6th ANNUAL Functional Pharmacy Symposium

FUNCTIONAL MEDICINE Continuing Education

Powering the Immune System

Key Nutrients for Mitochondrial Resuscitation and the Healing Cycle

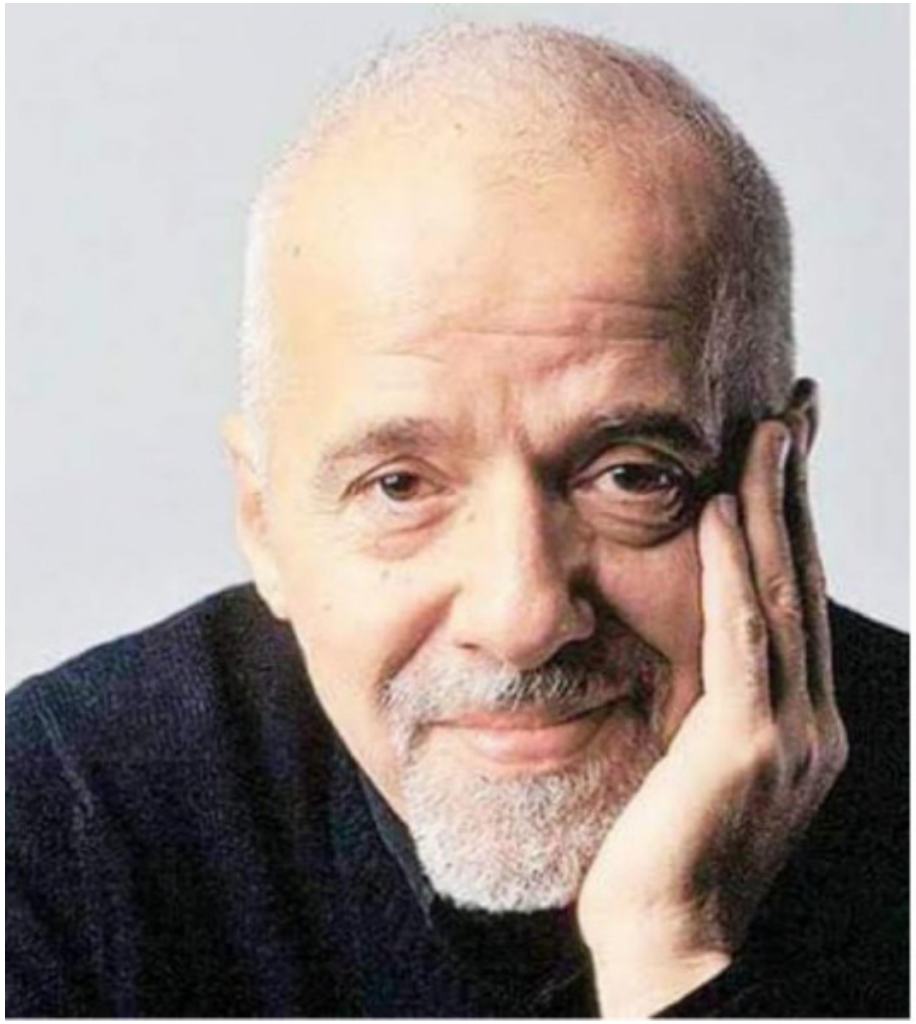
Lara Zakaria PharmD MS CNs CDN IFMCP

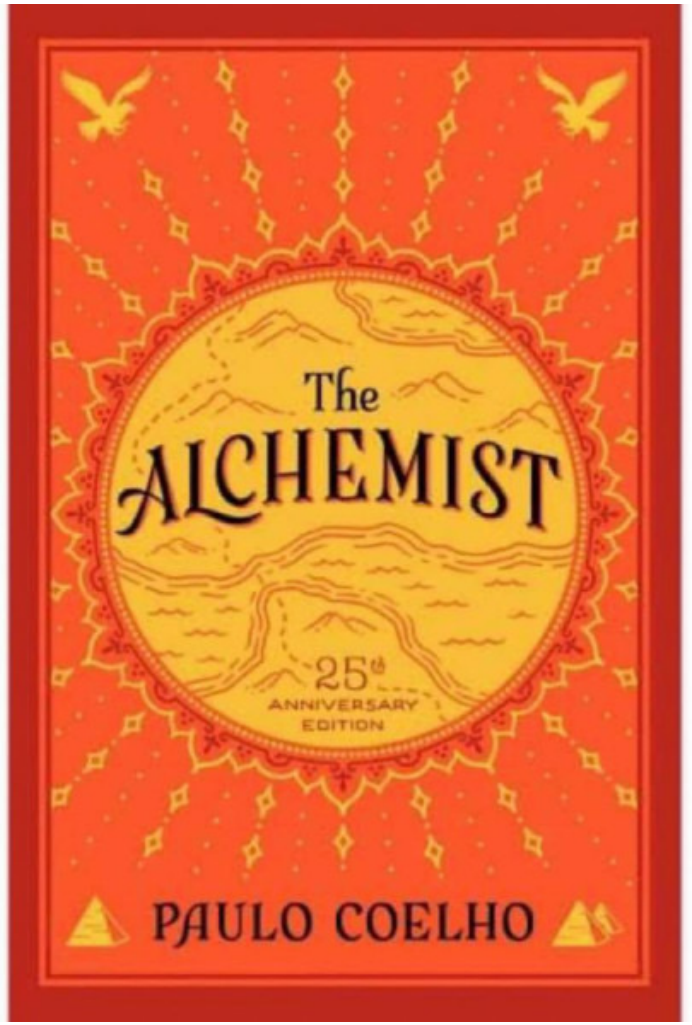
Disclosures

- Dr. Zakaria has nothing to disclose.

Objectives

- Define optimal mitochondrial reserves
- Explore optimal strategies to build mitochondrial reserves and enhance immune health
- Discuss nutrients needed to support mitochondrial health. (Technician)




The
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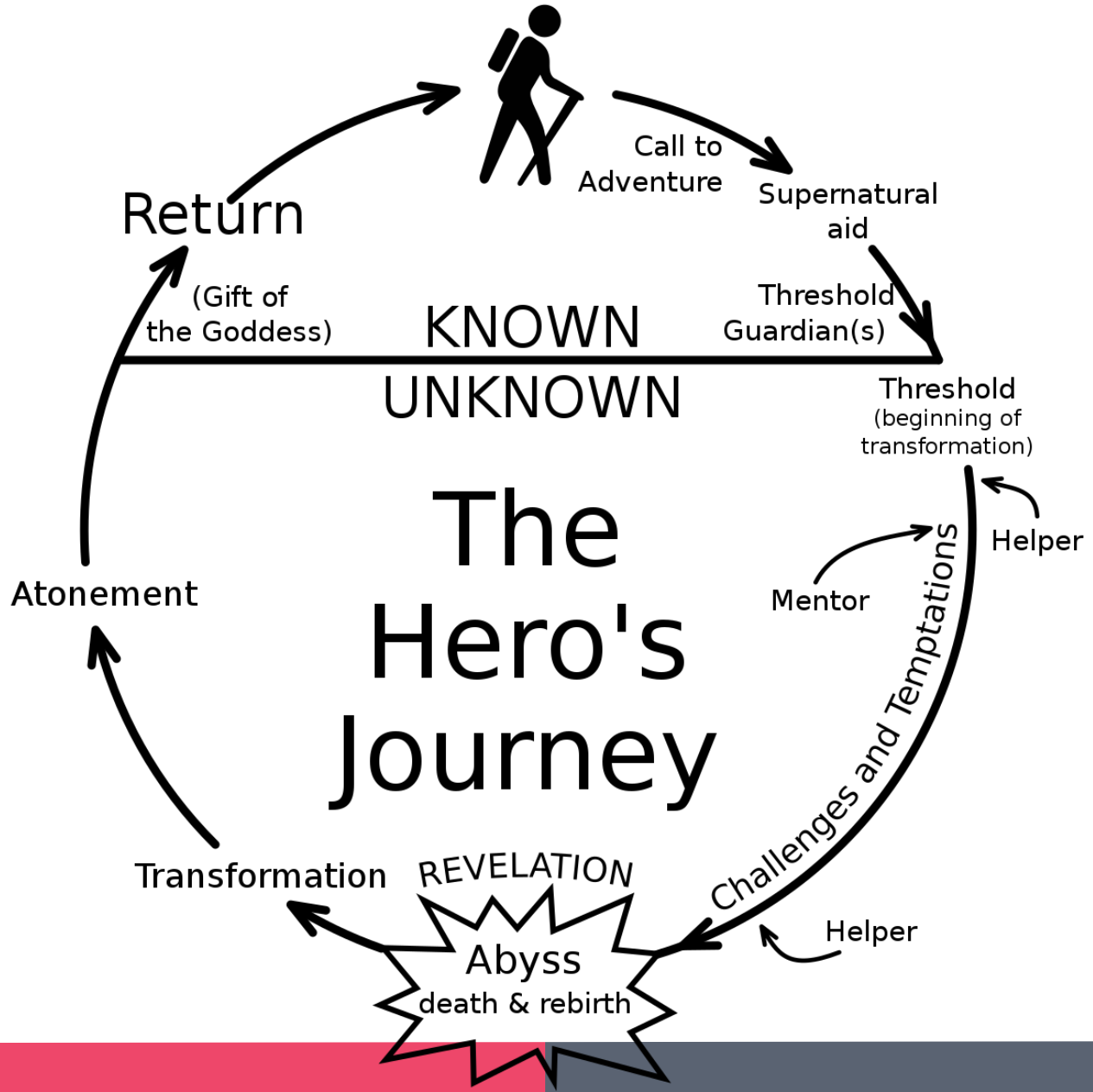
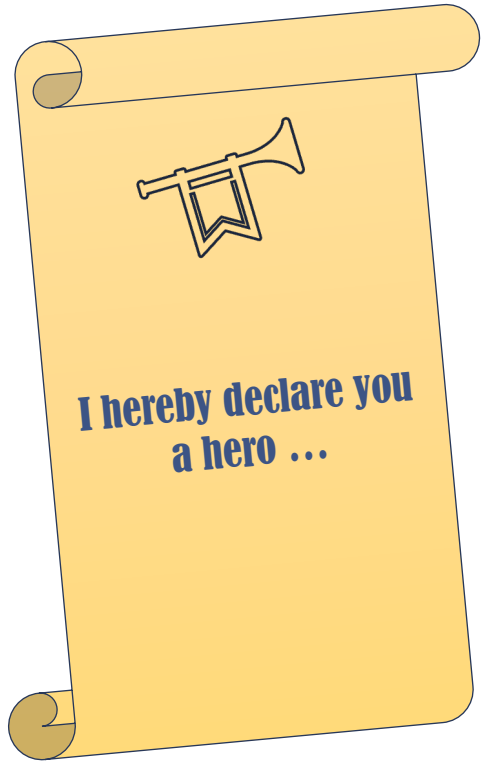
PAULO COELHO



https://en.wikipedia.org/wiki/Hero%27s_journey

A hero ventures forth from the world of common day into a region of supernatural wonder: fabulous forces are there encountered, and a decisive victory is won: the hero comes back from this mysterious adventure with the power to bestow boons on his fellow man.

Joseph Campbell



What defines a hero?

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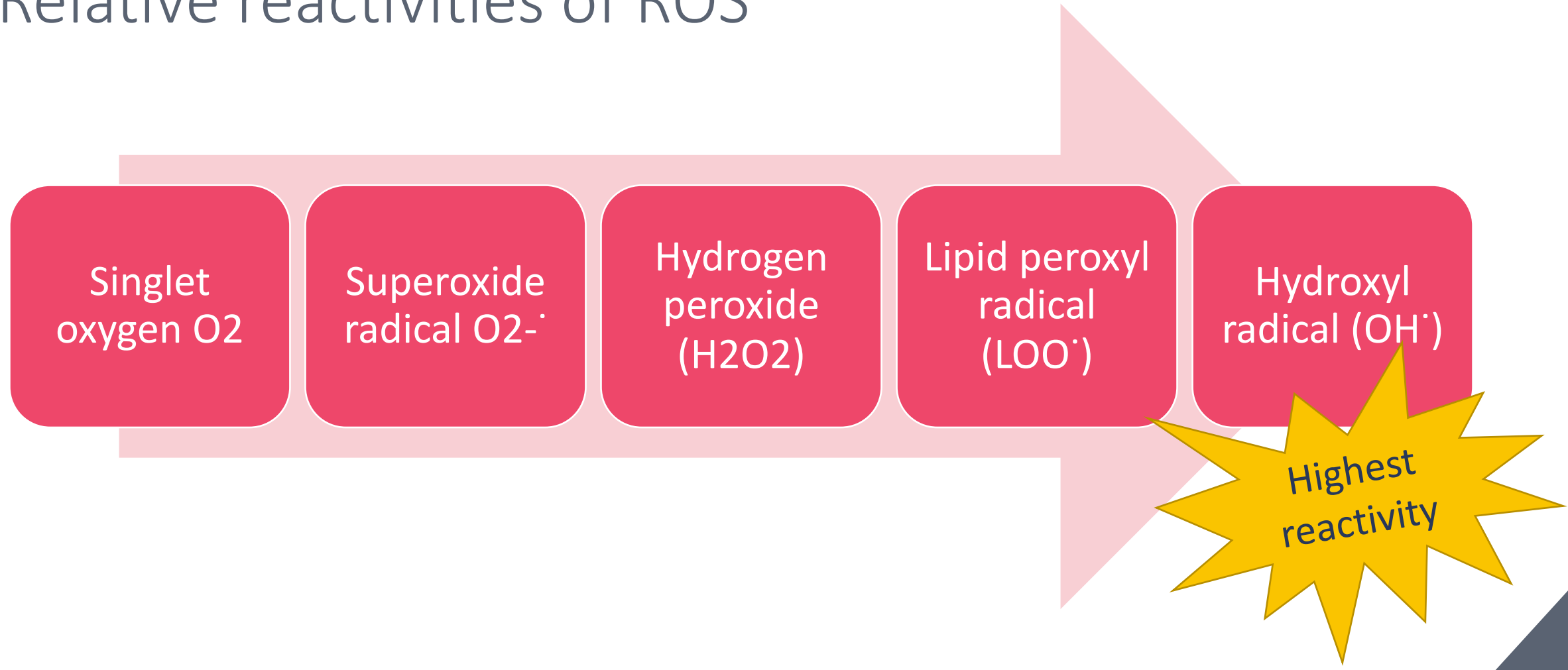
Where are You in Your journey?

