Nestlé Nutrition Institute

THE ROLE OF NUTRITION CARE IN MITOCHONDRIAL HEALTH

ASPEN Nutrition Science and Practice Conference

Presented on March 20, 2021

Sponsor Disclosure

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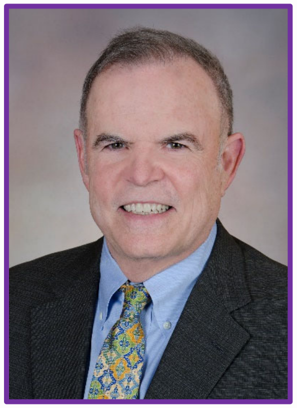
Speakers



Robert Martindale, MD, PhD

Professor of Surgery
Oregon Health and Science University
Portland, OR

Bret Goodpaster, PhD

Scientific Director
AdventHealth Research Institute
Orlando, FL

Eduardo Chini, MD, PhD

Professor of Anesthesiology,
Assistant Professor of Medicine,
Professor of Pharmacology
Mayo Clinic College of Medicine
Rochester, MN

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Program Objectives

1. Explain the central role of mitochondria in nutrition and metabolism
2. Describe the role of mitochondrial dysfunction in aging and the development and progression of disease
3. Identify nutritional interventions that support mitochondrial function and their impact on clinical outcomes

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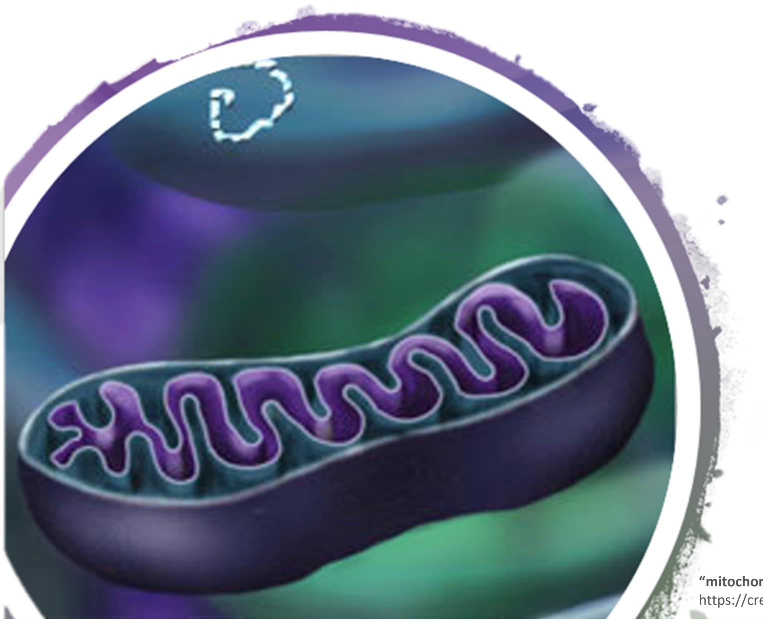


NUTRITIONAL MEDIATORS OF MITOCHONDRIAL FUNCTION

Robert G. Martindale, M.D., Ph.D.

Professor of Surgery

Oregon Health and Science University

Portland, Oregon

Disclosures

- No disclosures related to this symposium other than funding for participation in the symposium

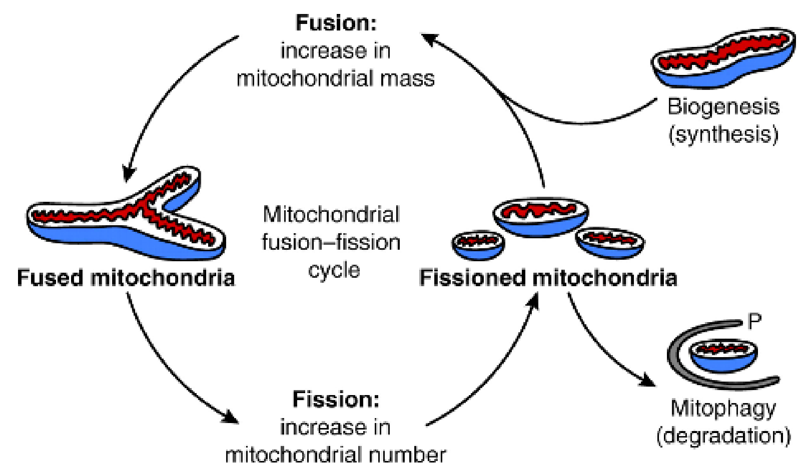
- Other non-related disclosures
  - Nestlé Nutrition Fellowship faculty
  - Lifecell advisory board
  - CR Bard advisory board
  - Baxter – educational faculty
  - Fresenius Kabi – Advisor and faculty in educational symposium

Objectives

- Review the multifaceted role of the mitochondria
- Discuss the role of nutrition to support mitochondrial function across the spectrum of nutritional care

Mitochondria- Brief Review

- **Present in both animals and plants**
  - **# of mitochondria vary in animal cells: RBC vs hepatocytes/cardiac cells**
  - **Evolutionarily mitochondria thought to arise from symbiotic relationship with intracellular bacteria (mtDNA)**



Seo AY et al. J Cell Sci 2010;123:2533-2542

- **Life cycle of a mitochondria**

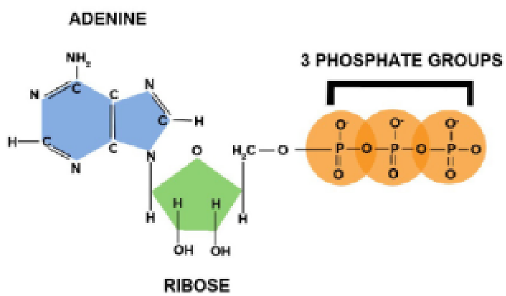
- **Mitochondrial dysfunction:**
  - **ICU patients show 50% reduction ATP synthesis compared to healthy controls**
  - **Excess oxygen free radical negatively effects ET chain**
  - **Loss of mitochondrial membrane integrity**
    - **mtDNA leak out (act as DAMPs)**

DAMPs = Danger-associated molecular patterns
mtDNA = mitochondrial DNA

Moonen HPFK et al Curr Opin Crit Care 2020;26(4):346-354
Supinski GS et al. Chest 2020;157(2):310-322

Mitochondrial function: old vs new concepts

- ***Classic*** **understandings of mitochondria function:**
  - **Production of ATP via oxidative phosphorylation**



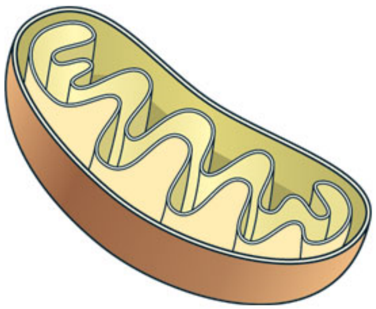
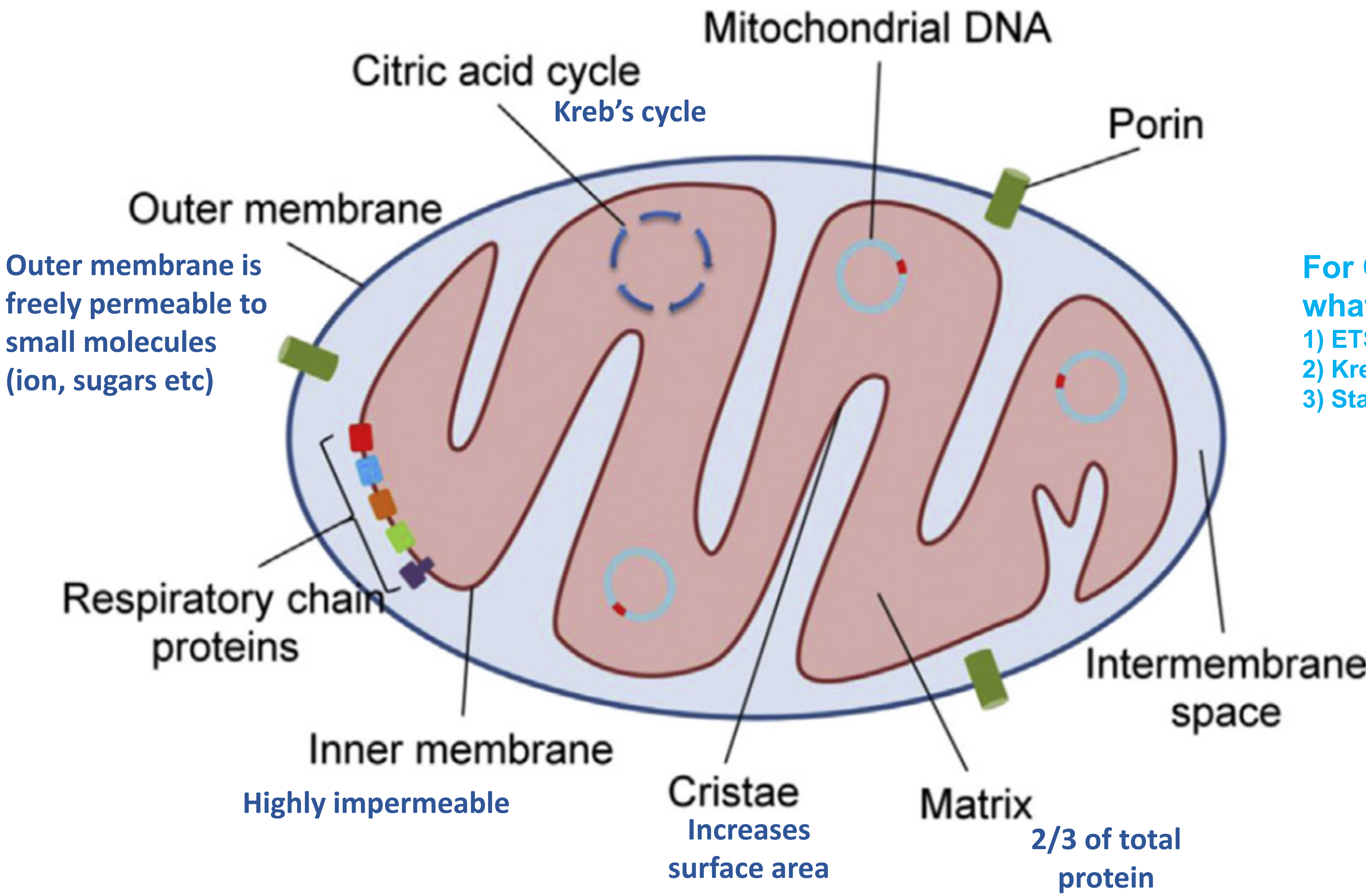


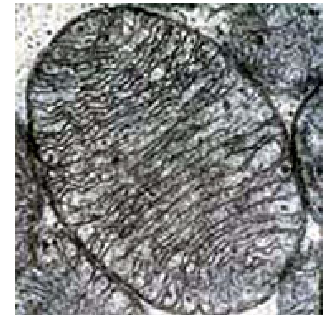
Image Source: clipart-library.com

- ***Enhanced*** **or** ***current*** **understandings of mitochondrial function:**
  - **Cell signaling**
  - **Regulation of gene expression**
  - **Cell growth**
  - **Ca++ regulation**
  - **Modulating cell death pathways and autophagy**
  - **Multiple other functions**

Supinski GS et al. Chest 2020;157(2):310-322
Wesselink E et al. Clin Nutr 2019;38:982-995
Moonen HPFK et al Curr Opin Crit Care 2020;26(4):346-354



