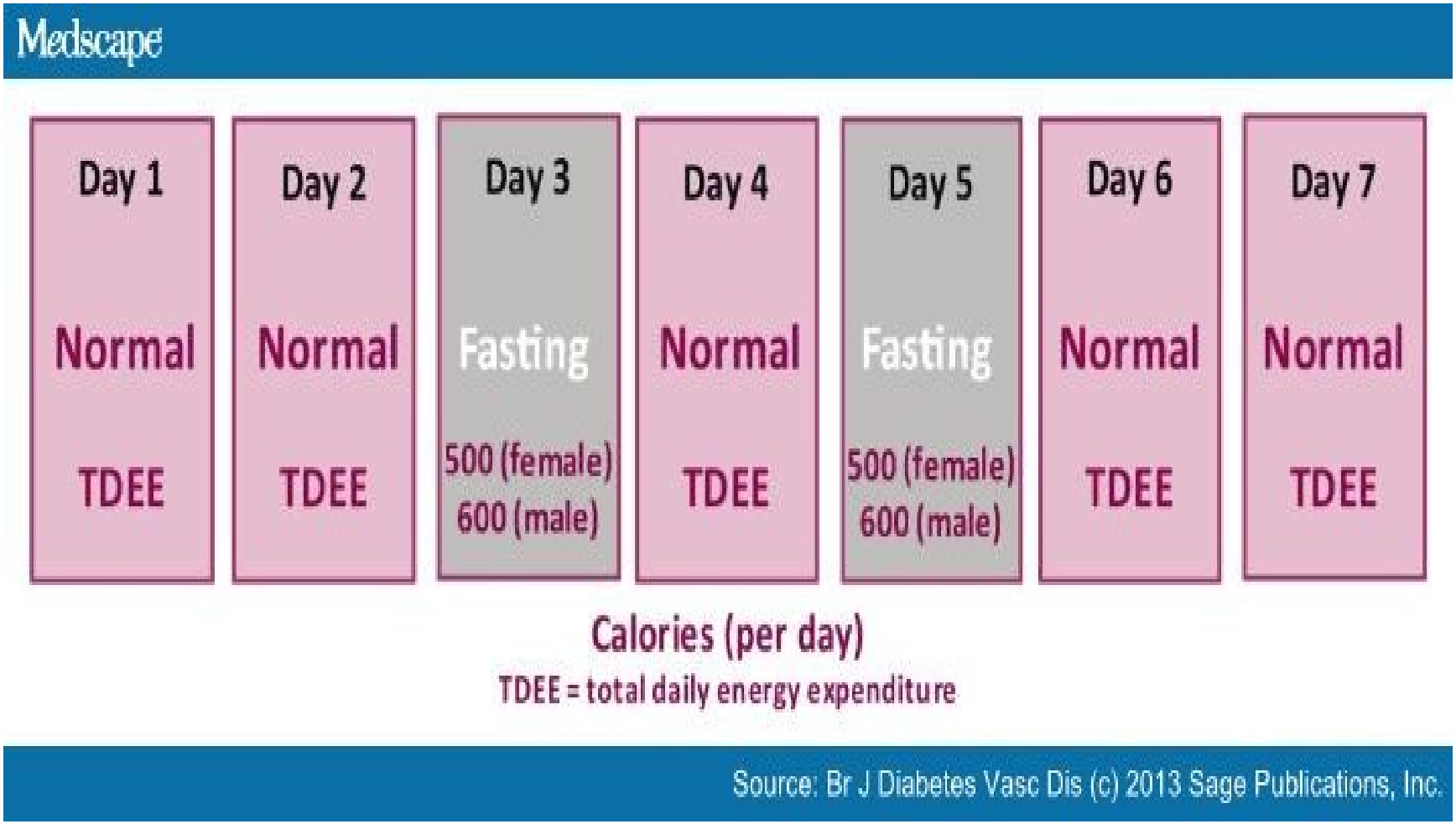
- L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: a randomized and controlled clinical trial.

- *Am J Clin Nutr. 2007 Dec; 86(6):1738-44. Malaguarnera M, Cammalleri L, Gargante MP, Vacante M, Colonna V, Motta M*