Meet Annie

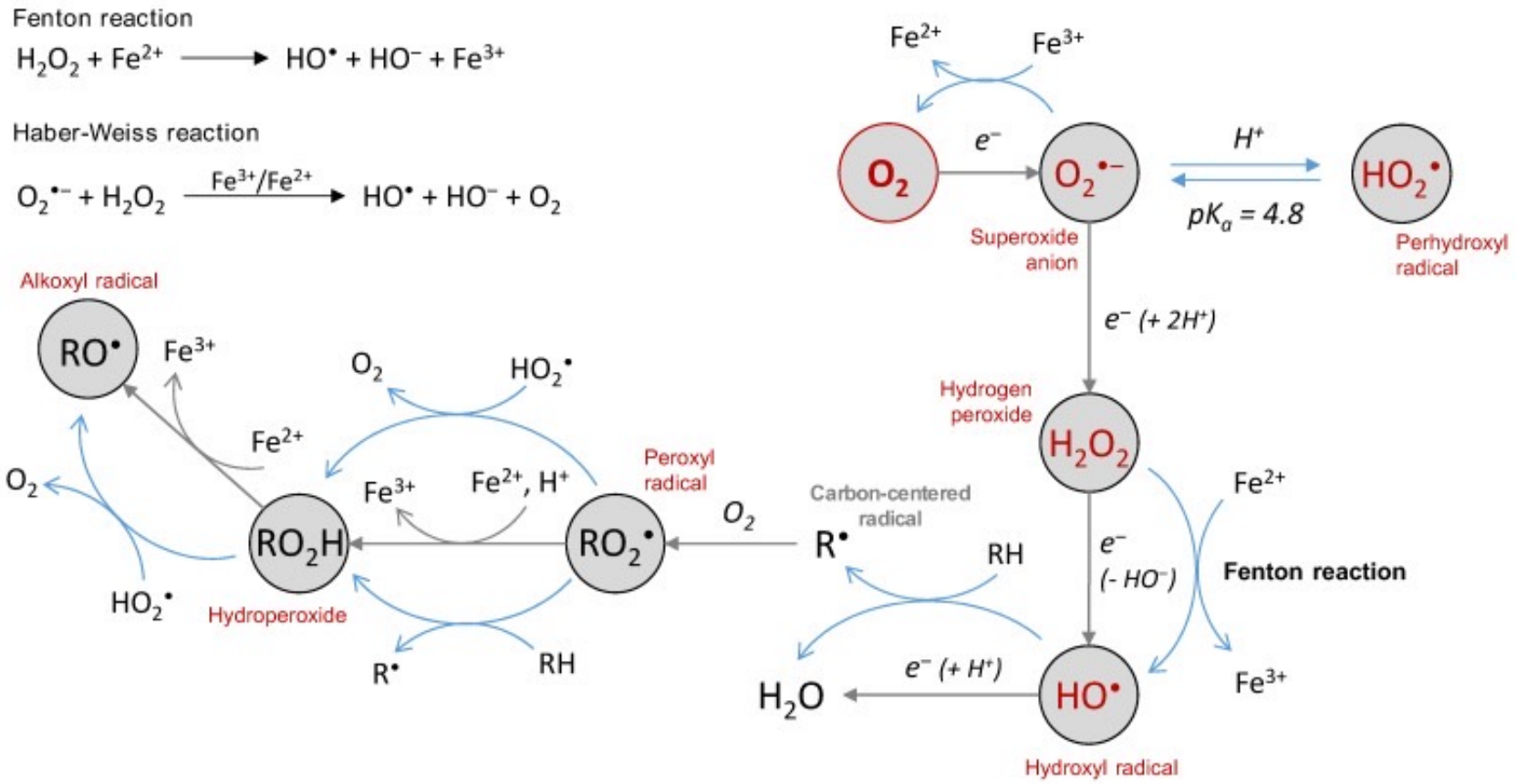
- 52-year-old AA woman
- History of hypertension, diabetes managed with **metoprolol and metformin**
- Hypothyroidism, managed with **levothyroxine**
- Concerned about her risks for COVID


ROS = SOS

Relative reactivities of ROS



Chemical basis of ROS generation



Diseases. Int J Mol Sci. 2019;20(10):2407.

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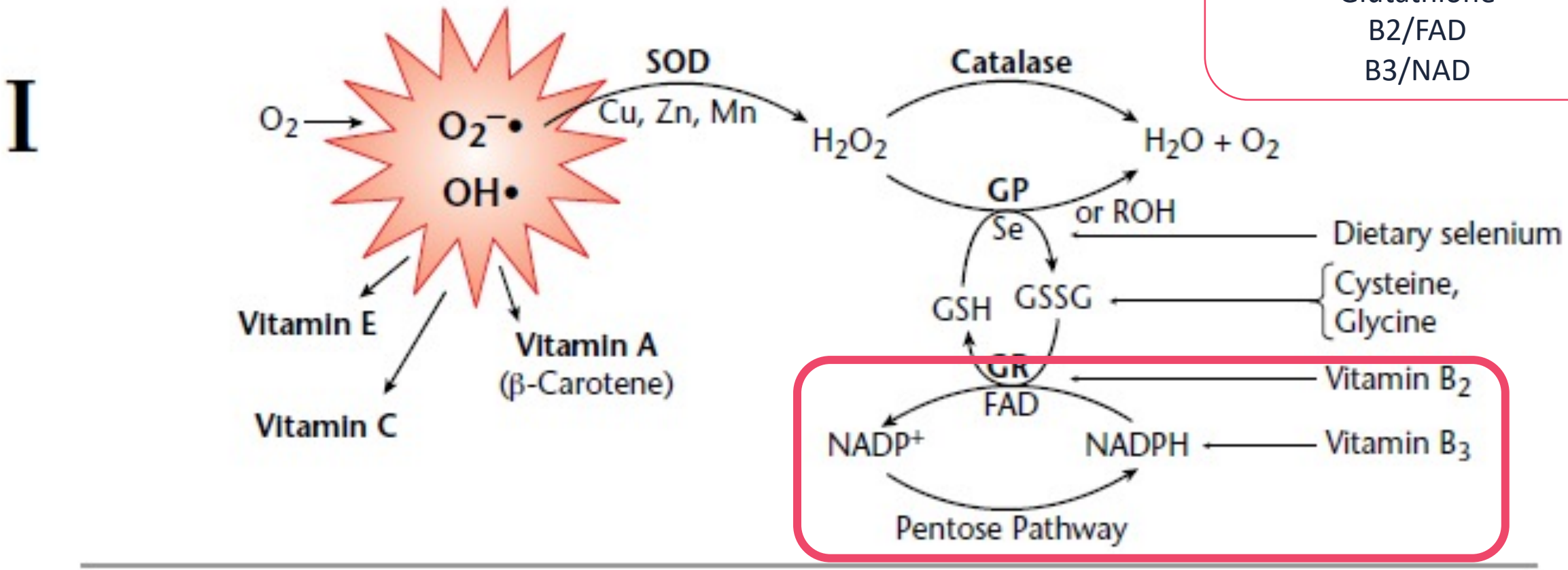
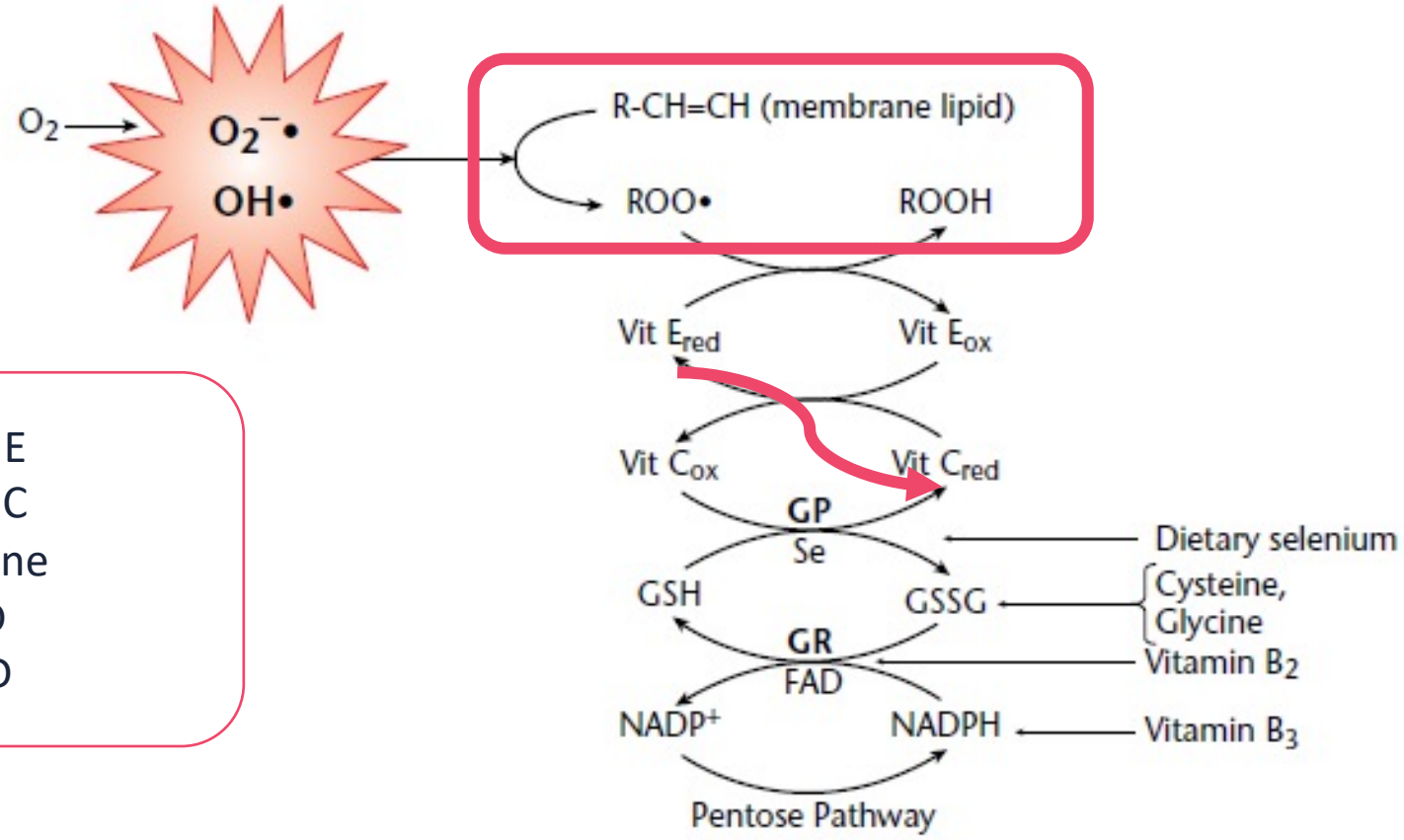
Figure 10.4 – Scenarios of Radical Formation and Removal