Modified from Supinski GS et al Chest 2020

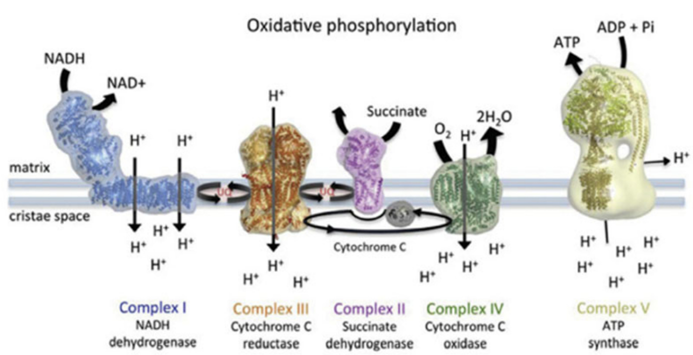


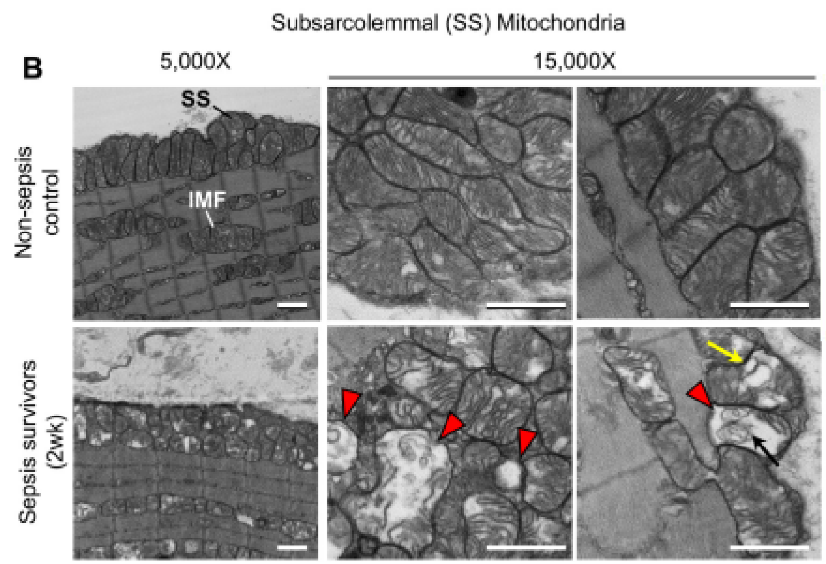
For Optimal Function what do we need ?

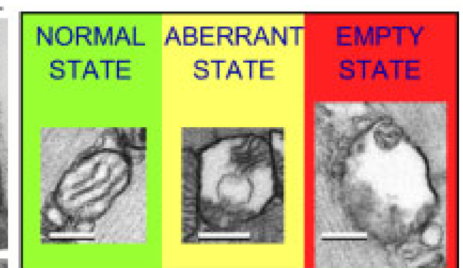
1) ETS proteins
2) Krebs cycle functioning
3) Stable membranes

How does critical illness alter the mitochondrial ability to oxidize nutrients for energy source for ETS

- **Depletion of required ETC proteins**
- **Leakage of protons across the normally impermeable inner mitochondrial membrane**
- **Incomplete delivery of electrons to molecular oxygen produces:**
  - **Superoxides, hydroxyl radicals, peroxynitrite**







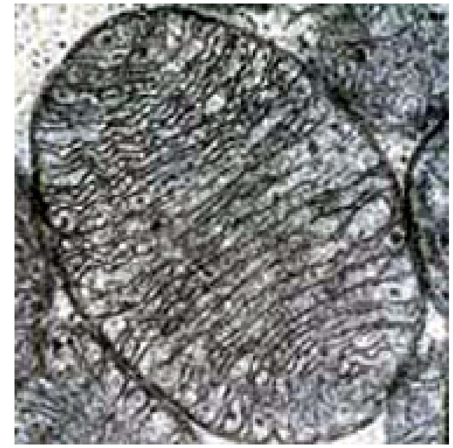
Supinski GS et al Chest 2020
Owen AM et al eLIFE 2019;8:e49920

Critical care

ORIGINAL ARTICLE

Metabolic phenotype of skeletal muscle in early critical illness

Zudin A Puthucheary,[1,2,3,4] Ronan Astin,[1,2] Mark J W Mcphail,[5,6] Saima Saeed,[7] Yasmin Pasha,[5] Danielle E Bear,[4,8,9,10] Despina Constantin,[11] Cristiana Velloso,[4] Sean Manning,[12,13,14] Lori Calvert,[15] Mervyn Singer,[3,7] Rachel L Batterham,[12,13] Maria Gomez-Romero,[16] Elaine Holmes,[16] Michael C Steiner,[17] Philip J Atherton,[11] Paul Greenhaff,[11] Lindsay M Edwards,[18] Kenneth Smith,[11] Stephen D Harridge,[41] Nicholas Hart,[10,191] Hugh E Montgomery[1,21]



- **Critical Illness**
  - **Decreased muscle mitochondrial biogenesis** (biogenesis = increasing mitochondrial mass)
  - **Dysregulated lipid oxidation**

- **End result:**
  - **Reduced ATP generation**
  - **Skeletal muscle wasting associated with impaired lipid oxidation, inflammation**
  - **Intramuscular inflammation**
    - **Impairs anabolic recovery**
    - **Alters lipid utilization in mitochondria**

Puthucheary ZA et al Thorax 2018;73(10):926-935
Wesselink E et al Clin Nutr 2019;38:982-995

Searching for the **magic bullet** to improve mitochondrial function

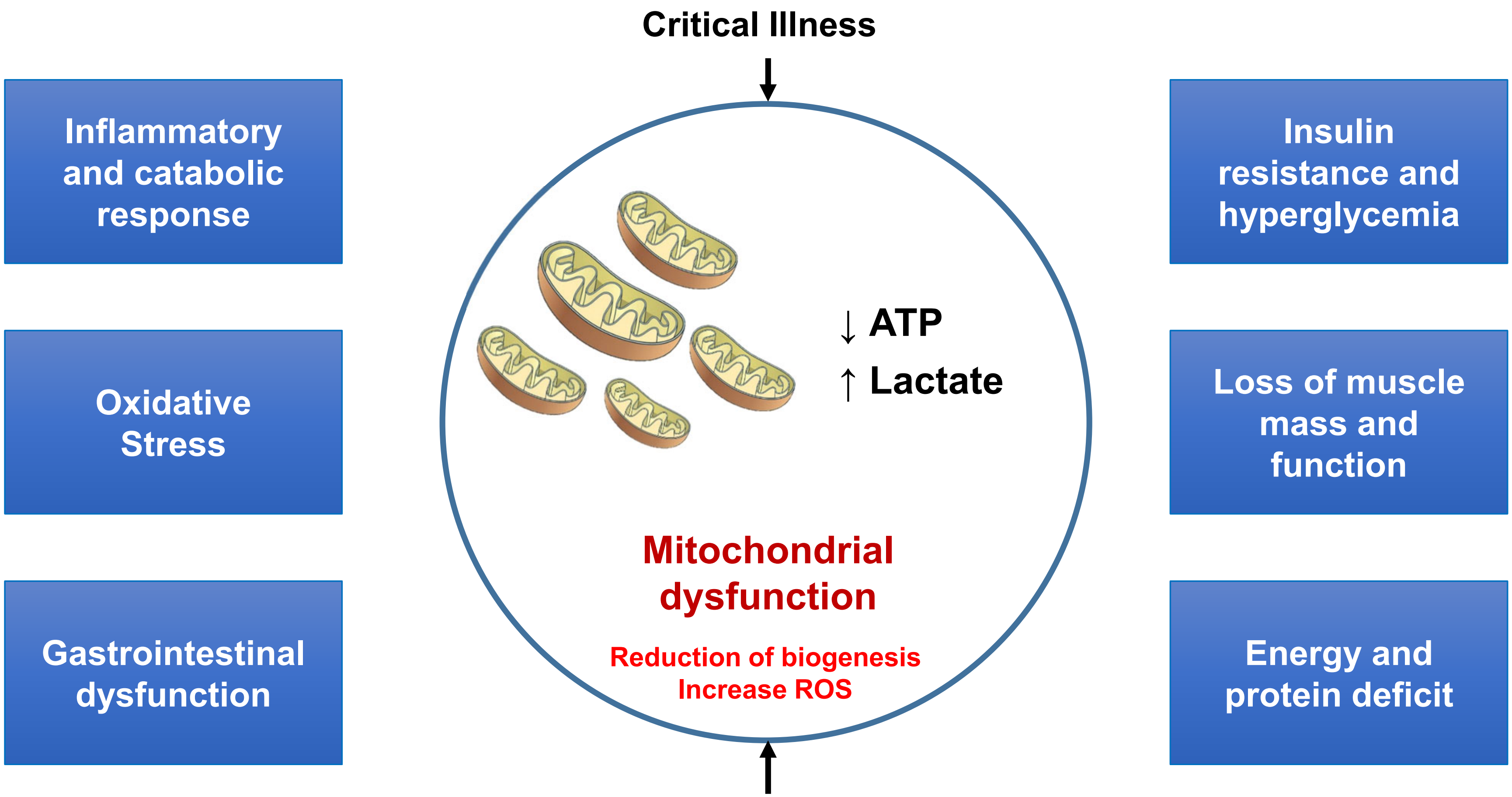


Figure adapted from Wesselink E et al Clin Nutr 2019;38:982-995

Moonen HPFX Curr Opin Crit Care 2020

Searching for the magic bullet to improve mitochondrial function

Critical Illness

Inflammatory and catabolic response

Insulin resistance and hyperglycemia

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Mitochondrial function was traditionally focused on augmenting O2 transport, blood flow

Is delivery of more macronutrients the answer ?

What about micronutrients ?

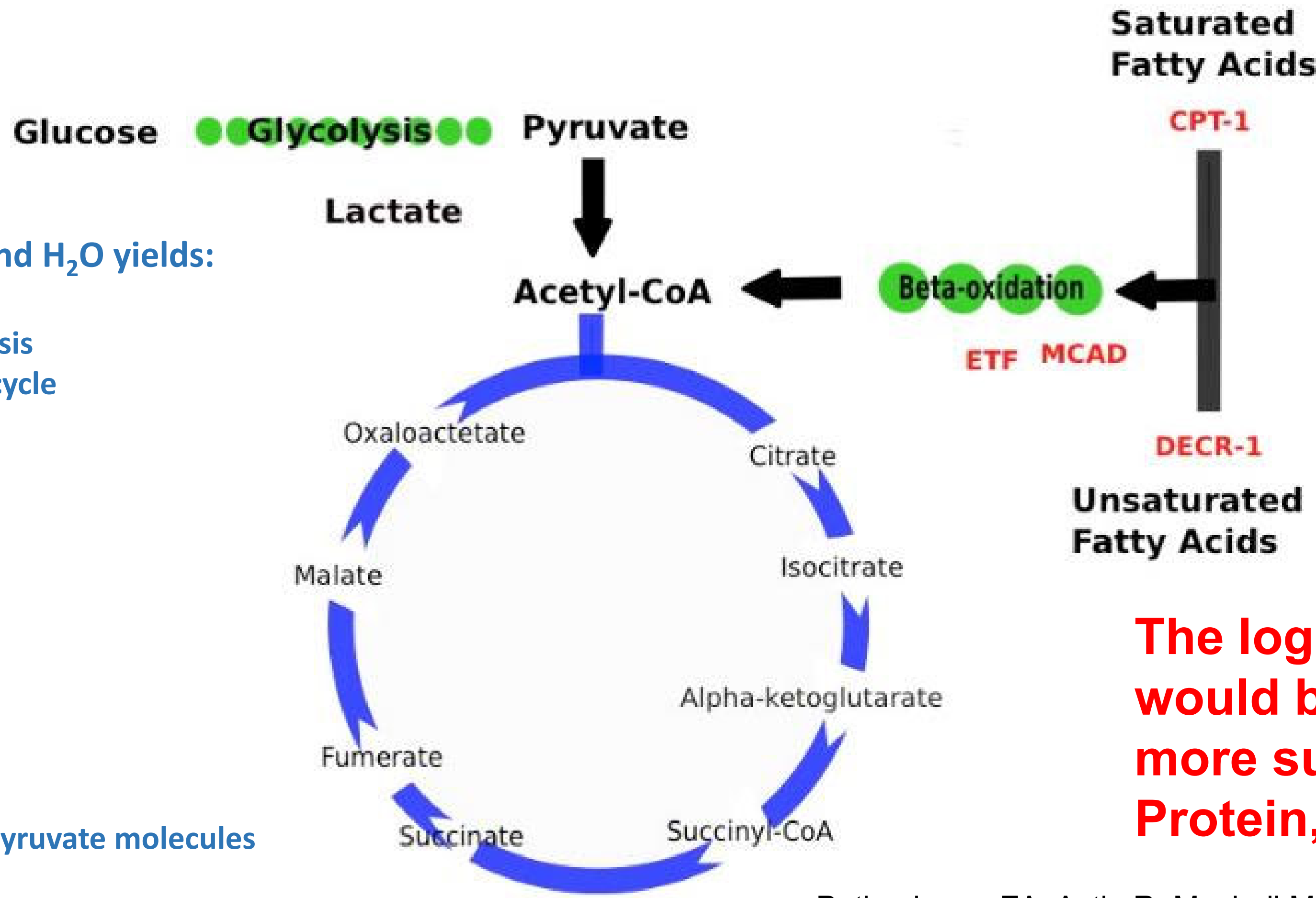
Opin Crit Care 2020

Glucose to CO_2 and H_2O yields:

- 38 ATP
  - 2 from glycolysis
  - 2 from Krebs cycle
  - 34 from ETS

Glycolysis yields:

- ATP, 2NADH, 2 pyruvate molecules

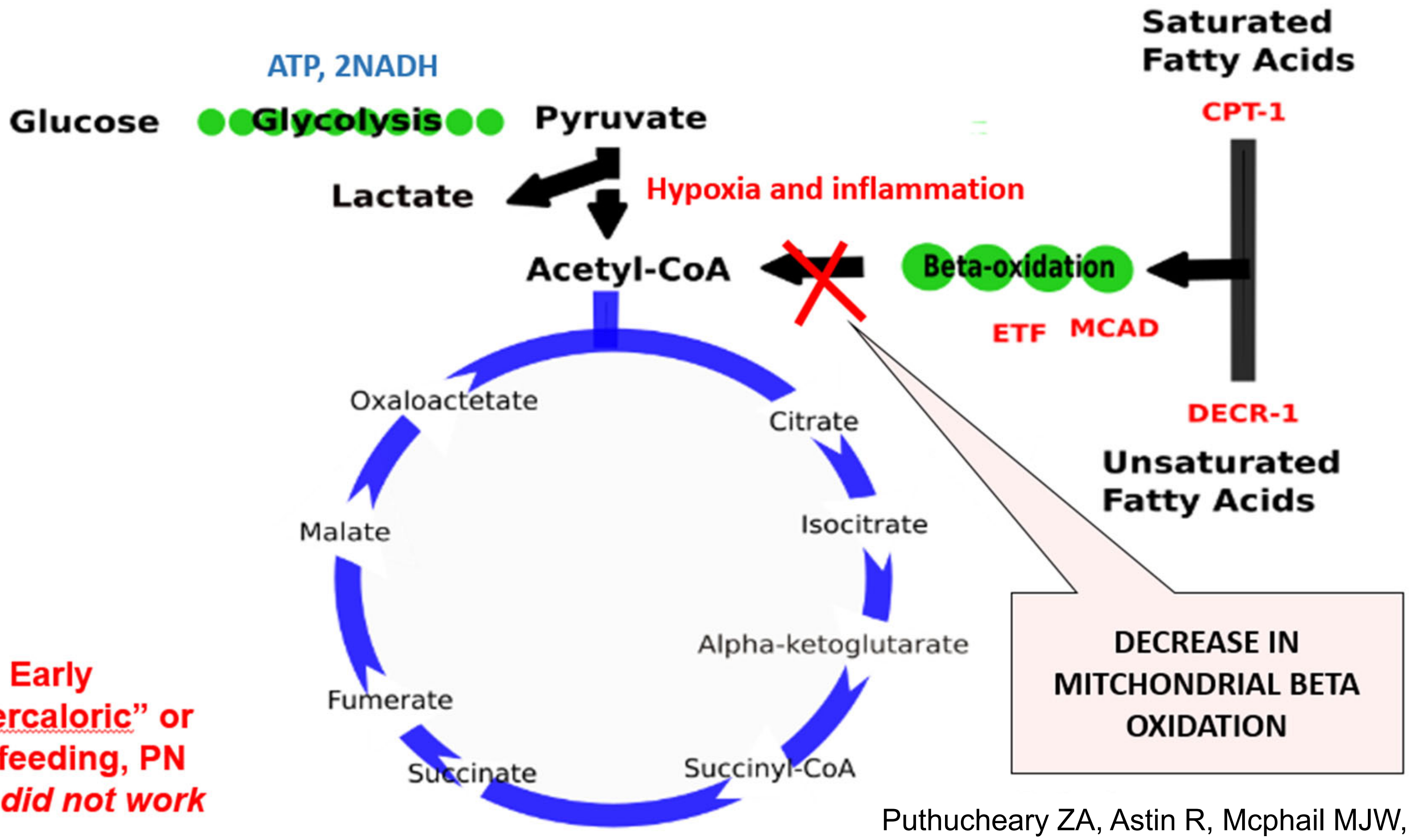


The logical approach would be to deliver more substrate (CHO, Protein, Lipid)

Puthucheary ZA, Astin R, Mcphail MJW, et al. *Thorax*. 2018;73(10):926-935.

Slide courtesy of Zudin Puthucheary with modifications

The problem: supplying traditional large quantity of macronutrients show *no* consistent data showing benefit



Early "hypercaloric" or goal feeding, PN or EN *did not work*

Puthucheary ZA, Astin R, Mcphail MJW, et al. *Thorax*. 2018;73(10):926-935.
Slide courtesy of Zudin Puthucheary with modifications

What about *micronutrients* ?
What do we know about specific micronutrient supplements and mitochondrial function in CC ?

- **Thiamine (B1)**
  - **Associations of low B1 and increased mortality noted**
  - **Some associations with B1 supplements and lower lactate**
  - **B1 preop cardiac surgery no changes in lactate**
- **Riboflavin (B2)**
  - **Variable results with riboflavin in ICU patients**
  - **Clearly altered plasma FAD and riboflavin in ICU populations**
- **B12**
  - **Both adverse and benefit with supplementation reported**
  - **No studies looking at B12 and specifically mitochondria in ICU**
- **Vitamin C**
  - **No specific benefit of supplemental in mitochondrial function noted in ICU mortality**
  - **If deficient can lead to increase ROS and impaired oxidative phosphorylation**
    - **Supplements in athletic stress human models:**
      - **decreases mitochondrial biogenesis**
      - **lower max O2 consumption**
- **Vitamin D**
  - **ICU trials show no benefit**
- **Vitamin E**
  - **Mito-Vit E**

Zhang M et al SAGE Open Med 2018
Fowler AA et al JAMA 2020
Moonen HPFX et al Curr Opin Crit Care 2020

Trace minerals and "other" agents

- **Se**
  - **Many *theoretical* potential benefits**
    - **During systemic inflammation and sepsis, Se redistributes to tissues involved in protein synthesis**
  - **Clinical *associations* in several animal models**
  - **Several observational ICU studies associated low Se with:**
    - **new onset organ failure and mortality**
    - **No studies in humans assessing effects on mitochondrial function**
  - **RCT systematic reviews supplemental Se in sepsis reports *no benefit***
- **Zn**
  - **Difficult to determine actual deficiency**
    - **Serum levels are useless**
  - **Low Zn has been associated with increase severity of critical illness, supplements *no change in survival***
- **CoQ 10 or "MitoQ"**
- **Caffeine**
- **Melatonin**
  - **Animal models:**
    - **Show benefit in septic model rescuing mitochondria from oxidative stress**
    - **Increase ETS and ATP production via closing mitochondrial permeability pore**
  - **Human critical care studies**
    - **Low in the critical illness**
    - **Low levels associated with more sepsis**
    - **Reduce oxidative stress in newborn sepsis**
- **Carnitine**
    - **Theoretical benefits of supporting LC fats transported to inner mitochondrial membrane**
- **Lipoic acid**
    - **RCT in pts with inherited mitochondrial disorders reported reduction in oxidative stress, resting lactate, with benefit in body composition**

Zhang M et al SAGE Open Med 2018
Fowler AA et al JAMA 2020
Moonen HPFX et al Curr Opin Crit Care 2020
Bloos F et al JAMA Int Med 2016;176(9):1266-76
Thiessen SE et al Biochim Biophys Acta 2017;1863

Why have nutrient supplements failed ?

- **Maybe we have tried the wrong mix**
  - **What about anti-oxidant “cocktails”**
- **Not yet able to consistently alter membrane solubility characteristics**
  - **Adding lipophilic side chains**
- **Metabolic reprogramming**
  - **Shifting aerobic glycolysis to oxidative phosphorylation**

Supplemental macro or micronutrients show no consistent benefit to enhancing mitochondrial function or biogenesis in critical care:

So, what now ?

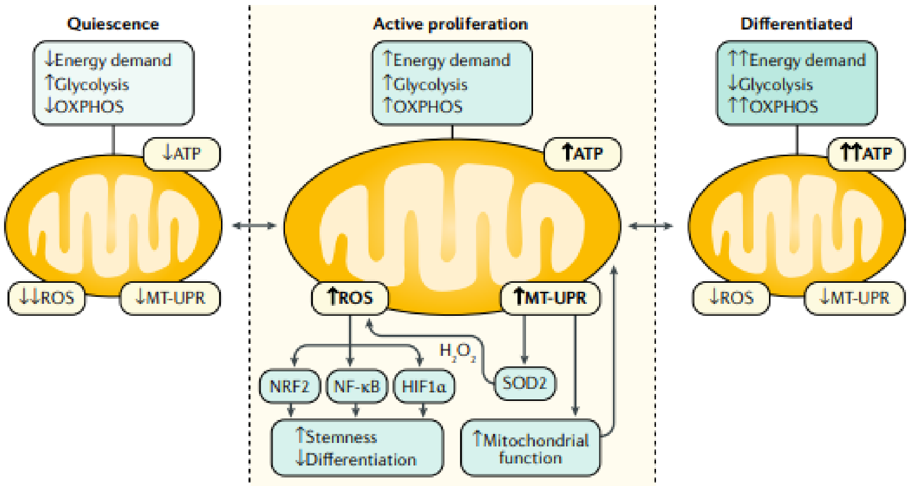
- What about timing of delivery – early vs late
  - Early full caloric requirements being met has never worked
    - PN experience
    - EN experience
      - Recent ICU studies

    (Rice JAMA 2012, Arabi NEJM 2015, EAT-ICU Int Care Med 2017, Target ANZICS trial NEJM 2018)
- Feeding and fasting cycles
- Correlate feeding (protein) with resistance exercise
    - Bed rest in healthy subjects induces significant decrease in mitochondrial respiration, content
- Microbiome ?
- Staged approach – slow ramp up with use of “biomarkers” as guide
- Individualized or personalized nutrition prescription

Puthucheary Z et al Curr Opin Clin Nutr Metab Care 2021;24(2):183-188
Moonen HPFX et al Curr Opin Crit Care 2020;26(4):346-354
Standley RA et al J Gerontol A Biol Sci Med Sci 2020;75(9):1744-1753

Is the future of nutritional management in critical care and sepsis metabolic reprogramming ?

- **Shifting aerobic glycolysis to oxidative phosphorylation**
  - **Mouse model Cecal Ligation Puncture (CLP) model**
    - **2-DG improves outcome and mortality** (2-DG glycolytic inhibitor)
  - **Mouse model AKI from CLP model**
    - **Multiple metabolic studies of mitochondria**
    - **Clear metabolic reprogramming**
      - **Reduced fatty acid oxidation, increased expression of glycolytic enzymes**



Rath E et al Nature Rev Gastro Hep 2018

Tan C et al Shock 2020;53(1):114-123
Li Y et al Am J Physiol Renal Physiol 2020;319(2):F229-F244
Rath E et al Nature Rev Gastro Hep 2018;15(8):497-516

Starve a Fever and Feed a Cold: Individualized Nutrition

Should the source of sepsis change our nutrition plan ?