Sulforaphane

- Oxid Med Cell Longev. 2017;2017:3839756. doi: 10.1155/2017/3839756. Epub 2017 Mar 12.
- **Sulforaphane Protects against High Cholesterol-Induced Mitochondrial Bioenergetics Impairments, Inflammation, and Oxidative Stress and Preserves Pancreatic β-Cells Function.**
- Carrasco-Pozo C[1], Tan KN[2], Gotteland M[3], Borges K[2].
- **Author information**
- **Abstract**
- Cholesterol plays an important role in inducing pancreatic *β*-cell dysfunction, leading to an impaired insulin secretory response to glucose. This study aimed to determine the protective effects of sulforaphane, a natural isothiocyanate Nrf2-inducer, against cholesterol-induced pancreatic *β*-cells dysfunction, through molecular and cellular mechanisms involving mitochondrial bioenergetics. Sulforaphane prevented cholesterol-induced alterations in the coupling efficiency of mitochondrial respiration, improving ATP turnover and spare capacity, and averted the impairment of the electron flow at complexes I, II, and IV. Sulforaphane also attenuated the cholesterol-induced activation of the NF*κ*B pathway, normalizing the expression of pro- and anti-inflammatory cytokines. In addition, it also inhibited the decrease in *sirtuin 1* expression and greatly increased *Pgc-1α* expression in Min6 cells. Sulforaphane increased the expression of antioxidant enzymes downstream of the Nrf2 pathway and prevented lipid peroxidation induced by cholesterol. **The antioxidant and anti-inflammatory properties of sulforaphane and its ability to protect and improve mitochondrial bioenergetic function contribute to its protective action against cholesterol-induced pancreatic *β*-cell dysfunction**. Our data provide a scientifically tested foundation upon which sulforaphane can be developed as nutraceutical to preserve *β*-cell function and eventually control hyperglycemia.
- PMID: 28386307 PMCID: PMC5366224 DOI: 10.1155/2017/3839756

Intermittent Fasting



Chronic Caloric Restriction Preserves Mitochondrial Function in Senescence Without Increasing Mitochondrial Biogenesis

- **Chronic Caloric Restriction Preserves Mitochondrial Function in Senescence Without Increasing Mitochondrial Biogenesis**
- Ian R. Lanza et al,
- **SUMMARY**

- Caloric restriction (CR) mitigates many detrimental effects of aging and prolongs lifespan. CR has been suggested to increase mitochondrial biogenesis, thereby attenuating age-related declines in mitochondrial function; a concept that is challenged by recent studies. Here we show that lifelong CR in mice prevents age-related loss of mitochondrial oxidative capacity and efficiency, measured in isolated mitochondria and permeabilized muscle fibers. We find that these beneficial effects of CR occur without increasing mitochondrial abundance. Whole-genome expression profiling and large-scale proteomic surveys revealed expression patterns inconsistent with increased mitochondrial biogenesis, which is further supported by lower mitochondrial protein synthesis with CR. We find that **CR decreases oxidant emission, increases antioxidant scavenging, and minimizes oxidative damage to DNA and protein.** These results demonstrate that **CR preserves mitochondrial function by protecting the integrity and function of existing cellular components rather than by increasing mitochondrial biogenesis.**

- **Keywords:** Caloric Restriction, Calorie restriction, dietary restriction, aging, mitochondria, protein synthesis, skeletal muscle, mitochondrial biogenesis

Sirtuins in aging and disease

- Cold Spring Harb Symp Quant Biol. 2007;72:483-8. doi: 10.1101/sqb.2007.72.024.

- **Sirtuins in aging and disease.**

- Guarente L[1].