Vitamins A, E
Vitamin C
Cu, Zn, Mn
Glutathione
B2/FAD
B3/NAD



Antioxidant regenerative capacity

II

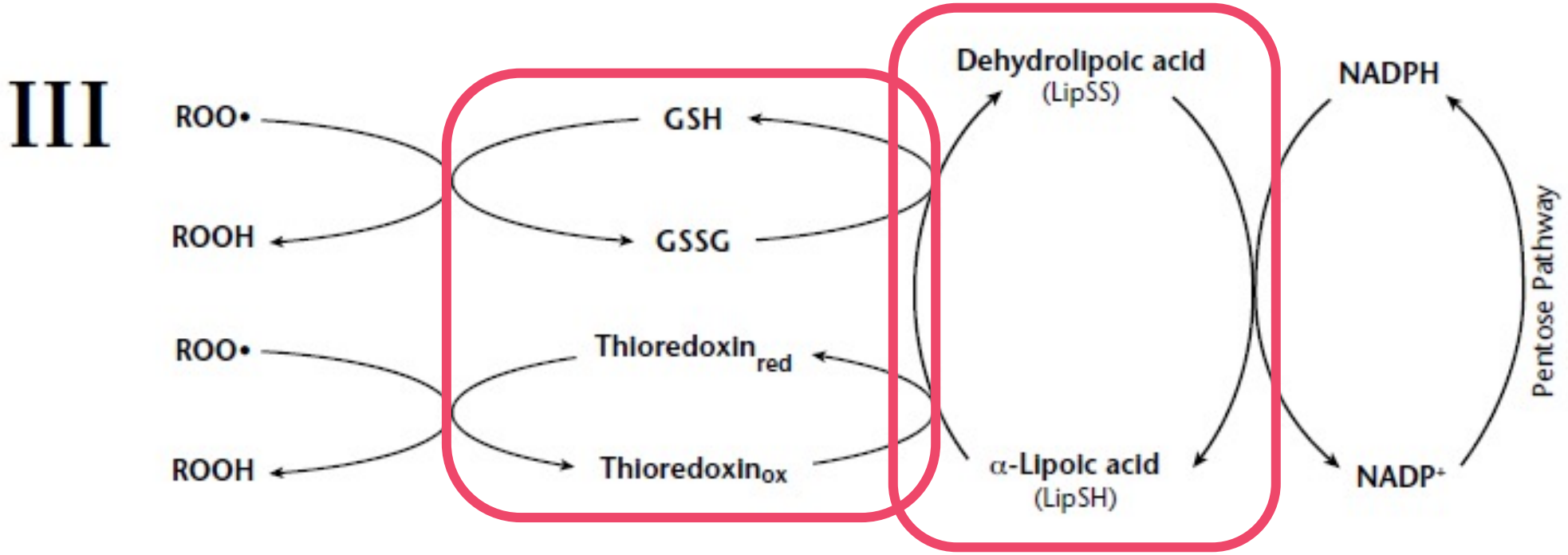


Vitamin E
Vitamin C
Glutathione
B2/FAD
B3/NAD

Lord R. Laboratory Guides to Health. Arrowhead Bioscience Inc. 2020. Fig 10.4

Lipoic Acid Regeneration

Glutathione
Lipoic acid
B3/NAD



Lord R. Laboratory Guides to Health. Arrowhead Bioscience Inc. 2020. Fig 10.4

The most significant source of ROS is mitochondrial respiration

The reaction occurs in particular in the mitochondrial respiratory chain, where 85% of O2 is metabolized and where partially reduced O2 intermediates are produced in low quantity

Tissue damage occurs unless free radicals are neutralized via electron transfer requiring enzymatic conversion (i.e. Glutathione peroxidase, Glutathione reductase, SOD) or vitamin transfer to eventually turn into water

Imbalances of key vitamins including **vitamins A, C, or E** or minerals like **zinc, copper, selenium** or ETC cofactor insufficiencies of **CoQ10, iron, heme or cytochromes** can cause disruptions in the massive flow of electrons through these systems

Lord R, Bralley JA. Laboratory Evaluations for Functional and Integrative Medicine. 2012

Antioxidants

Antioxidants function in concert → single supplementation increases potential for imbalance

When antioxidants are consumed out of proportion, can become part of the problem

High reactivity ROS initiate electron transfer to lower redox potential

Radicals removed as water and reduced antioxidant

Remember Annie?

- Tends to eat the same thing every day
- High stress job, exhausted at the end of the workday
- Frequent headaches (attributed to stress and dehydration) managed with **acetaminophen**
- Sleep is inconsistent, racing mind makes it hard to fall asleep

Important Antioxidant Compounds

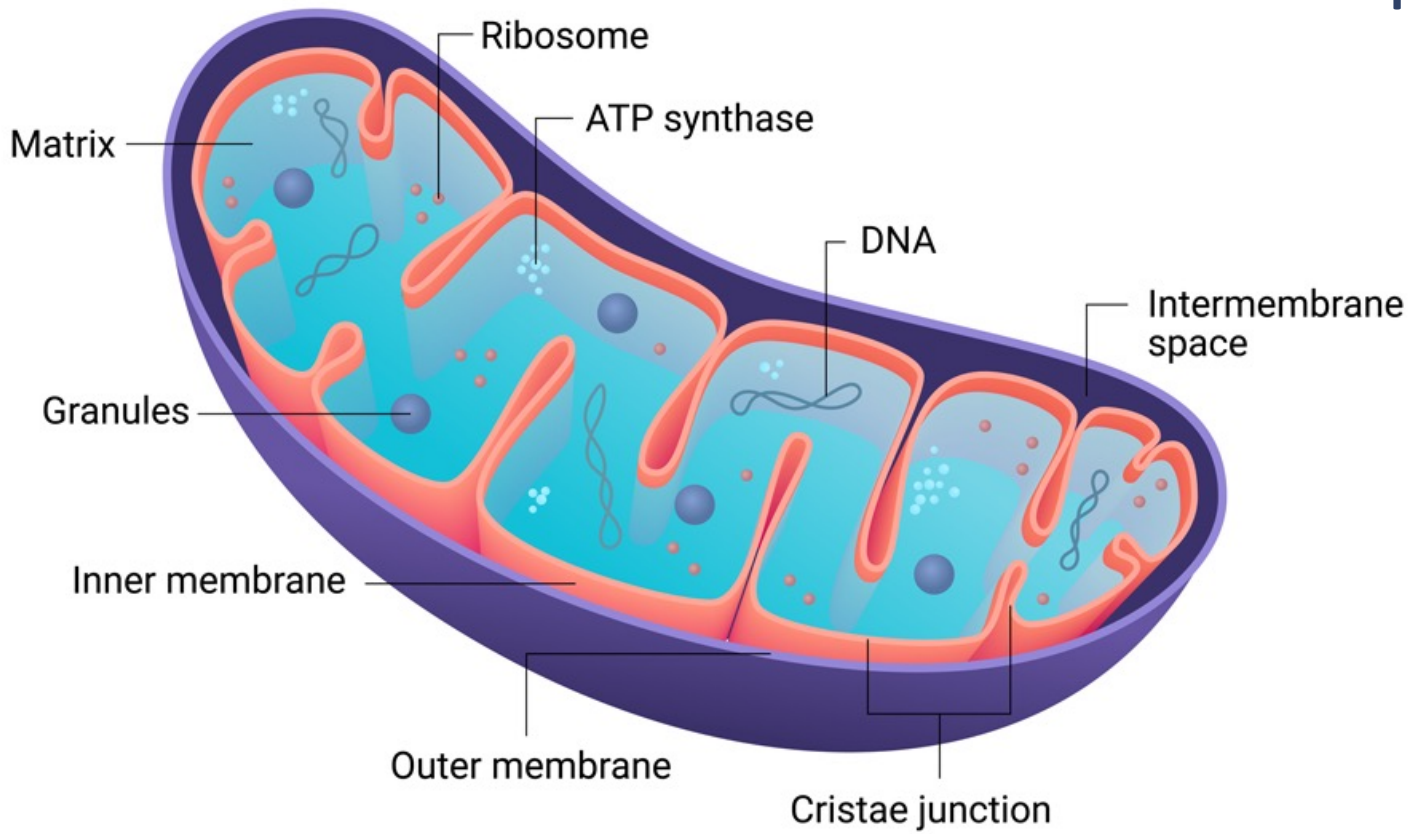
Major antioxidants

- Ascorbate (vitamin C)
- Vitamin E
- Vitamin A/B-carotene
- Riboflavin
- Selenium
- Zinc
- Copper
- Manganese
- Glutathione
- Isoflavones

Building blocks or cofactors

- Cysteine, Glycine, Mg (glutathione building blocks)
- Selenium, copper, zinc (glutathione peroxidase)
- Riboflavin (glutathione reductase)
- Copper, Zinc, Manganese (SOD)

Mitochondria



Powerhouse of the cell

https://researchoutreach.org/articles/identifying-mitochondrial-dna-mutations-cause-cancer/

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Mitochondria & the bacterial microbiome have a lot in common

We have ~10x the number of bacteria vs human cells in our body

But we ~1,000x mitochondria per cell

~10 million billion total mitochondrion in the body, which equals ~10% of a person's body weight

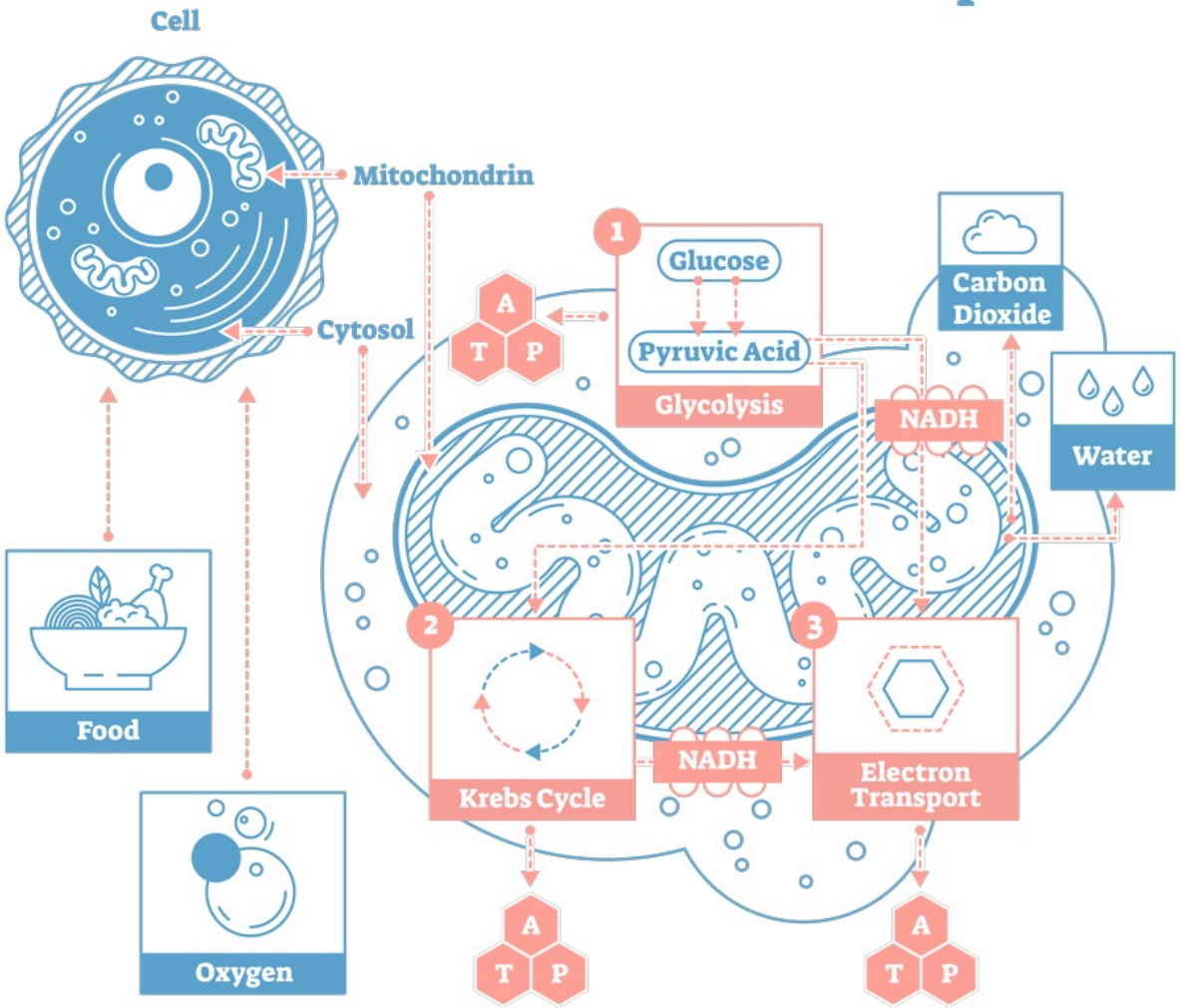
On average each cell contains 200-2,000 mitochondrion with the concentrations varying based on energy demand (cardiac, liver, kidney, and neurons are the most *mito-rich*)

Mitochondria are thought to be evolutionary "leftovers" from bacteria

Mitochondria: Why all the fuss?