Opposing Effects of Fasting Metabolism on Tissue Tolerance in Bacterial and Viral Inflammation

Andrew Wang[1,2,7], Sarah C. Huen[1,3,7], Harding H. Luan[1,7], Shuang Yu[1], Cuiling Zhang[1], Jean-Dominique Gallezot[4], Carmen J. Booth[5], and Ruslan Medzhitov[1,6,*]

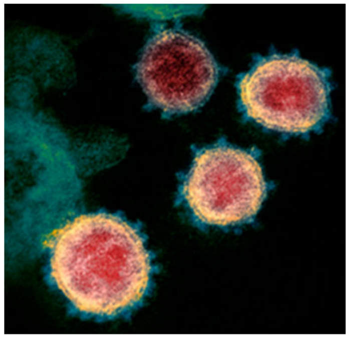


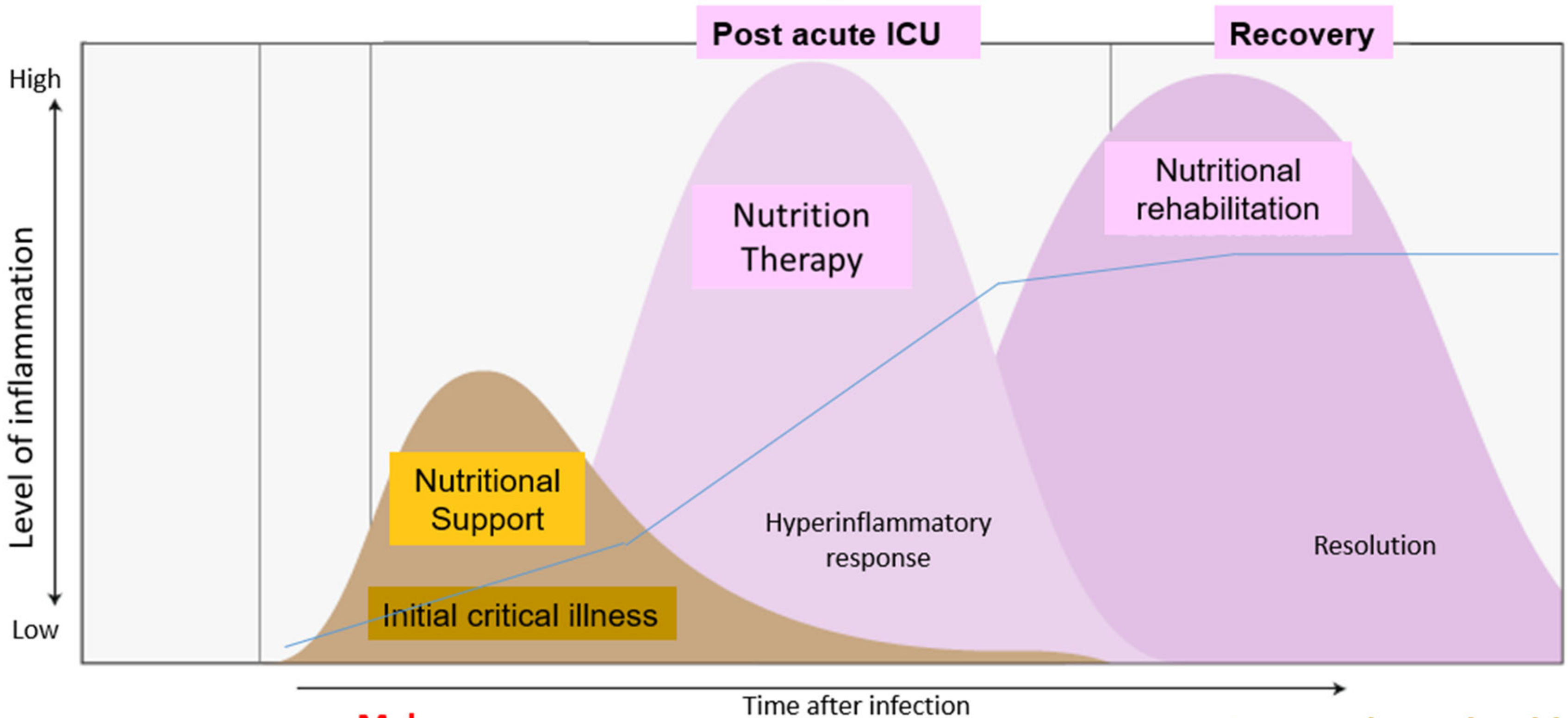
Photo Credit: National Institute of Allergy and Infectious Diseases, Rocky Mountain Laboratories

Murine model

- Compared viral vs bacterial infection with feeding vs fasting
  - **Bacterial infections:** Listeria monocytogenes or LPS
    - Anorexia protective while nutritional supplementation yielded poor outcome
    - Glucose needed to show detrimental effect
      - Glucose supplementation increase ROS and induced brain damage
      - Ketogenesis necessary to limit ROS
  - **Viral infections:** Influenza virus or polyI:C
    - Nutritional supplementation protected against mortality
    - Blocking glucose utilization was lethal
      - Glucose mediates tissue tolerance to virus by maintaining ER stress responses

Cell 2016;166(6):1512-1525

Nutritional Considerations in optimizing mitochondrial function: Should our nutrient delivery change with phases of disease



Attempts to maintain optimal nutritional health

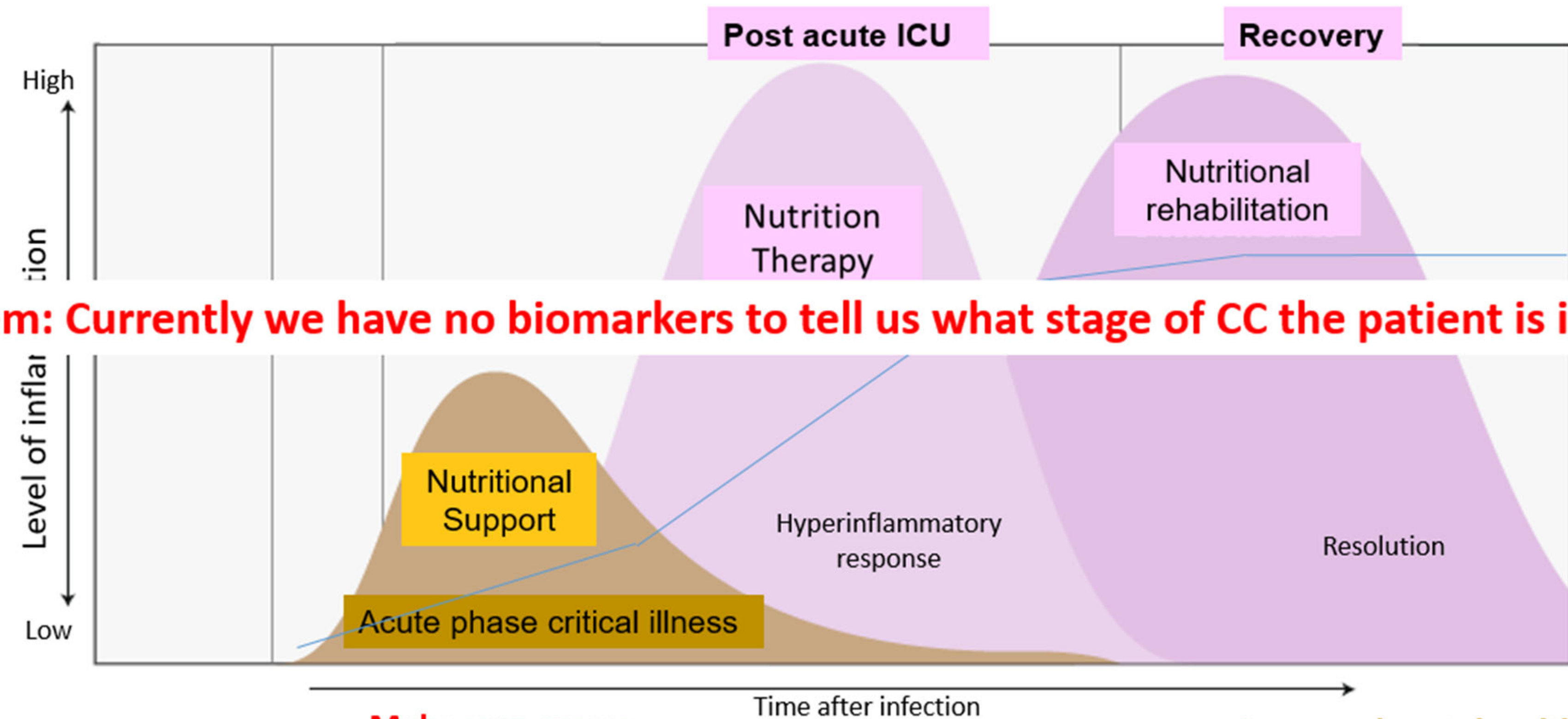
Make sure excess nutrients are not delivered
(EN to support microbiome, "adequate" macronutrients and micronutrients)

Consider antioxidants to decrease damage from ROS (vit A,C,E, and Se, Zn) and increase protein to support acute phase response

Increased protein with resistance exercise. Maintain vitamins and trace minerals Consider EPA/DHA

Modified from Ayres JS. Nature Metabolism 2020

Nutritional Considerations in optimizing mitochondrial function: Should our nutrient delivery change with phases of disease



Problem: Currently we have no biomarkers to tell us what stage of CC the patient is in

Attempts to maintain optimal nutritional health

Make sure excess nutrients are not delivered
(EN to support microbiome, "adequate" macronutrients and micronutrients)

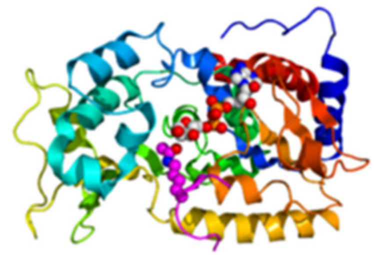
Consider antioxidants to decrease damage from excess ROS (vit A,C,E, and Se, Zn) and increase protein to support acute phase response

Increased protein with resistance exercise. Maintain vitamins and trace minerals Consider EPA/DHA

Modified from Ayres JS. Nature Metabolism 2020

Potential Agents to Enhance Biogenesis

- Adding lipophilic side chains has been shown to partially circumvent this issue
    - Liposomal encapsulation of antioxidants
    - Mitoquinone, mitotempol, SKQ1, SS31
        - Reported animal models of sepsis
            - Maintain mitochondrial membrane potential
            - Reduced cardiac mitochondrial and contractile dysfunction, reduced renal and hepatic injury
            - Reduced ventilator induced diaphragm dysfunction
- Sirtuins
    - Enhances mitochondrial biogenesis, augments oxidative pathways
        - eg: resveratrol
    - Animal models
        - Protective in CV disease, metabolic syndrome, muscle disease



- Activate cell programs for repair or replace damaged mitochondrial proteins
    - PPAR gamma coactivator 1
        - Major regulator of production of mtDNA dependent mitochondrial proteins
        - Early work in both animals and humans shows promise
- Human recombinant transcription factor mitochondrial protein (rhTFAM)
    - Regulator of mtDNA replication
    - Reduces mortality in animal models
- Mitochondrial transplantation
    - Most work done in cardiac cells
        - Transplanted mitochondria are rapidly internalized in-vivo
        - Augments – cardiac function, improves contractility, reduces cell death

Supinski GS et al Chest 2020
Thiessen SE et al Biochim Biophys Acta 2017
Jiang Q et al Oxidative Med Cellular Longevity 2020
Prasum P BBA-Molecular Basis of Disease 2020

Summary and Conclusions:

Nutritional modulation of mitochondrial function in critical illness

- **Currently most data is extrapolated from human muscle biopsy data, in-vitro and animal studies**
- **When it comes to mitochondrial function in critical illness and other disease states**
  - **Expecting one nutritional agent to make a difference is *very* naïve**
    - **Exceptionally complex network constructed of numerous components and signaling systems**
  - **Numerous knowledge gaps:**
    - **Ideal level of each component allowing optimal mitochondrial biogenesis**
    - **Serum levels of nutrients are not useful, they do not reflect cellular levels**
    - **What are the effects on the long term – outcomes at 6 months from injury/illness/sepsis**
    - **How to alter changes in permeability of membranes, cell and mitochondrial (inner and outer) ?**
    - **Altered protein binding or distribution ?**
    - **Redistribution in intracellular organelles, tissues ?**
- **For now:**
  - **Deliver "moderate" amount of macronutrients as a slow escalation**
  - **Judicious micronutrient delivery to promote anti-oxidant defenses**
  - **EN to support microbiome**
  - **Meticulous glucose control – preventing end products of glycolysis which are toxic to mitochondria**
  - **Additional protein in post acute and recovery phase to support acute phase response, immune and muscle**

Optimizing Mitochondrial Function:
What are the potentials to fill the knowledge gaps ?