- **Abstract**

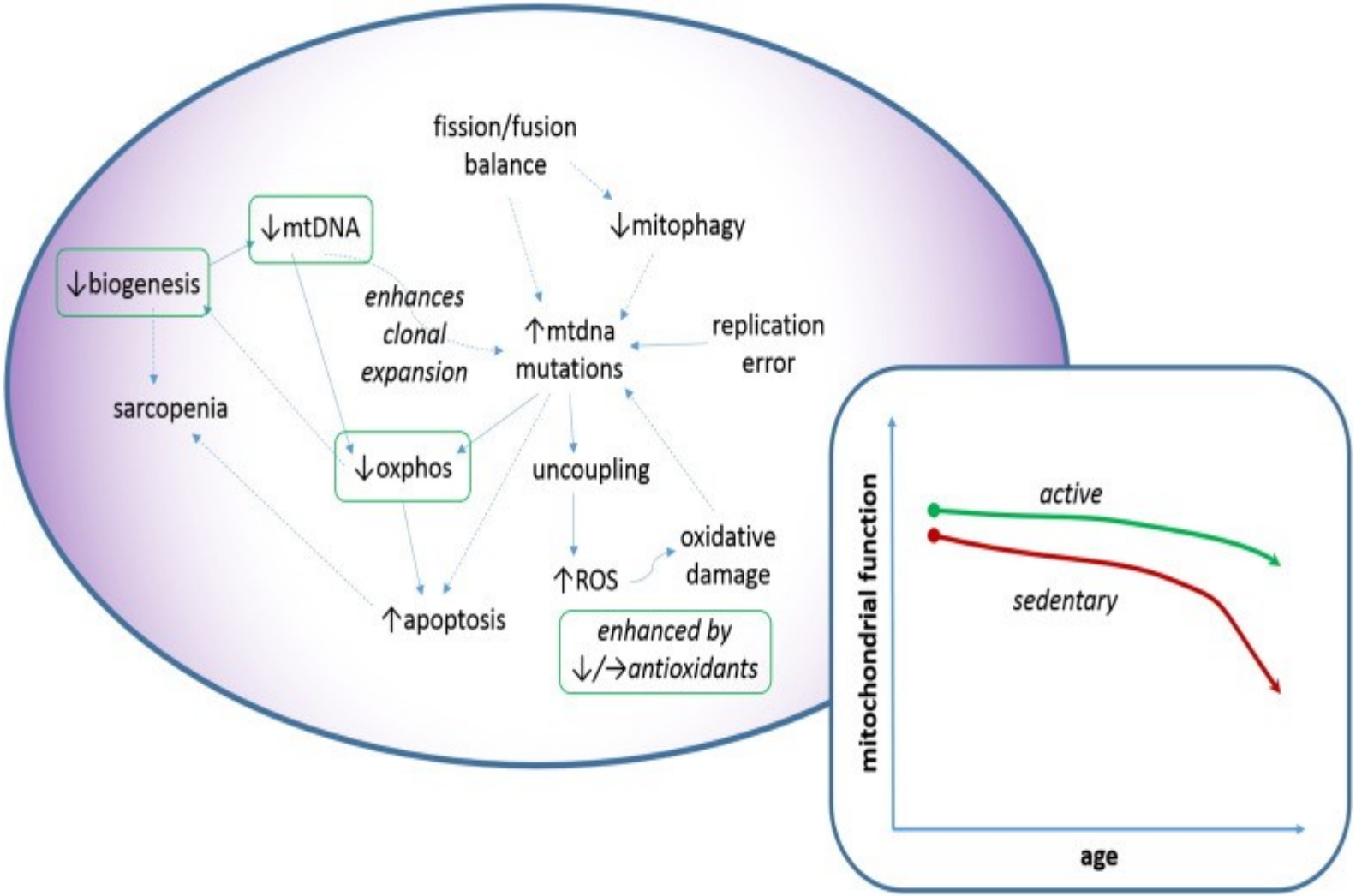
- Sirtuin genes function as anti-aging genes in yeast, Caenorhabditis elegans, and Drosophila. The NAD requirement for sirtuin function indicates a link between aging and metabolism, and a boost in **sirtuin activity may in part explain how calorie restriction extends life span**. In mammals, one of the substrates of the SIR2 ortholog, SIRT1, is a regulator of mitochondrial biogenesis, PGC-1alpha. Indeed, the putative **SIRT1 activator resveratrol** has been shown to **stimulate mitochondrial biogenesis and deliver health benefits in treated mice.** I explore here how mitochondrial biogenesis may have beneficial effects on aging and, perhaps, diseases of aging. In particular, I speculate that SIRT1-mediated mitochondrial biogenesis may reduce the production of reactive oxygen species, a possible cause of aging, and offer two possible mechanisms for this effect. An understanding of how calorie restriction works may lead to novel drugs to combat diseases of aging.

Microbiota-mitochondria inter-talk: consequence for microbiota-host interaction

- New discoveries in metagenomics and clinical research have highlighted the importance of the gut microbiota for human health through the regulation of the host immune response and energetic metabolism. The microbiota interacts with host cells in particular by intermingling with the mitochondrial activities. This mitochondria-microbiota cross-talk is intriguing because mitochondria share many common structural and functional features with the prokaryotic world. Several studies reported **a correlation between microbiota quality and diversity and mitochondrial function.** The mitochondrial production of reactive oxygen species (ROS) plays an important role during the innate immune response and inflammation, and is often targeted by pathogenic bacteria. Data suggest that excessive mitochondrial ROS production may affect ROS signaling induced by the microbiota to regulate the gut epithelial barrier. Finally, the microbiota releases metabolites that can directly interfere with the mitochondrial respiratory chain and ATP production. **Short chain fatty acids have beneficial effects on mitochondrial activity**. All these data suggest that the microbiota targets mitochondria to regulate its interaction with the host. Imbalance of this targeting may result in a pathogenic state as observed in numerous studies. The challenge to find new treatments will be to find strategies to modulate the quality and diversity of the microbiota rather than acting on microbiota metabolites and microbiota-related factors.