- 90% of the oxygen consumed by mitochondria for oxidative phosphorylation (ATP)
- There is a complete turnover of myocardial ATP pools every 10 seconds
- Mitochondria generate and consume the body's weight in ATP every day
- 95% of antioxidants we take in are used in the wall of mitochondria
- 15% on the body's glutathione is found in the mitochondria
- Mitochondrion have separate DNA (mtDNA)

Celluar Respiration



https://researchoutreach.org/articles/identifying-mitochondrial-dna-mutations-cause-cancer/

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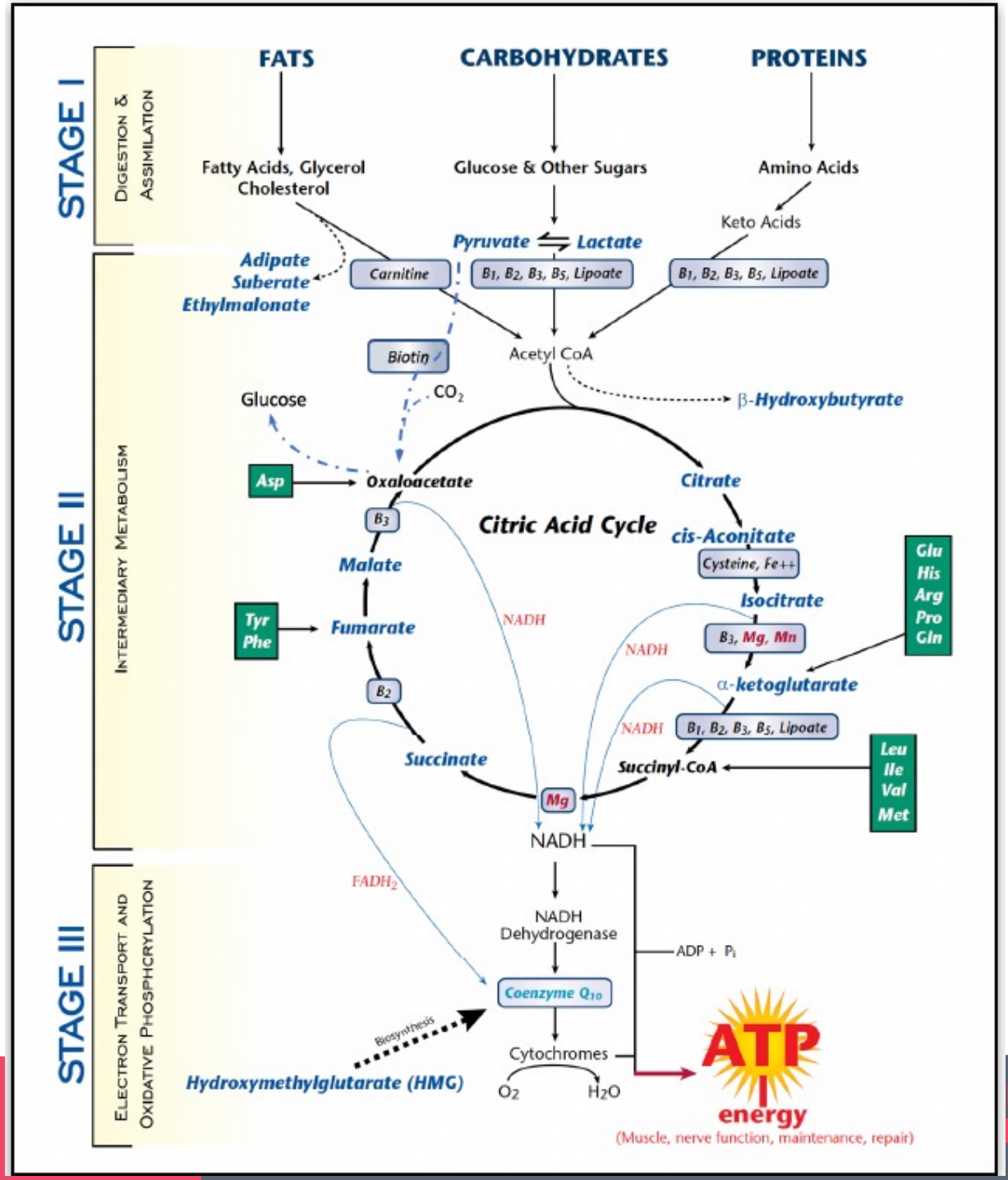
Energy pathways and cofactors



Lord R. Laboratory Guides to Health. Arrowhead Bioscience Inc. 2020. Fig 10.4

Citric Acid Cycle (CAC)

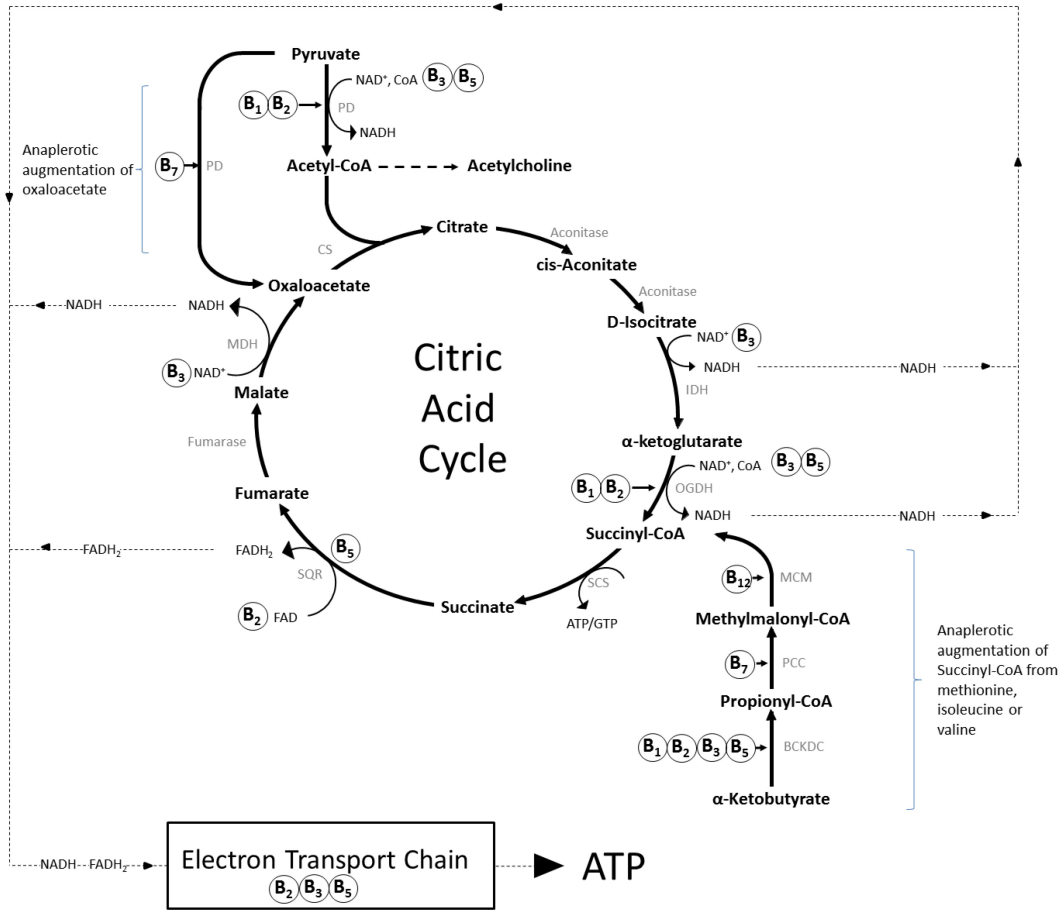
Energy generating pathway catabolic pathway of **Acetyl-coA to CO2**

Primary location of enzymes is the mitochondria

Primary sources of acetyl-CoA are the **pyruvate dehydrogenase complex** and **beta oxidation**, which are also in the mitochondria

Cycle transfers electrons to **NAD+ or FAD → NADH or FADH2**

NADH and FADH2 are then used in the ETC to generate ATP via **oxidative phosphorylation**



Nutrients 2016, 8(2), 68; fig 2

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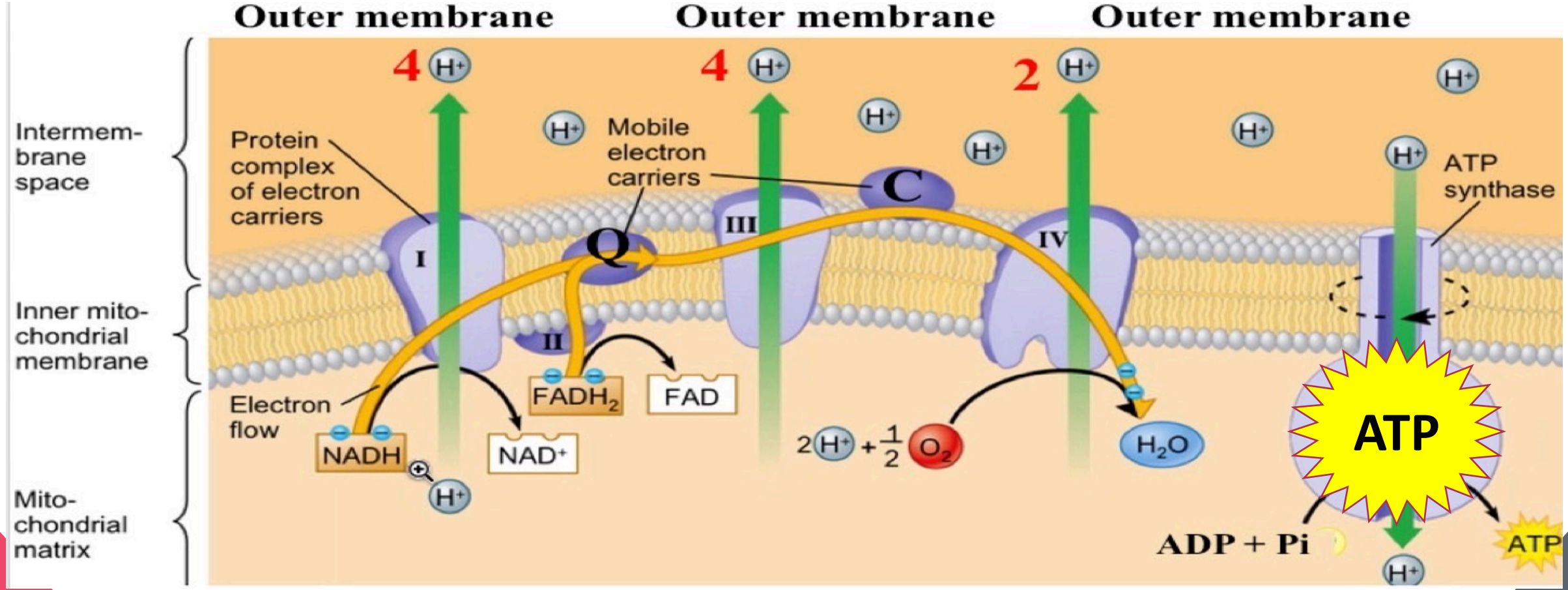
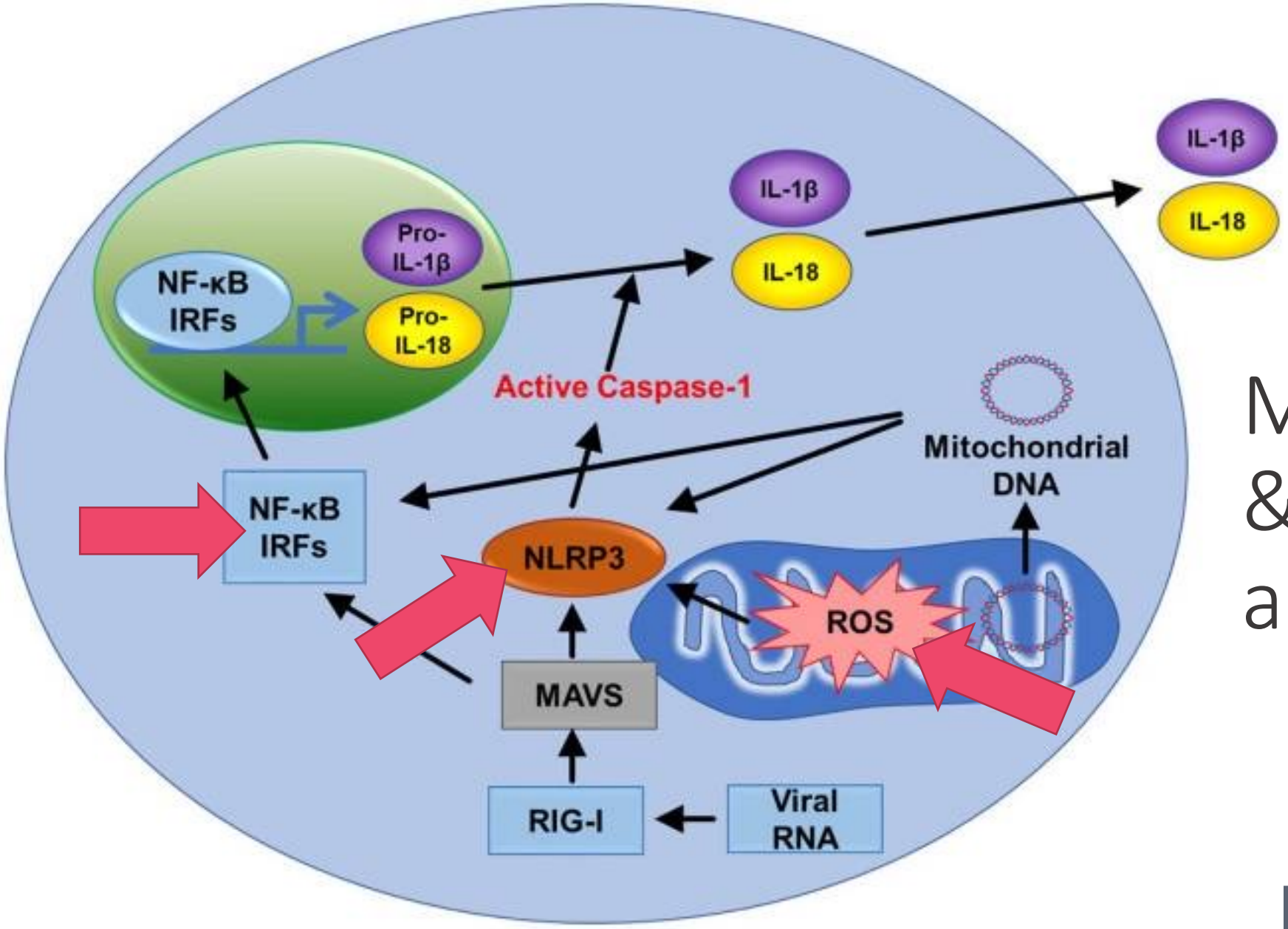
The Electron Transport Chain (ETC)