- **Using continuous indirect calorimetry to measure *in-vivo* substrate oxidation**
- **Near-infrared spectroscopy (NIRS) measuring *in-vivo* muscle oxygen consumption**
- **Phosphorus NMR spectroscopy to measure total high energy phosphate components in the cell in real time**
    - **Phosphocreatine, ATP, ADP, in-organic phosphate**
- **Proteomics, transcriptomics, metabolomics**

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March 20, 2021

INNOVATIVE NUTRIENTS SUPPORTING CELLULAR HEALTH DURING AGING

Bret Goodpaster, PhD – Scientific Director,
AdventHealth Translational Research Institute

Disclosures

- Advisory Boards for Nestlé, and Emmyon, Inc.

Objectives

- Discuss the role of mitochondrial energetics in human aging
- Interrogate the roles of obesity and exercise in ‘aging’
- Highlight data supporting the roles of calorie restriction for weight loss and exercise in mitochondrial biology of aging
- Discuss potential nutritional strategies to enhance mitochondrial energetics in human aging

Aging is associated with declines in function and increased risk of disease

Declines in energy, strength and resilience are commonly reported.

Fatigue is reported in ~1/3 of US adults over 51 years[1]

Muscle strength declines by 1.5% per year between 50 and 60 years and by 3% a year thereafter[2]

Aging is associated with increased oxidative stress and reduced immune response[3]

78% of US adults over age 55 have at least 1 chronic condition[4]

1. Meng H et al. J Am Geriatr Soc. 2010 Oct; 58(10): 2033–2034.
2. Goodpaster et al. J Gerontol Med Sci 2006;61A(10): 1059–1064.
3. Pereira BI et al. Front Immunol 2016;7:445. 4. CDC National Center for Health Statistics

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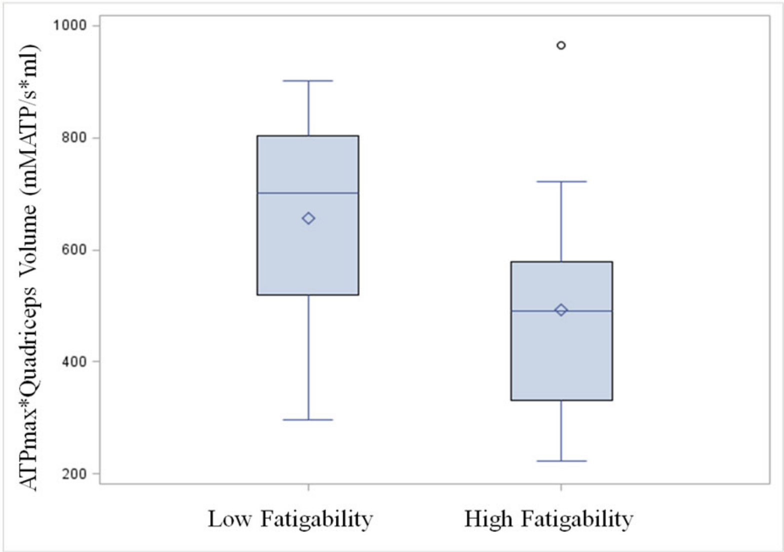
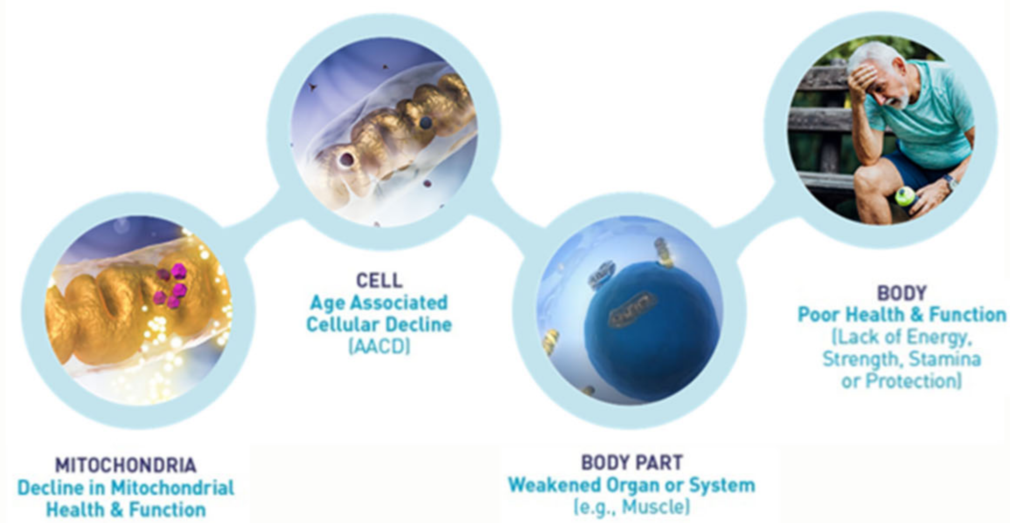
Skeletal Muscle Mitochondrial Function and Fatigability in Older Adults



Santanasto AJ et al. J Gerontol A Biol Sci Med Sci. 2015;70(11):1379-1385.

Age-Associated Cellular Decline (AACD)

- Describes cellular changes underlying the aging process and development of age-related conditions
- Cellular changes precede clinical signs
- Key manifestations of AACD to target for intervention:
  - Declines in self-perceived energy and engagement physical & social activity
  - Declines in mobility, muscle function, and resilience
- Interventions should target the fundamental mechanisms of aging, including mitochondrial dysfunction



Cesari M et al. Experimental Gerontology 2021;146:111242

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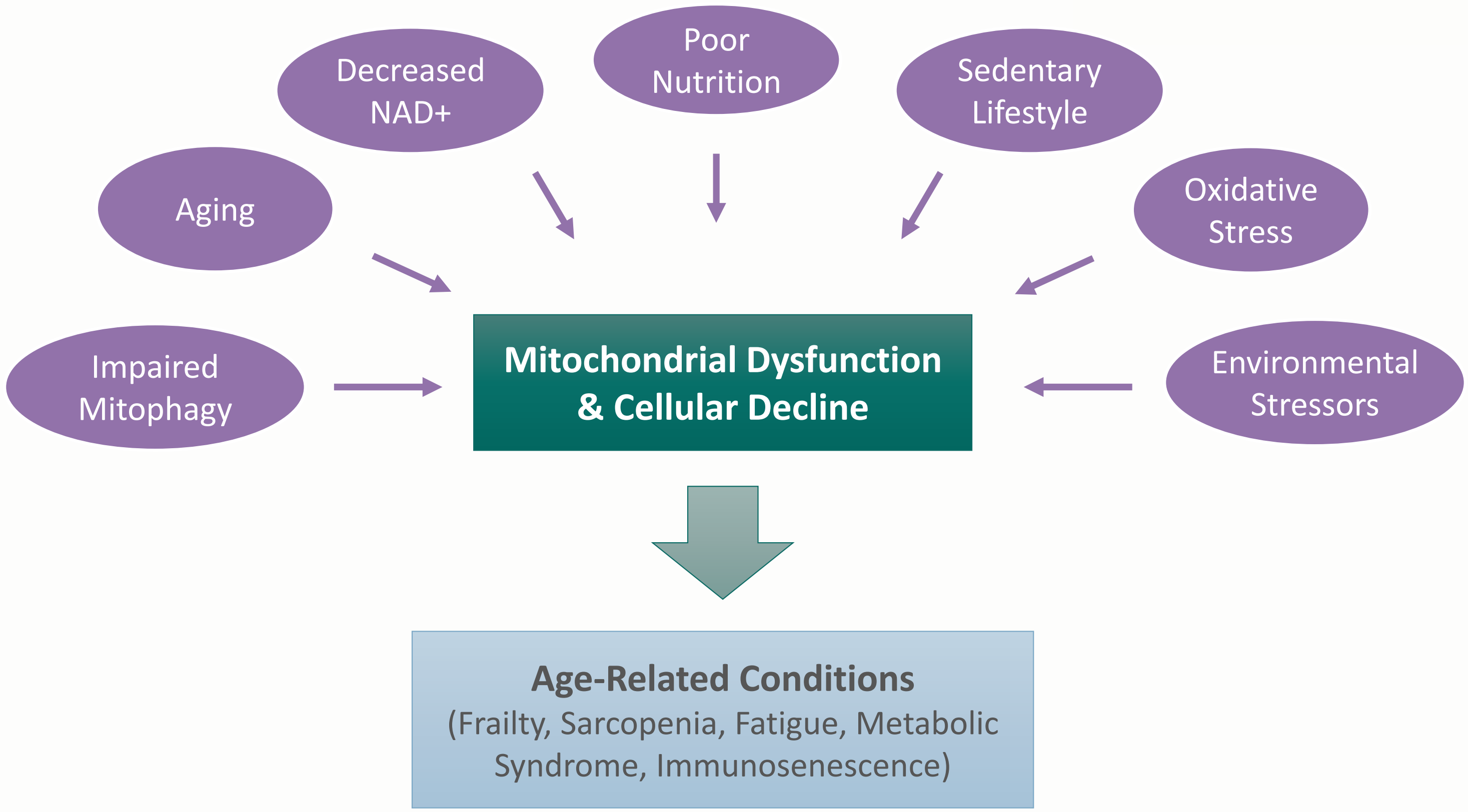
Factors contributing to AACD and mitochondrial dysfunction



M et al. Experimental Gerontology 2021;146:111242. Filler K et al. BBA Clinical 2014;1:12-23.
cca E et al. Nat Commun 2019;10(1):5808.