- Pathog Dis. 2016 Feb;74(1):ftv096. doi: 10.1093/femspd/ftv096. Epub 2015 Oct 23.**Microbiota-mitochondria inter-talk: consequence for microbiota-host interaction.**

PHYSICAL ACTIVITY AND MITOCHONDRIAL FUNCTION



Pharmacokinetics of Hydrogen

Molecular hydrogen is an odourless and tasteless gas that has the ability to rapidly diffuse through lipid membranes and enter the cell, where it easily penetrates organelles such as mitochondria as well as the nucleus. It is inert at room temperature and in the absence of catalysts. It additionally easily crosses the blood brain barrier, which facilitates access to the target organs and subcellular components. Its adverse event profile is reportedly benign. **Physiologically, hydrogen is produced by intestinal microbiota from fermentation of complex carbohydrates**. Arterial blood contains higher levels of hydrogen that tissue, suggesting some uptake and utilization of hydrogen in tissues**. Hydrogen reacts with free hydroxyl radicals but does not appear to react to other reactive oxygen species.** This is a theoretical advantage, as low levels of these radicals have physiologically relevant signaling effects. It protects against secondary oxidative damage to the brain in a variety of models by reacting with hydroxyl radicals Hydrogen is potentially available as a medical gas, hydrogen enriched water, taking a hydrogen bath, injecting hydrogen saline, hydrogen saline eye drops, and augmenting bacterial production of intestinal hydrogen. It penetrates glass but not aluminum containers.

VDAC1 : new molecular target for CBD

- VDAC1 as a new molecular target for CBD. Our study suggests that **CBD-induced cell death** may occur through the **inhibition of VDAC1 conductance** and that this interaction may be **responsible for the anticancer and immunosuppressive properties of CBD**. However, we cannot rule out the possibility that the **interaction of VDAC1 with CBD leads to cell death indirectly**, for example by **increasing the concentration of CBD in the mitochondria**, thus leading to the **increased formation of ROS and mitochondrial membrane permeability**. We **hypothesize that cancer and immune cells are more susceptible to CBD-induced cell death compared with other cell types due to their high proliferative rate, metabolic rate, and VDAC1 activity**.

BOTTOM LINE: MITOCHONDRIAL RESCUE & RESTORATION

- Reduce or eliminate mitotoxins (targeted therapeutic interventions)
- Reduce or eliminate mitotoxicants (reduce exposome, alternatives to pharmaceuticals, organic foods, EWG.org [Skin deep, Dirty Dozen, Clean Fifteen], saunas, remediation [home, office, school])
- Remove other causes of chronic inflammation
- Restore circadian rhythm and supplement with melatonin
- Replenish mitochondrial micronutrients such as Co Q10
- Bioactive compounds that stimulate mitochondrial biogenesis (eg Rhodiola) & function (eg CBD)
- Restore the microbiome
- Restore voltage
- Regular exercise
- Healthy emotions
- Caloric restriction
- Intermittent fasting

Q & A

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- Wioleta Grabowska,[1] Małgorzata Suszek,[1] Maciej Wnuk,[2] Anna Lewinska,[3] Emilia Wasiak,[1] Ewa Sikora,[1] and Anna Bielak-Zmijewska[1]

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- Kevin R. Short, Niels Moller, Maureen L. Bigelow, Jill Coenen-Schimke, and K. Sreekumaran Nair

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- Chowanadisai W[1], Bauerly KA, Tchaparian E, Wong A, Cortopassi GA, Rucker RB.

- **Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network**
- Richard C.Scarpulla Department of Cell and Molecular Biology, Northwestern Medical School, 303 East Chicago Avenue, Chicago, IL 60611, USA
- Received 14 July 2010, Revised 14 September 2010, Accepted 27 September 2010, Available online 6 October 2010.
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- Published online 2011 May 4. doi: 10.4061/2011/326320
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Published online 2012 May 29. doi: 10.1186/1472-6882-12-70

PMCID: PMC3541197

***Rhodiola rosea* for physical and mental fatigue: a systematic review**

Sana Ishaque,[1] Larissa Shamseer,[1,2] Cecilia Bukutu,[3] and Sunita Vohra[1]

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  Salidroside Stimulates Mitochondrial Biogenesis and Protects against H_2O_2-Induced Endothelial Dysfunction

  Shasha Xing,[1,2] Xiaoyan Yang,[1,2] Wenjing Li,[1,2] Fang Bian,[1,2] Dan Wu,[1,2] Jiangyang Chi,[1,2] Gao Xu,[1,2] Yonghui Zhang,[1,2] and Si Jin[1,2]
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- **Pyrroloquinoline quinone stimulates mitochondrial biogenesis through cAMP response element-binding protein phosphorylation and increased PGC-1alpha expression.**
- Chowanadisai W[1], Bauerly KA, Tchaparian E, Wong A, Cortopassi GA, Rucker RB.

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