Pearson Education Inc 2016 figure 6.10
https://www.unm.edu/~lkravitz/Exercise%20Phys/ETCstory.html

What we know about COVID complications



Mitochondria & Immune activation

Front Immunol. 2018; 9: 1605. doi: 10.3389/fimmu.2018.01605

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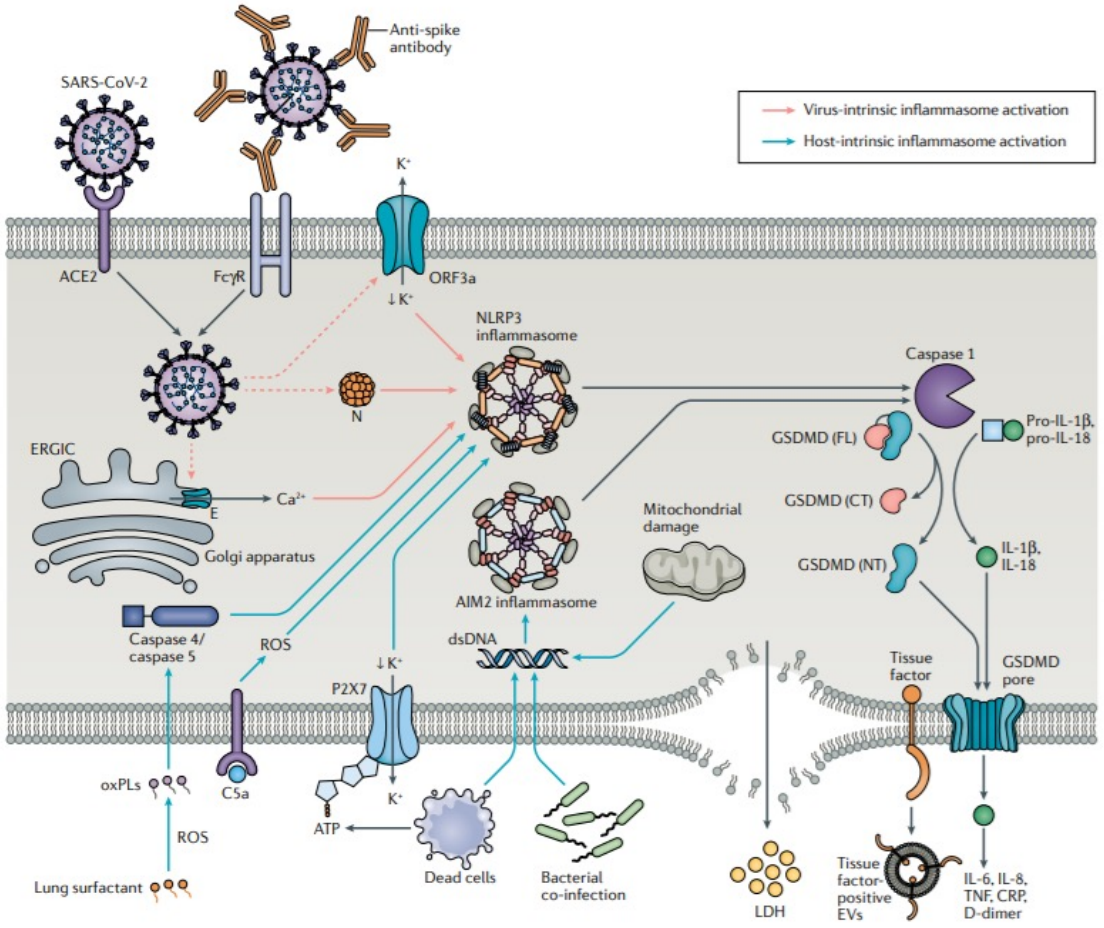
Inflammasome activation at the crux of severe COVID-19

Setu M. Vora, Judy Lieberman and Hao Wu

Abstract | The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), results in life-threatening disease in a minority of patients, especially elderly people and those with co-morbidities such as obesity and diabetes. Severe disease is characterized by dysregulated cytokine release, pneumonia and acute lung injury, which can rapidly progress to acute respiratory distress syndrome, disseminated intravascular coagulation, multisystem failure and death. However, a mechanistic understanding of COVID-19 progression remains unclear. Here we review evidence that SARS-CoV-2 directly or indirectly activates inflammasomes, which are large multiprotein assemblies that are broadly responsive to pathogen-associated and stress-associated cellular insults, leading to secretion of the pleiotropic IL-1 family cytokines (IL-1β and IL-18), and pyroptosis, an inflammatory form of cell death. We further discuss potential mechanisms of inflammasome activation and clinical efforts currently under way to suppress inflammation to prevent or ameliorate severe COVID-19.



Nat Rev Immunol (2021).

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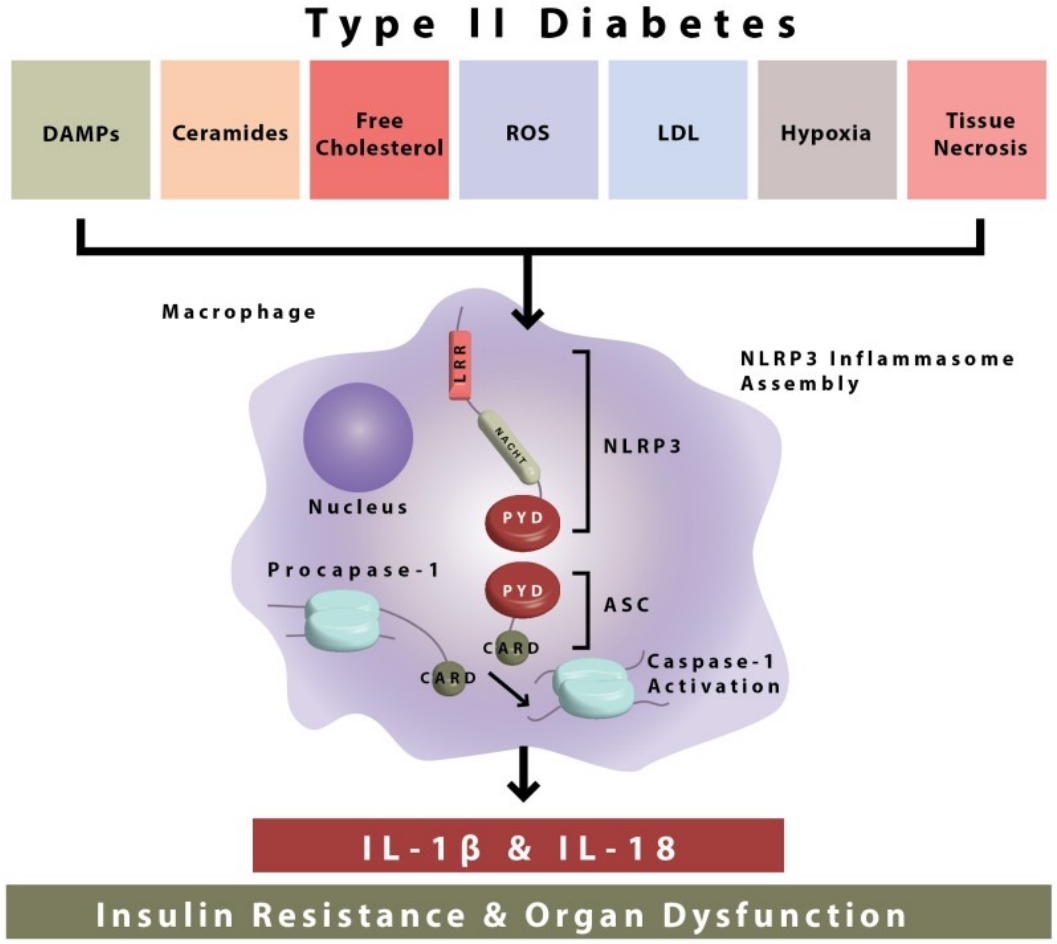
NLRP3 inflammasome activation T2DM

Accumulation of DAMPs (ROS, oxidized LDL, ceramides, glycation products etc…)

NLRP3 is triggered by DAMPs

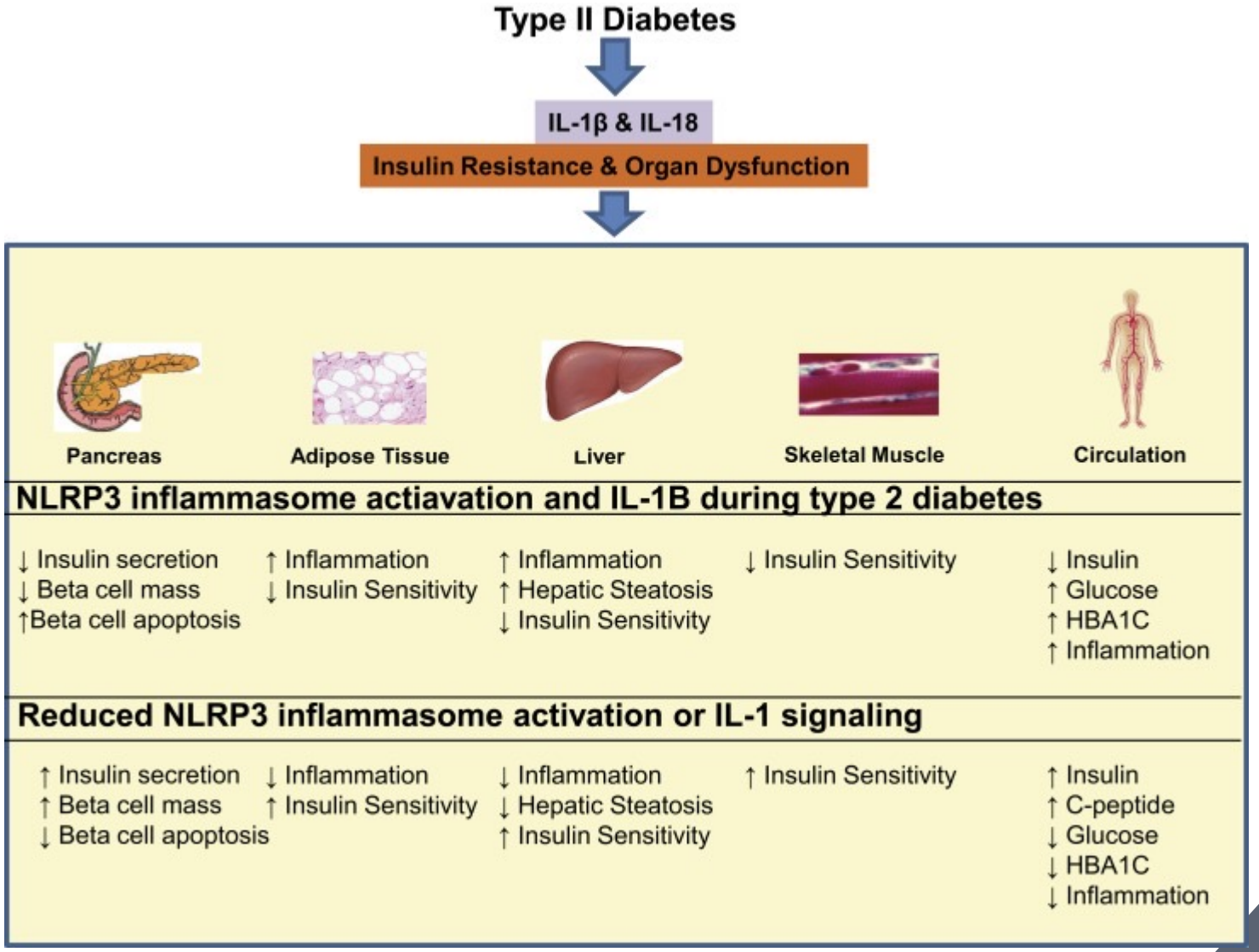
Activation of cytokine response (IL-1β + IL-18)

Insulin resistance and organ dyfunctions



Front Immunol. 2013;4:50. Fig 1.

Inflammasome COVID & Cardiometabolic Disease



Front Immunol. 2013;4:50. Fig 1.