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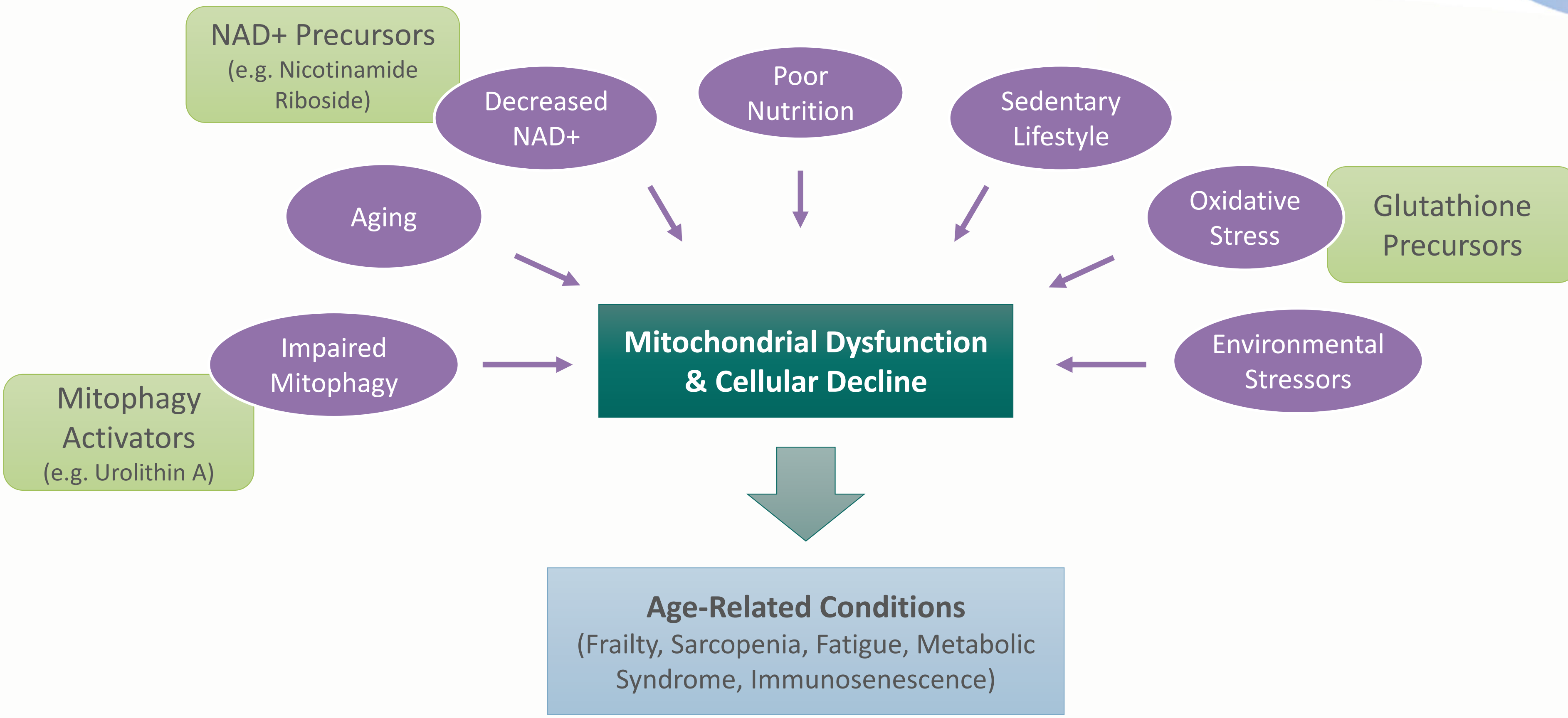
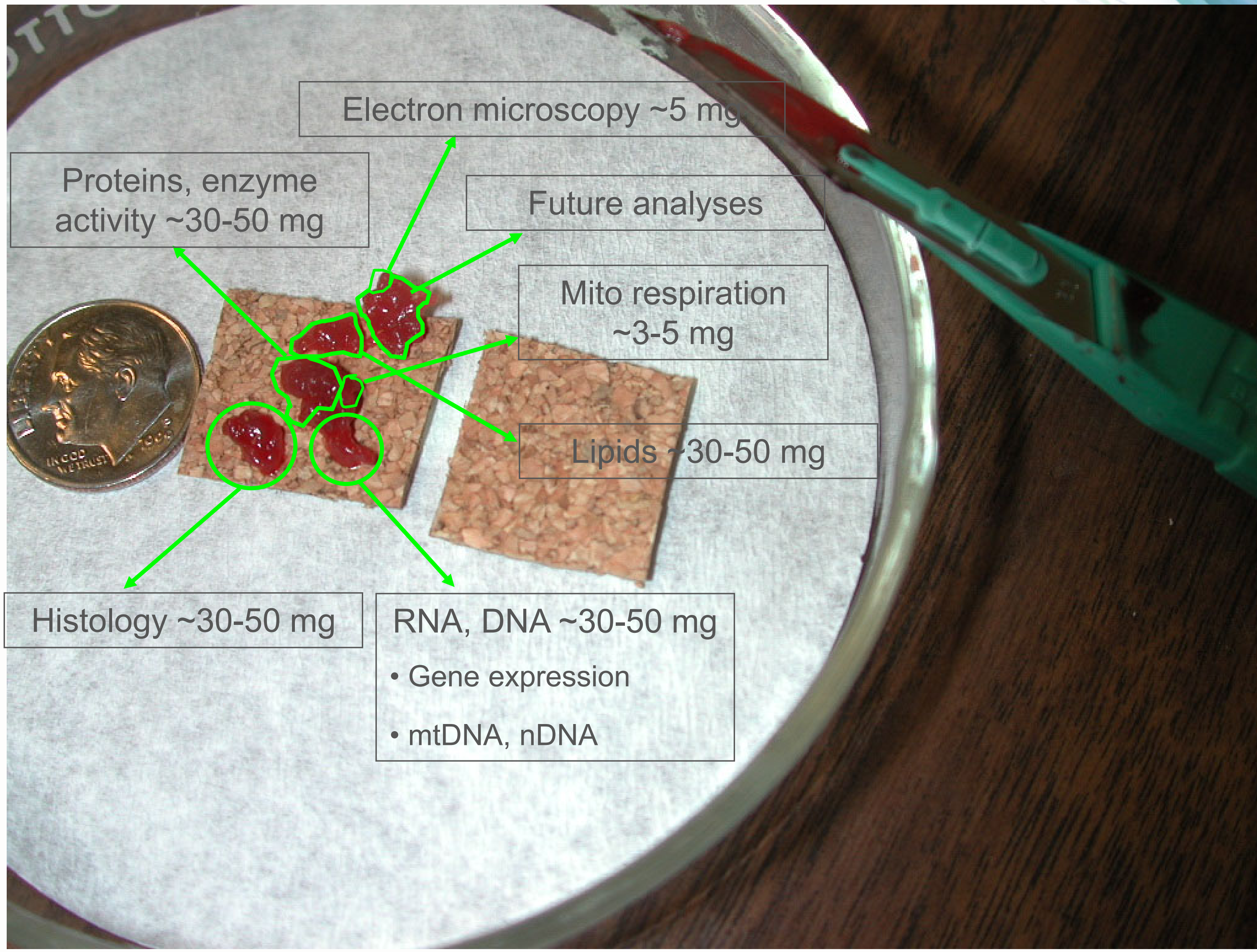
Targeted nutritional interventions



Cesari M et al. Experimental Gerontology 2021;146:111242. Filler K et al. BBA Clinical 2014;1:12-23. Migliavacca E et al. Nat Commun 2019;10(1):5808. Andreux PA et al. Nature Metabolism. 2019; 1:595-60. Conze D et al. Sci Rep 2019;9(1)::9772. Sekhar RV et al. Am J Clin Nutr. 2011;94:847-53.



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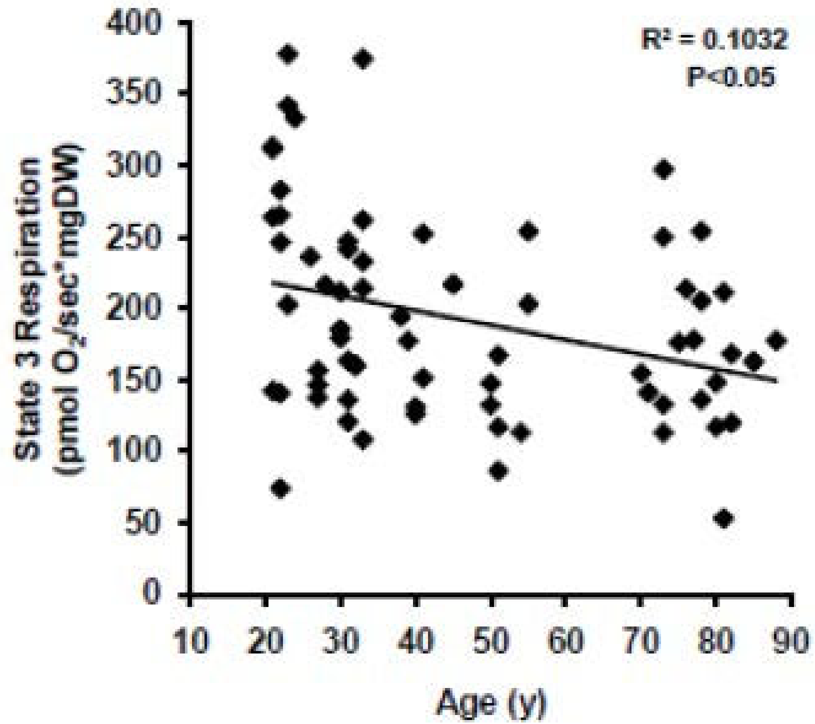
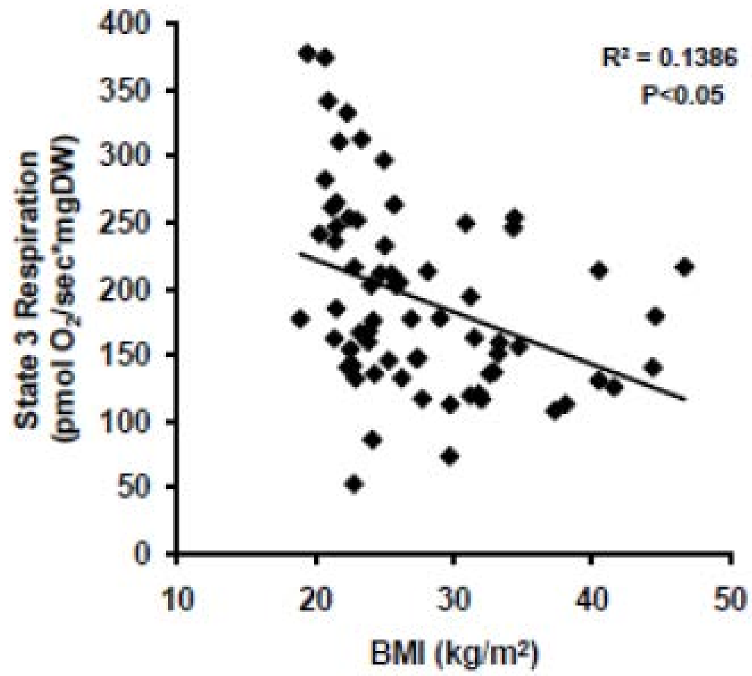
Maximal coupled respiration is weakly associated with age



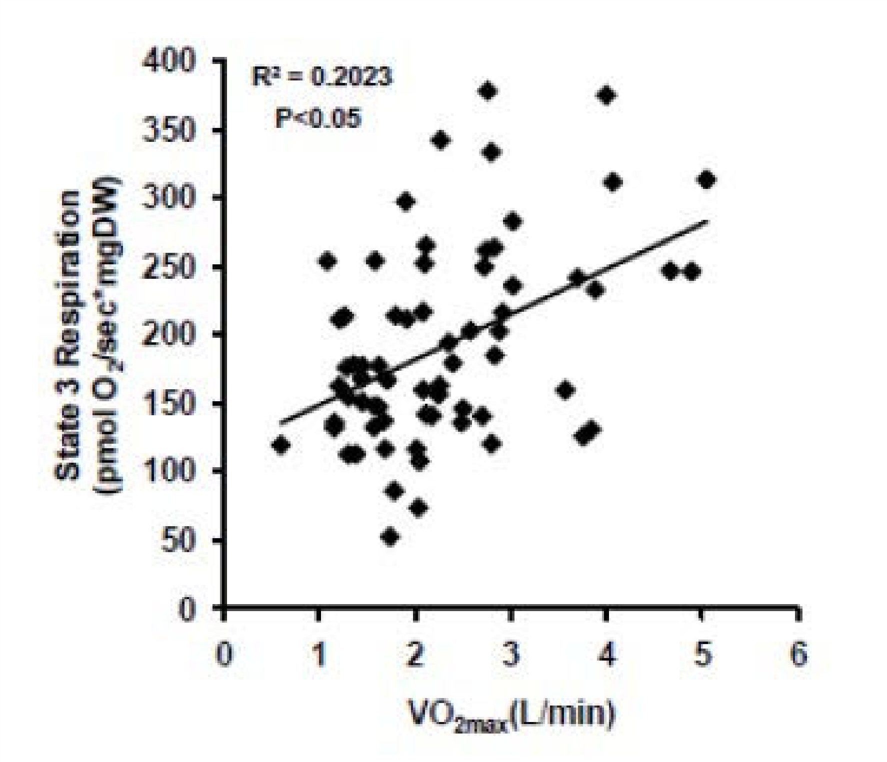
Distefano G et al. J Gerontol Med Sci 2017;72(4):535-542