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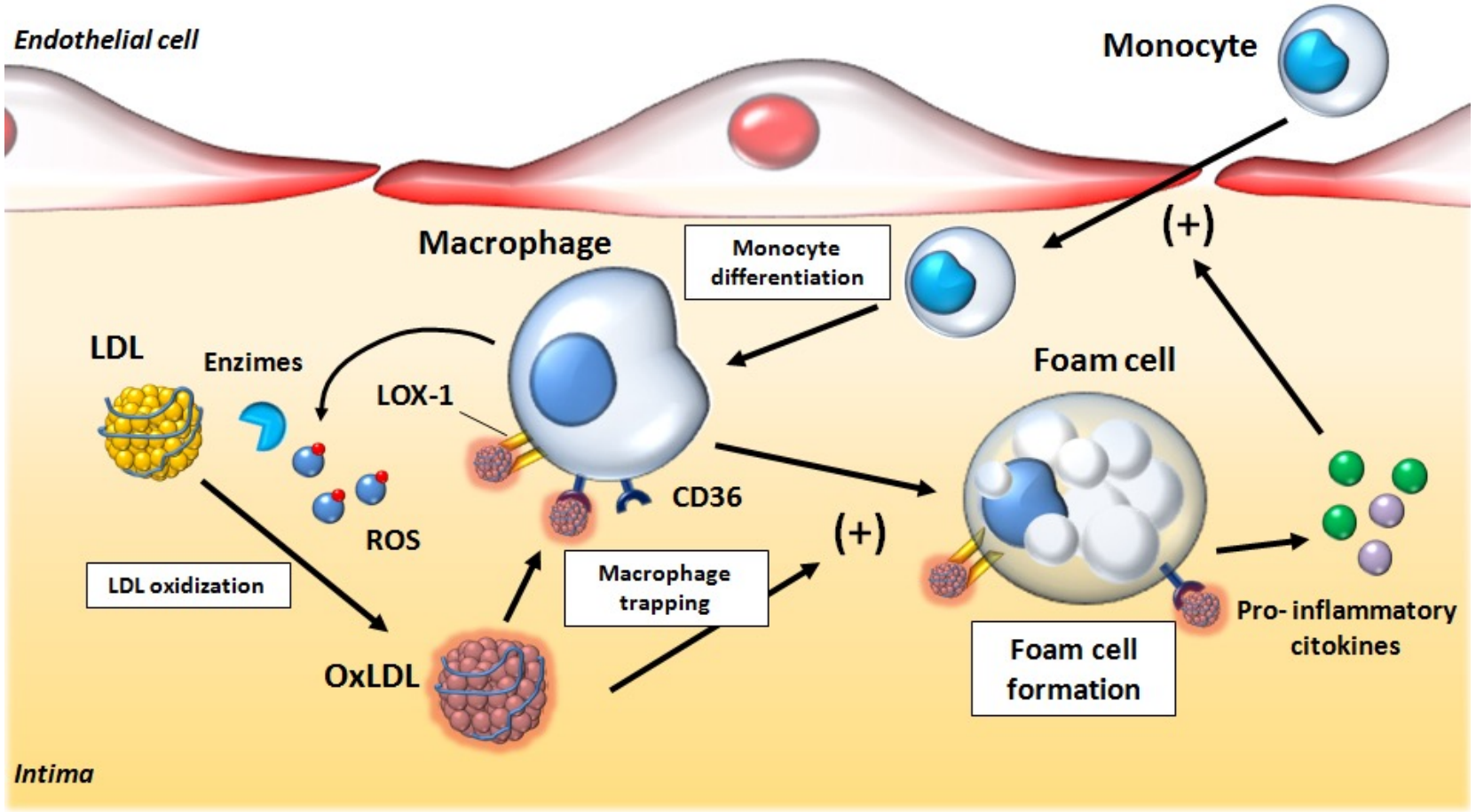
Oxidized LDL & Cardiometabolic risk



Role of Oxidized LDL in Atherosclerosis, Hypercholesterolemia, Sekar Ashok Kumar, IntechOpen, DOI: 10.5772/59375

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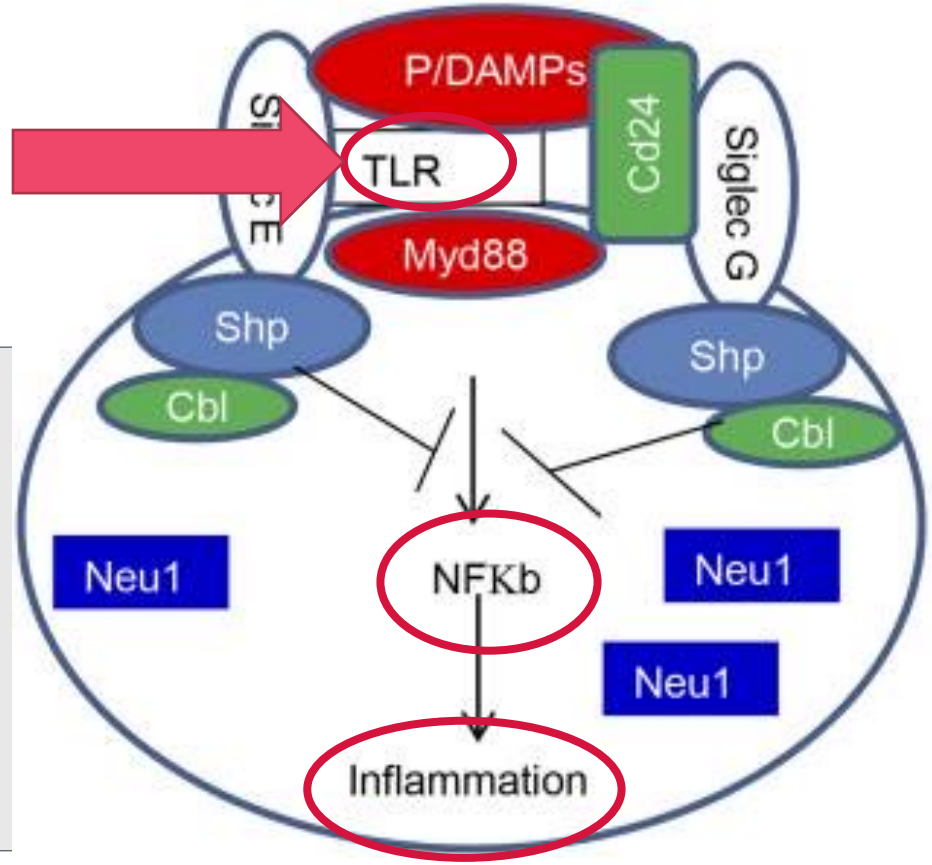
NF-kB transcription factor involved in cytokine production

NF-κβ is involved in cellular responses to stimuli such as:

- Stress
- Cytokines
- Free radicals/ROS
- Heavy metals
- Oxidized LDL
- Bacterial or viral antigens



Oncogene. **25** (51): 6680–4. doi:10.1038/sj.onc.1209954
eLife. 2014; 3: e04066. doi: 10.7554/eLife.04066

PRR = Pattern recognition receptors

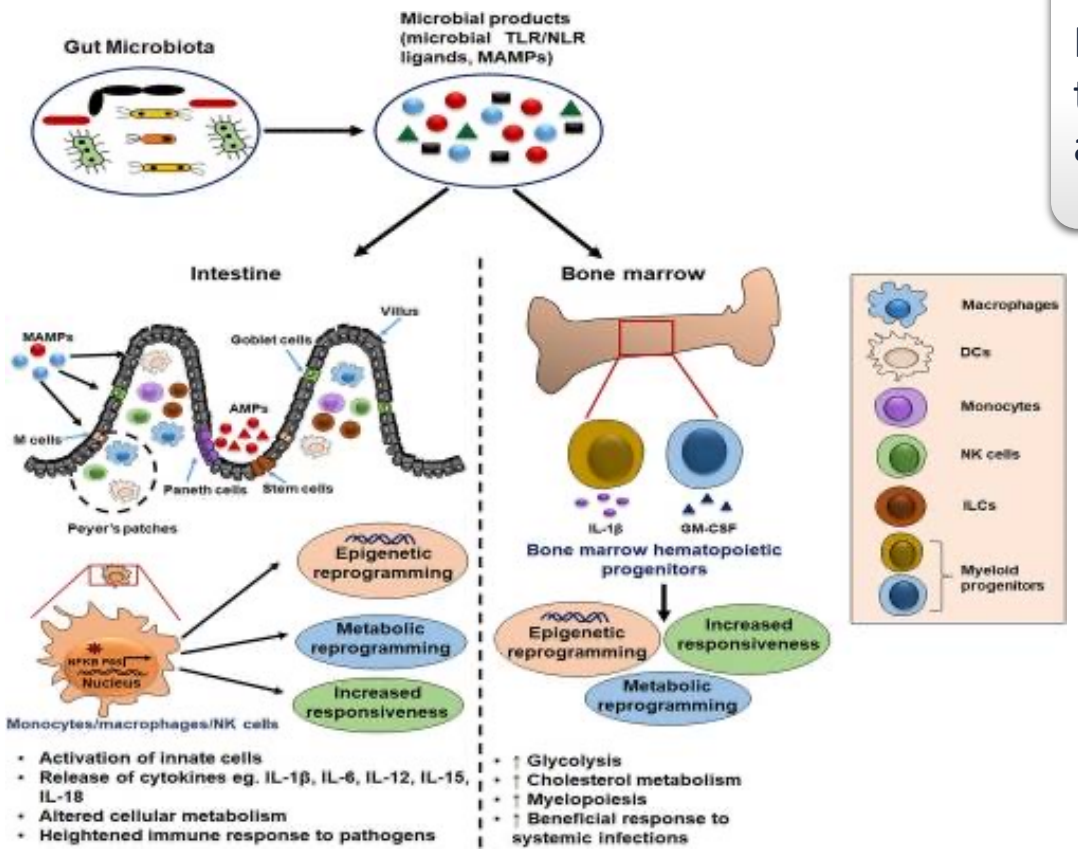
PRR recognize General patterns associated with PAMPS and DAMPS

Mitochondria regulate PRR expression and signaling

Therefore, requires intact and healthy mitochondria to mount a response to foreign invaders

Mitochondria are severely compromised by HPA-axis and metabolic stressors, and antibiotic use leading to altered immune response

Pattern Recognition Receptors (PRR)



PRR act within innate system when they come into contact with Pathogen-associated molecular patterns (PAMPs)

Gut microbes act as PAMPs that bind PRRs

In turn, this activates the nonspecific arm of the immune system

Front Immunol. 2019; 10: 2441.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6842962/

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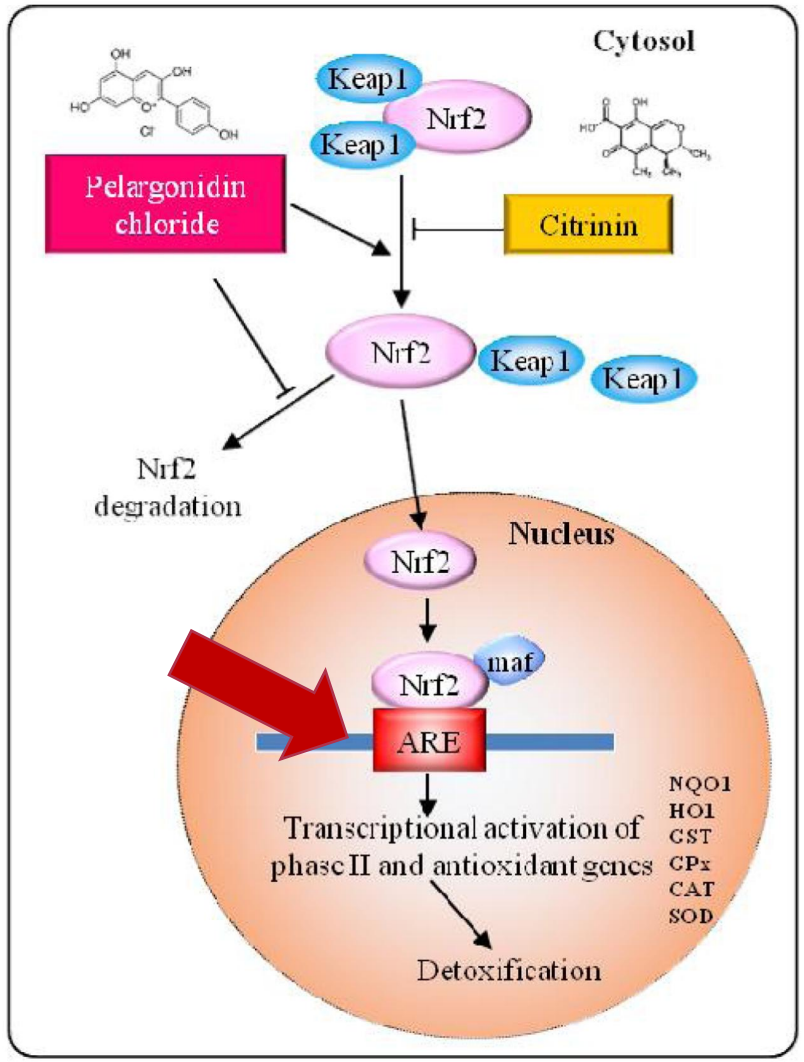
Keap1-Nrf2 & ARE*

NRF2 is a transcription factor. In short, it is a protein that when it binds to AREs on a cell's nucleus, it activates certain gene sequences.

Nrf2 can attenuate and minimize many of the chronic stresses that cause illness through damage prevention, damage control, and cellular renewal



**ARE = Antioxidant Response Element*
Front. Pharmacol., 27 November 2017

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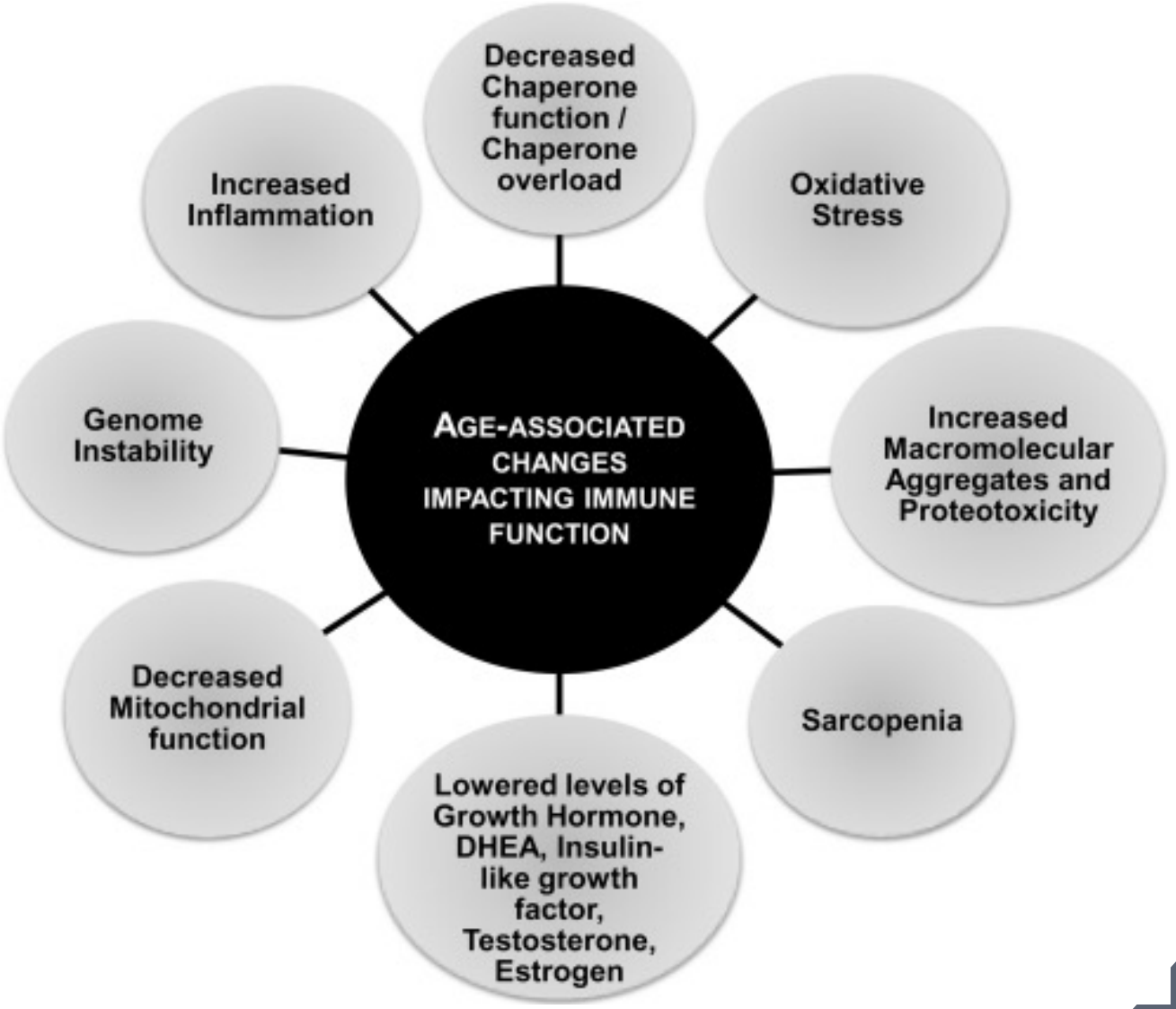
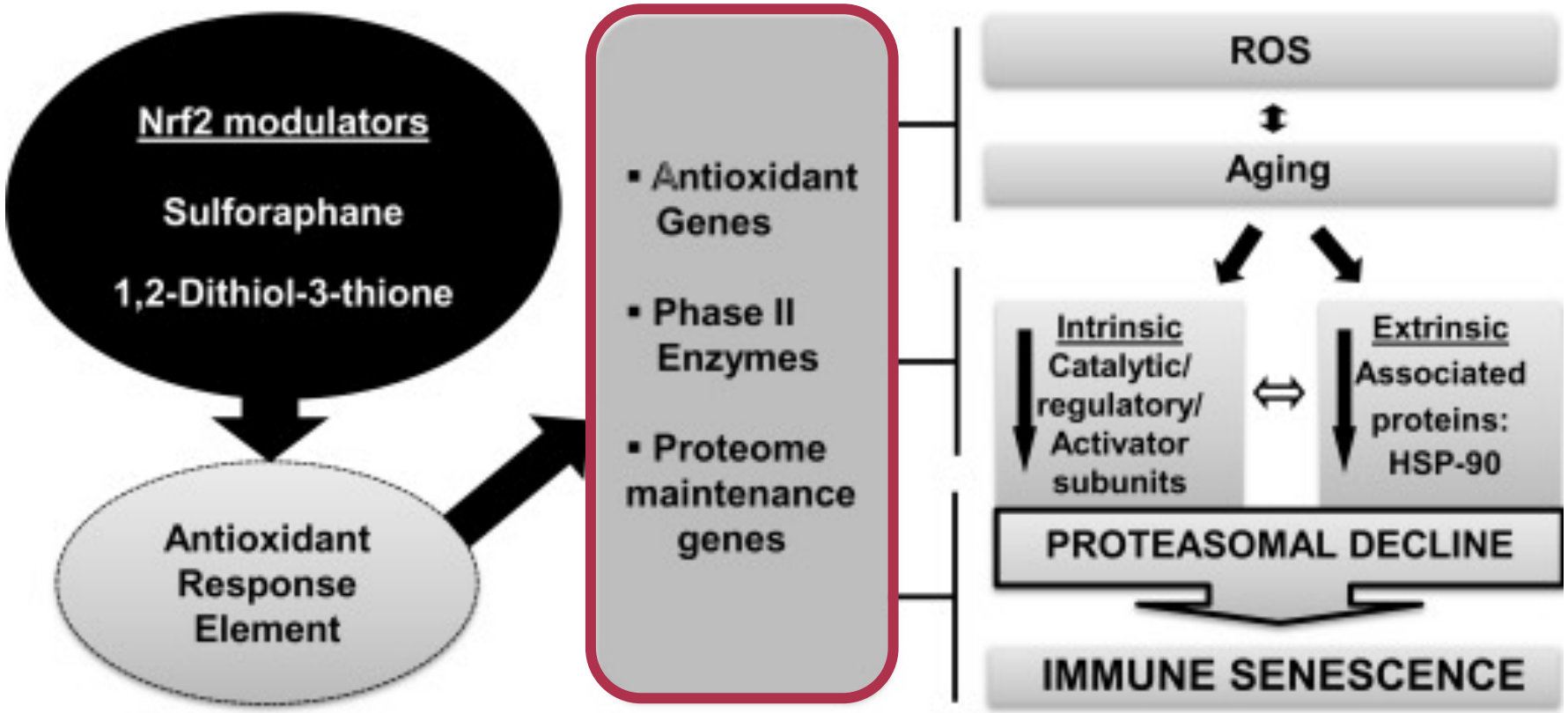
Immune status changes associated with aging



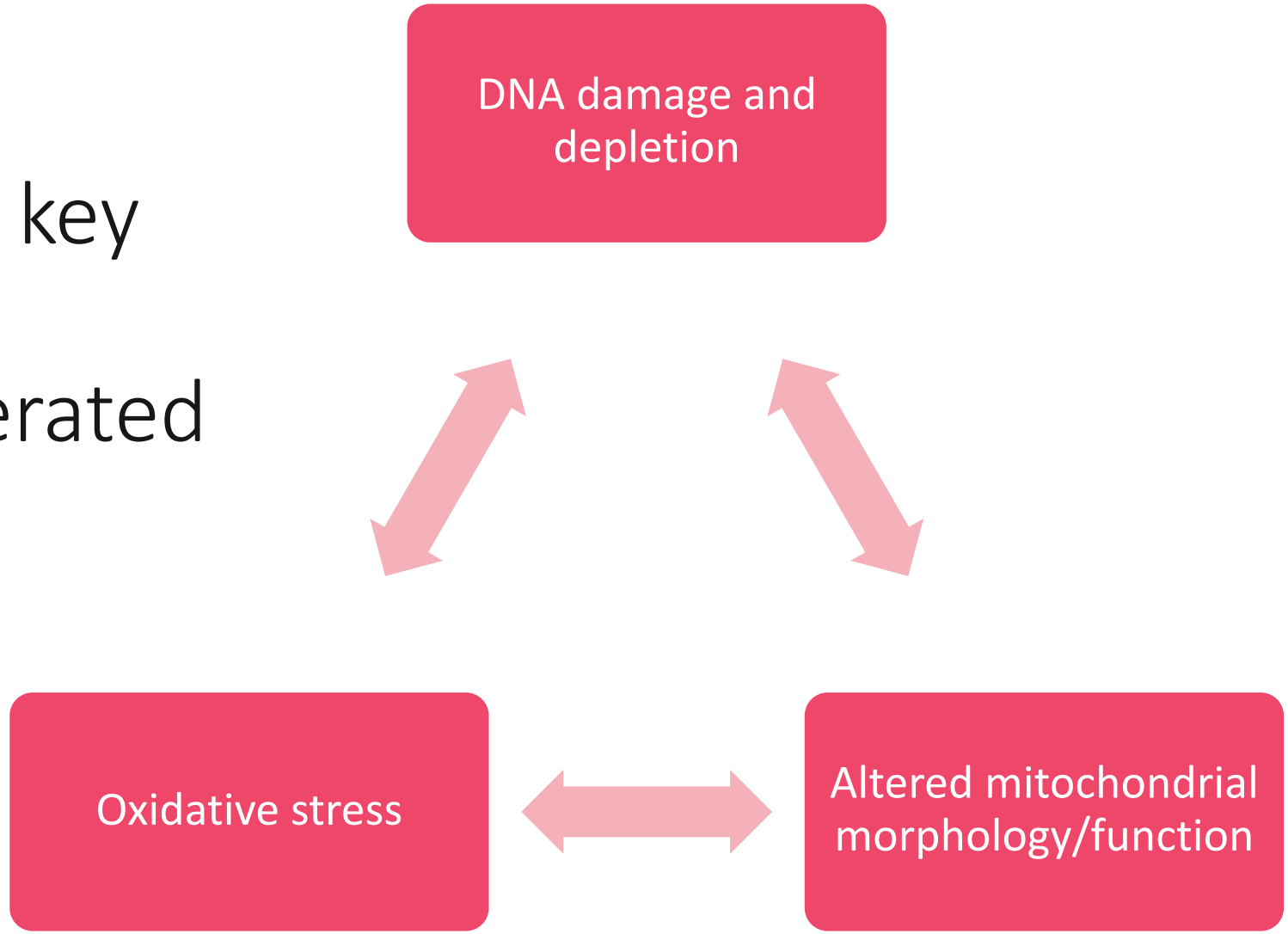
Antioxid Redox Signal. 2011;14(8):1551-1585. Fig 1.

Nrf2 modulators and their mode of action in overriding immune dysfunction during aging



Antioxid Redox Signal. 2011;14(8):1551-1585. Fig 11.

Mitochondria are key component for premature/accelerated aging



Immunosenescense = The loss of immune “reserve”

“Inflammaging”→ drive chronic diseases

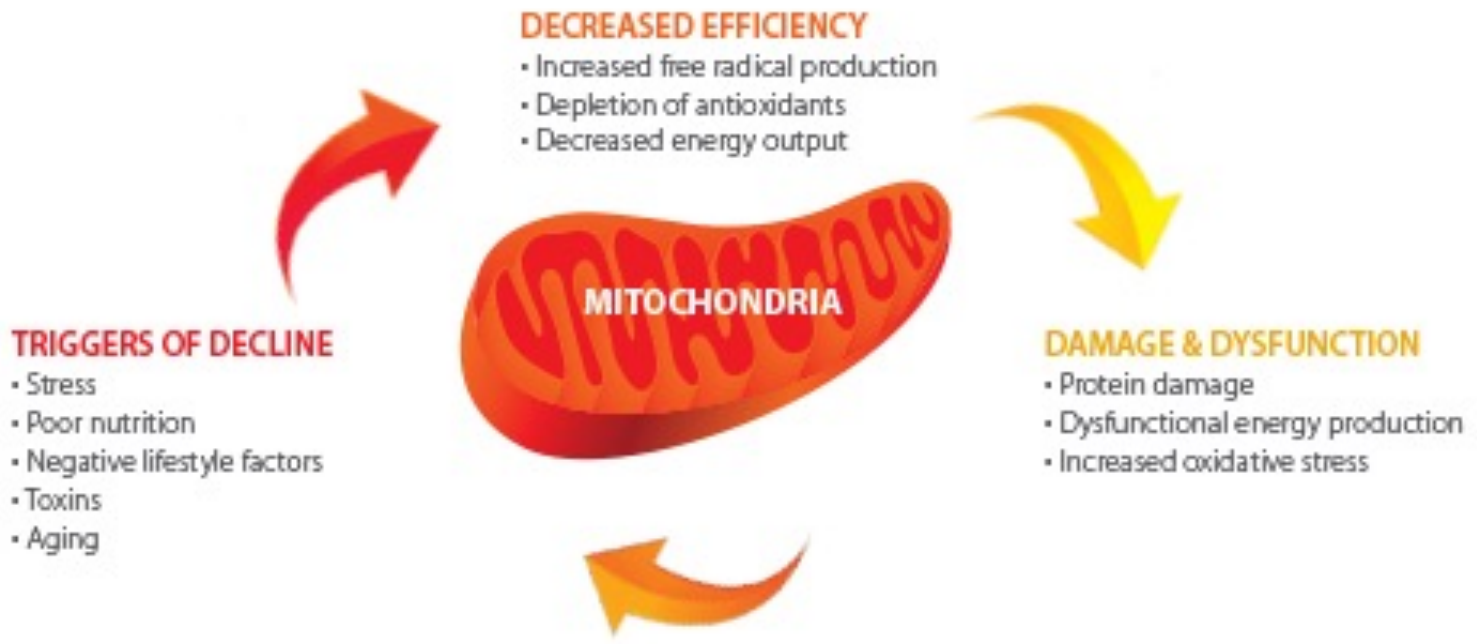
- Changes in immune function with age
- Influenced by years of immune training and stress
- Depletion of naïve cells in the Adaptive immune system
- NK-cells increase in number but less active
- Decreased numbers of neutrophils/monocytes

Changes in gut microflora and barrier function influence immune function

Increased frequency of auto-immune and allergic disease progression

Accumulations of HPA axis dysregulation

“Inflammaging”



Remember Annie?