Maximal coupled respiration is more strongly associated with body fat



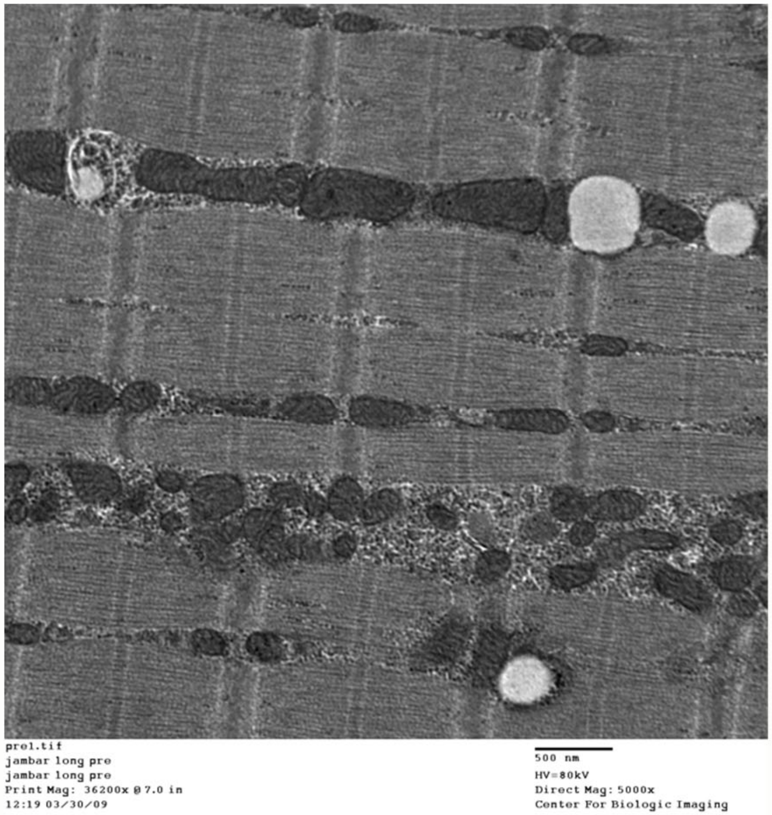
Distefano G et al. J Gerontol Med Sci 2017;72(4):535-542

Maximal coupled respiration is also more strongly associated with aerobic fitness

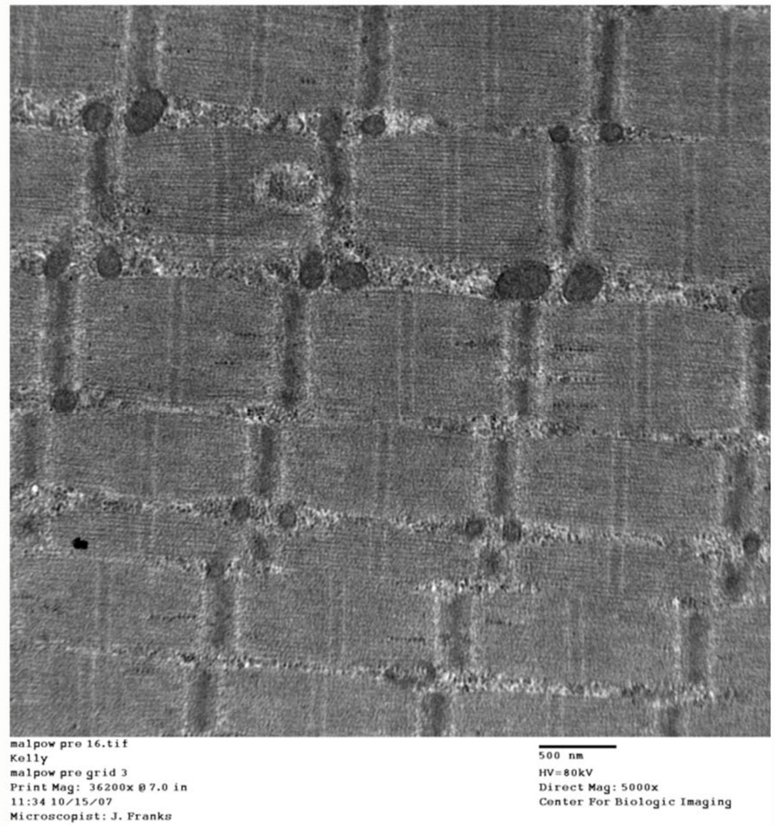


Distefano G et al. J Gerontol Med Sci 2017;72(4):535-542

Mitochondria content with exercise



Master athlete 60-75 years



Sedentary 60-75 years

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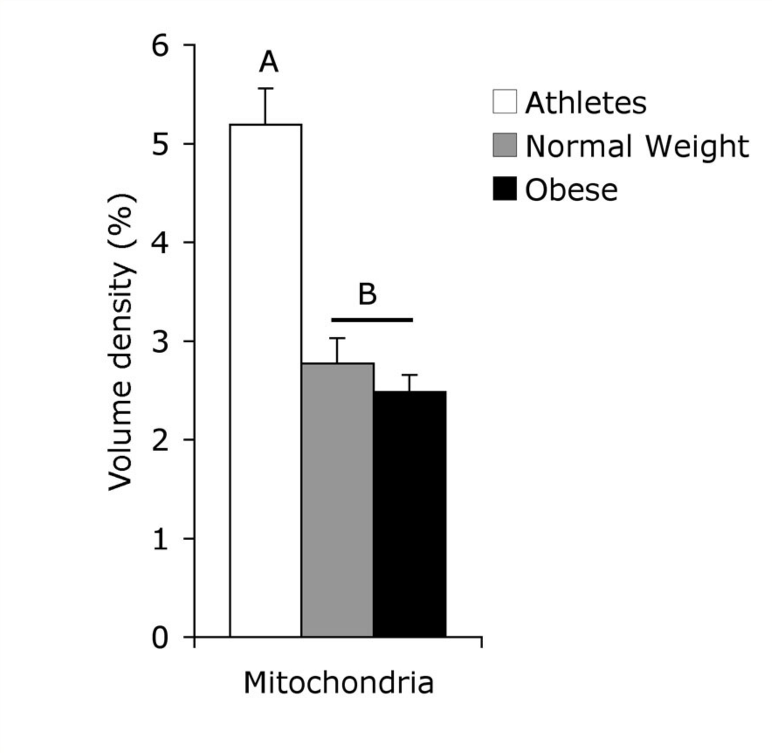
Mitochondria content is higher in older athletes



Amati et al. Diabetes 2011;60(10):2588-2597

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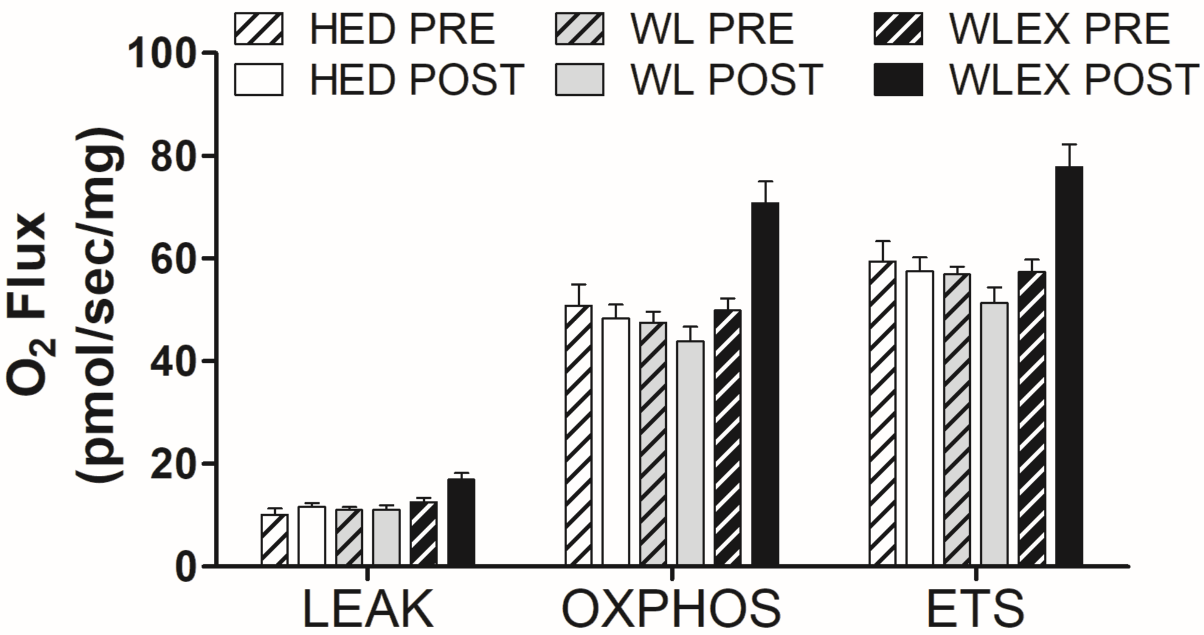
Calorie restriction and exercise effects on mitochondrial function in older adults



Key Cellular Drivers of AACD

Decline in NAD+

↓

Reduced cell energy (ATP) production

Decline in mitophagy & mitochondrial health

↓

Reduced efficiency in fueling muscle cell function

Decline in glutathione

↓

Reduced ability to protect cells from toxins & free radicals

Cellular Mechanisms Impacting Mitochondrial Health

- The human body is made of cells, which are powered by the **Mitochondria**, the powerhouse of our cells
- Mitochondria are organelles found in almost every cell

Image Source: http://clipart-library.com/

Some key functions of mitochondria:

- Converts fat and carbohydrates to energy
- **NAD+** plays an important role in producing ATP (main cell energy source)

Mitochondria energy production also generates free radicals which can damage proteins, lipids & DNA

- **Glutathione** is a powerful intracellular antioxidant that helps to neutralize the free radicals created in the mitochondria

Damaged mitochondria are cleared through a process called Mitophagy (Quality control degradation of malfunctioning mitochondria)

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NAD+ is essential for cell energy production

› NAD+ is crucial for many cell functions
  - Mitochondrial function
  - Cell energy metabolism
  - DNA repair

› NAD+ levels and mitochondrial function have been shown to decrease with age or the onset of many diseases

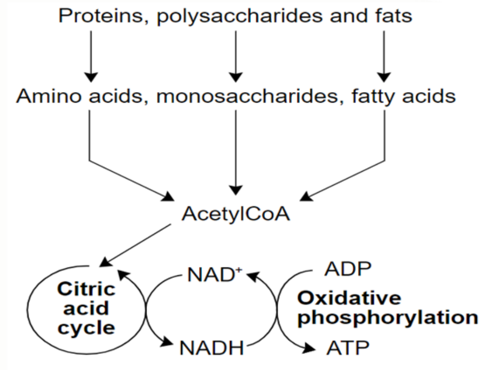
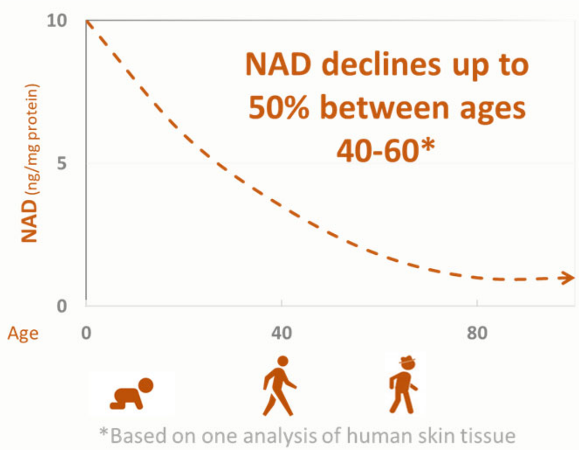