- What concerns do you have about Annie's risk factors for complications form COVID?
- *Hint: consider disease state complications*

Core Principles for Improving Immune Function

Barriers/Triggers

- Avoiding pathogens through good hygiene, distancing, masks, etc…
- Maintaining/protecting barrier functions
- Reducing stress (psychological and physiological)
- Identifying and avoiding antigens and allergens and other chronic inflammatory triggers/mediators

Systems/metabolic reserve

- Supporting a balanced microbiome and GI integrity
- Supporting mitochondrial energy capacity
- Supporting detoxification capacity
- HPA-axis
- Hormone balance

Nutrients

- Building micronutrient and antioxidant reserve
- Adaptogens and immune modulators

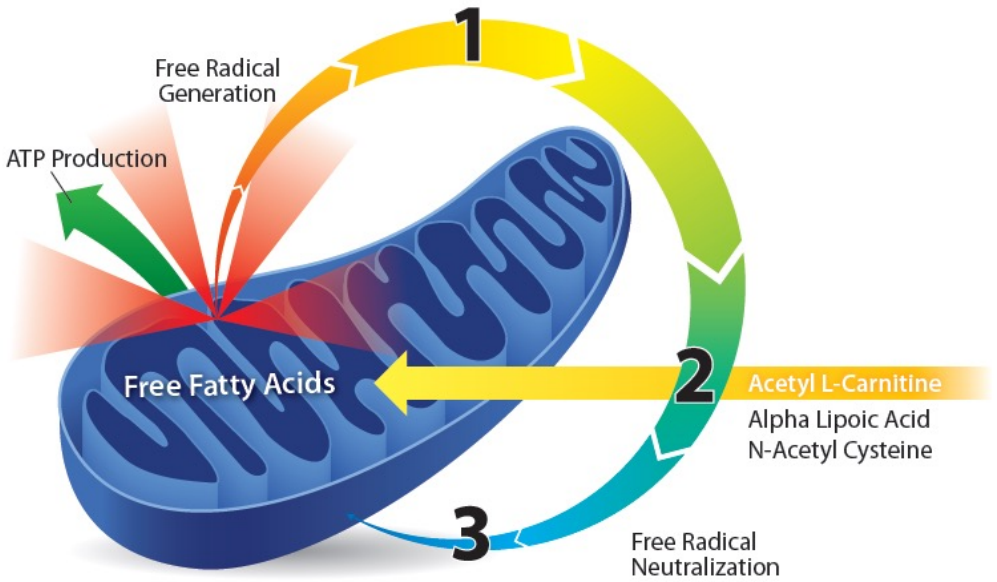
Energy for Immune function

The immune function is an energy demanding system (feeling “drained” is a common system)

This increases mitochondrial demand to keep up with energy need

Enhanced ATP production leads to more ROS

Not a problem as long as antioxidant reserve and mitochondrial cofactors are available



Building metabolic reserve

Adequate macronutrient balance

- Amino acids
- Antiinflammatory fats
- Fiber

Adequate micro-nutrient reserve

- Cofactors for energetic/metabolic and enzymatic pathways

Strong antioxidant reserve

- Neutralizing ROS
- Modulating transcription factors

Mitochondrial

- Intermediate and cofactors for ATP production
- Antioxidants to quench oxidative stress as mitochondrial demand increases

Choline

Choline plays a lipotropic role in lipid metabolism as an essential nutrient

Low choline is associated with reduced mitochondrial potential, ATP production, and fatty liver

Deficiency of choline has been associated with lipid peroxidation and mtDNA damage

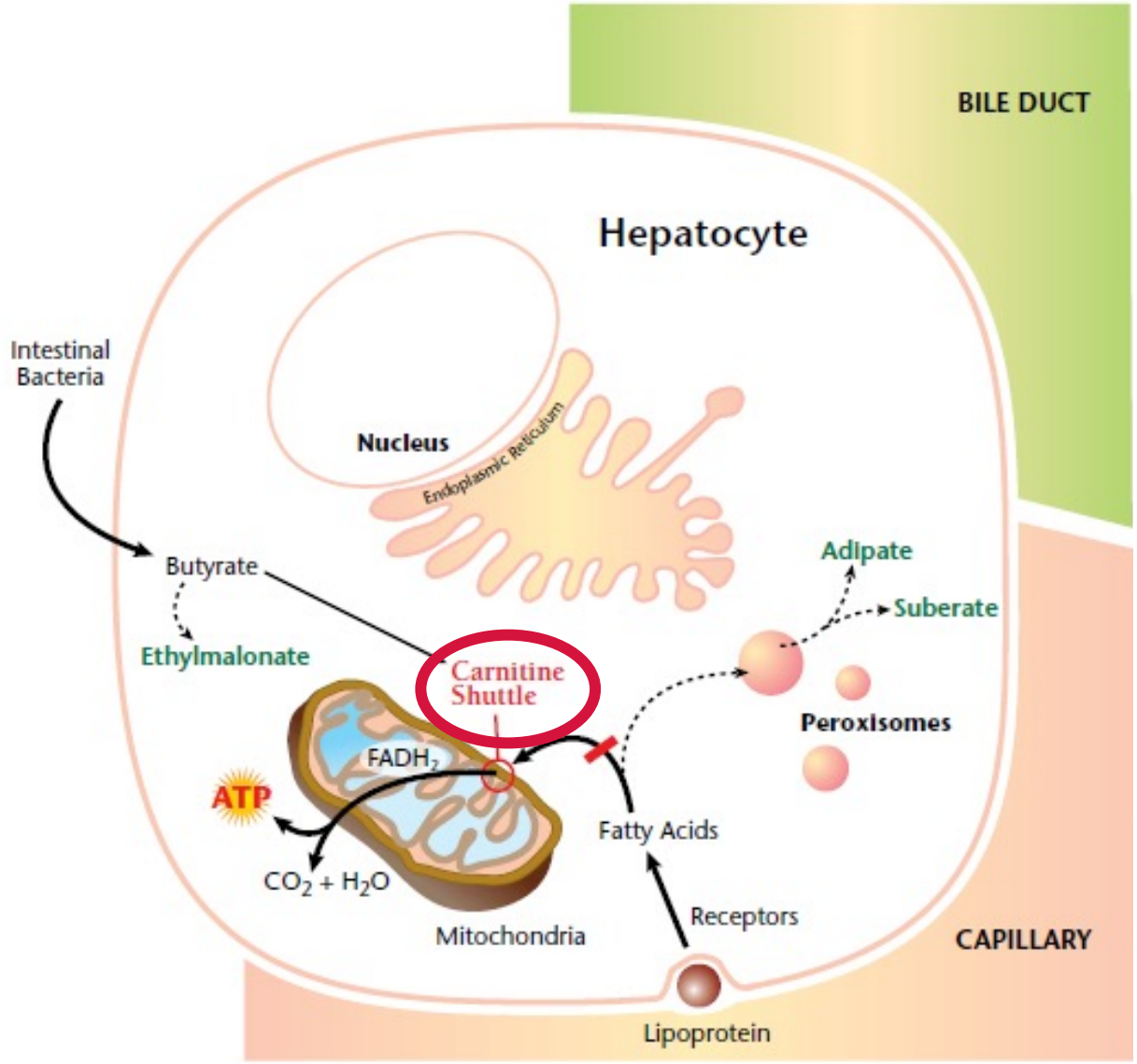
Carnitine

Fatty acids are transported via carnitine into mitochondria for their subsequent oxidation to generate ATP.

Carnitine has a protective effect both on mitochondria and in whole cells by inhibiting free fatty acid-induced mitochondrial membrane damage and/or its secondary effects

Carnitine might be an effective treatment for cardiovascular disorders via mitochondria

Carnitine Shuttle



Lord R. Laboratory Guides to Health. Arrowhead Bioscience Inc. 2020.

Glutathione: The master antioxidant

Low glutathione (GSH)

- Reduced antioxidant capacity and ROS
- Reduced energy production
- Reduced detoxification capacity
- Compromised GI barrier
- Altered immune response

Precursors of GSH

- Cysteine
- Glycine
- Glutamine
- Serine
- Taurine
- N-acetylcysteine (NAC)

Nutritional considerations

- Diet rich in protein, colorful fruits and vegetables
- Digestive support (see 5R)
- NAC and AA building blocks
- Micronutrient cofactors (Vitamin C & E, Mg, Se, Zn, B2, B5, B6, and folate)
- Alpha lipoic acid, curcumin, milk thistle

Two major antioxidants worth emphasizing

N-actyl-l-cysteine (NAC)

- Building block for glutathione
- Chelator
- Microbiome impact (biofilm disruptor)

Alpha lipoic acid (ALA)

- Powerful antioxidant, glutathione “sparing”
- Fasting mimetic
- Known metal chelator

Spoiler alert

Green Tea Leaf Extract

- Decreases NF-kβ
- Contains PQQ

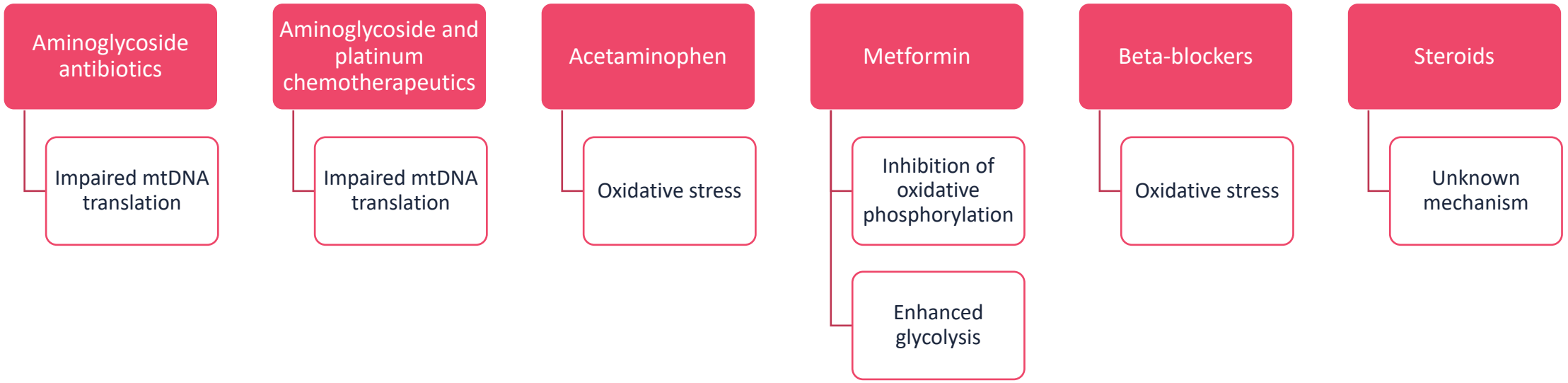
Broccoli Seed Extract

- Sulphoraphane
- Supports Th1 and NK cell activity which antagonizes Th17

Trans-Resveratrol

- Decreases NF-kβ
- Fasting mimetic
- SIRT1 is a master regulator of mitochondrial biogenesis and is stimulated by resveratrol (SIRT1 activates PGC-1α)

Medications impacting mitochondrial toxicity



Remember Annie?

- What concerns do you have about Annie's risk factors for complications form COVID?
- *Hint: Consider her medications*

Treatment Options

Pathogens	Reduce Pro-Oxidants	Increase Antioxidants	Lifestyle Factors
• Increased oxidative stress • Presence of pathogen induces production ROS to stimulate protective mechanism (apoptosis/PAMP) • “5R” - remove and repair	• Reduce or avoid exposure to environmental toxins • Organic vs conventional • Avoid smoking, excessive alcohol consumption, excessive exercise, stress	• Macronutrients • Micronutrients • Phytonutrients • (see next slide)	• Sleep (melatonin) • Excessive exercise • Stress management

Nutrients for neutralizing oxidative stress

Adequate macronutrient balance for metabolic reserve

- Amino acids
- Anti-inflammatory fats
- Fiber (diverse sources)

Adequate micro-nutrient reserve

- B-complex especially B2 & B3
- Lipoic acid
- Mg, Mn
- Fe, CoQ10

Strong antioxidant reserve

- Antioxidant nutrients (Vit C, beta-carotene, vitamin E)
- ALA
- CoQ10
- NAC
- B2, B3
- Selenium, Zinc, Copper, Manganese, Magnesium
- Modulating transcription factors (Sulforaphane, Resveratrol Curcumin, EGCG, anthocyanines/Pterostilbine (berries))

Mitochondrial

- Choline
- Carnitine
- NAC
- ALA
- Resveratrol, curcumin, EGCG, sulforaphane

Thank You!

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