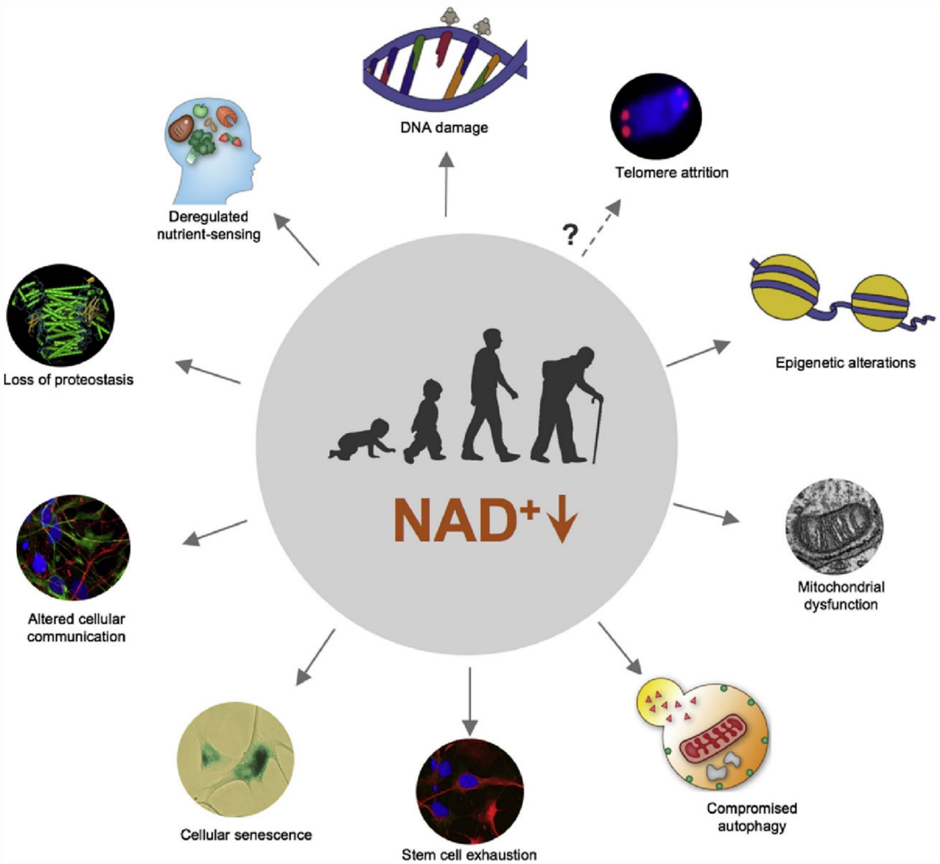
Image: Wikimedia Commons

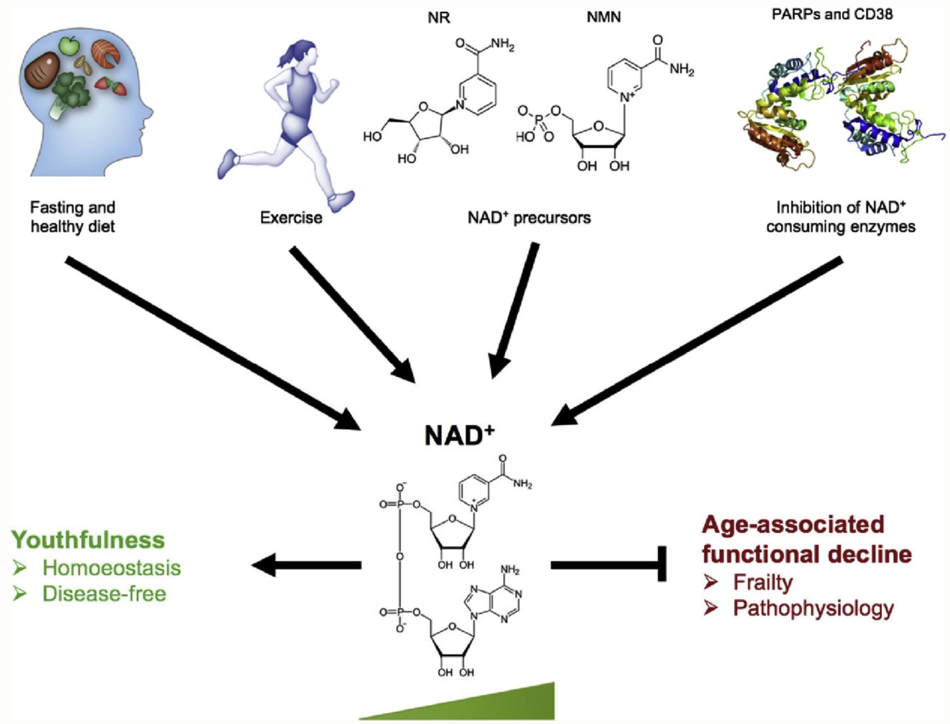


Adapted from: Massudi H et al. PLoS One 2012;7(7):e42357

McReynolds MR et al. Experimental Gerontol 2020;134:110888.
Aman Y et al. Transl Med Aging 2018;2:30-37.

Therapeutic potential of boosting NAD+ in aging and age-related diseases





Aman Y et al. Transl Med Aging 2018;2:30-37.

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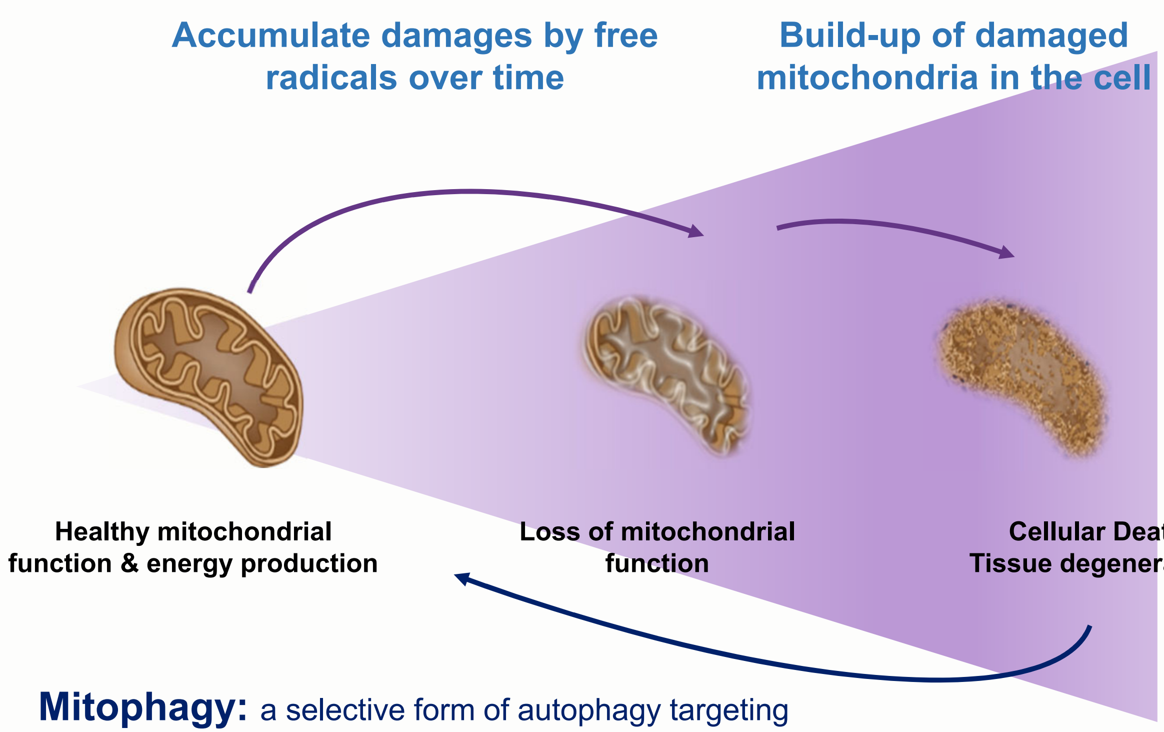
Mitophagy is key to mitochondrial and cellular health



Mitophagy: a selective form of autophagy targeting defective mitochondria

Defective mitophagy contributes to:

- Aging
- Age-related functional declines
- Age-predisposed neurodegeneration

A NEW APPROACH TO TARGET MUSCLE HEALTH
(mitochondrial function vs. muscle mass)

Morales PE et al. Mol Aspects Med 2020;71:100822. Garza-Lombó C et al. Mitochondrion. 2020;51:105-117. Roque W et al. Int J Mol Sci 2020;21(2):643. Lou G et al. Trends Mol Med. 2020;26(1):8-20.

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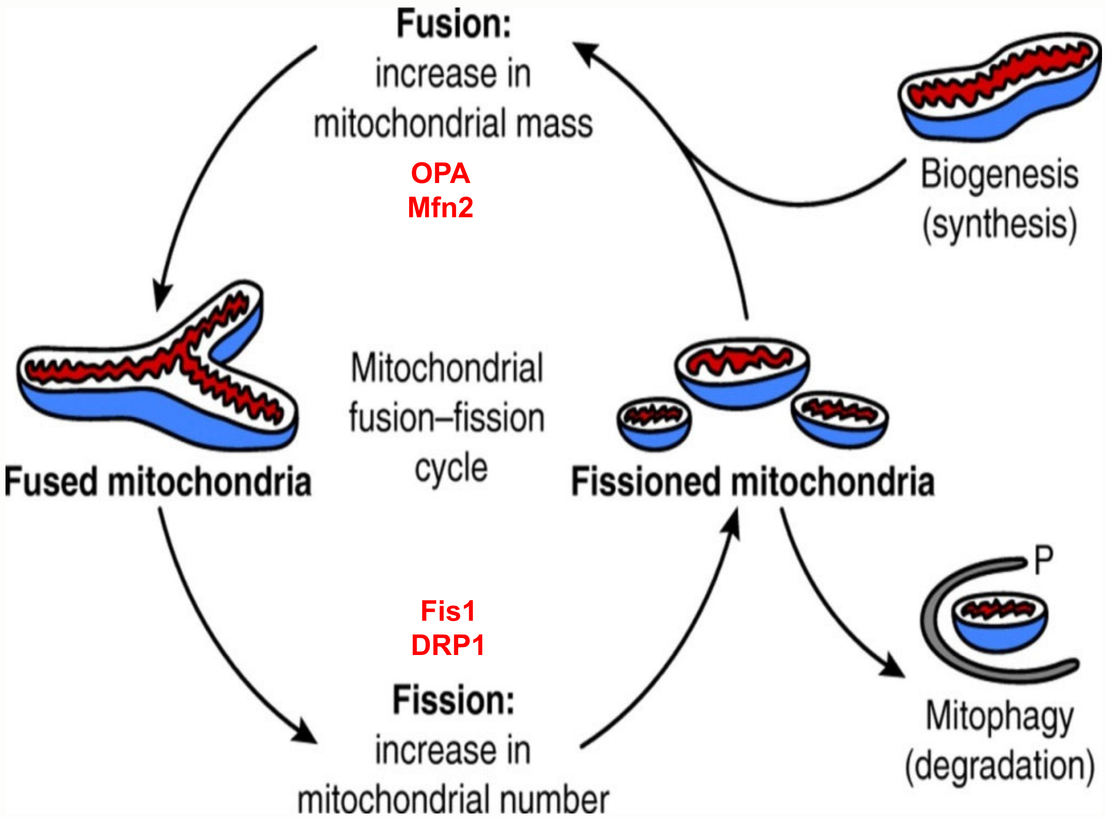
Mitochondrial Dynamics



Adapted from Seo et al. J Cell Sci 2010

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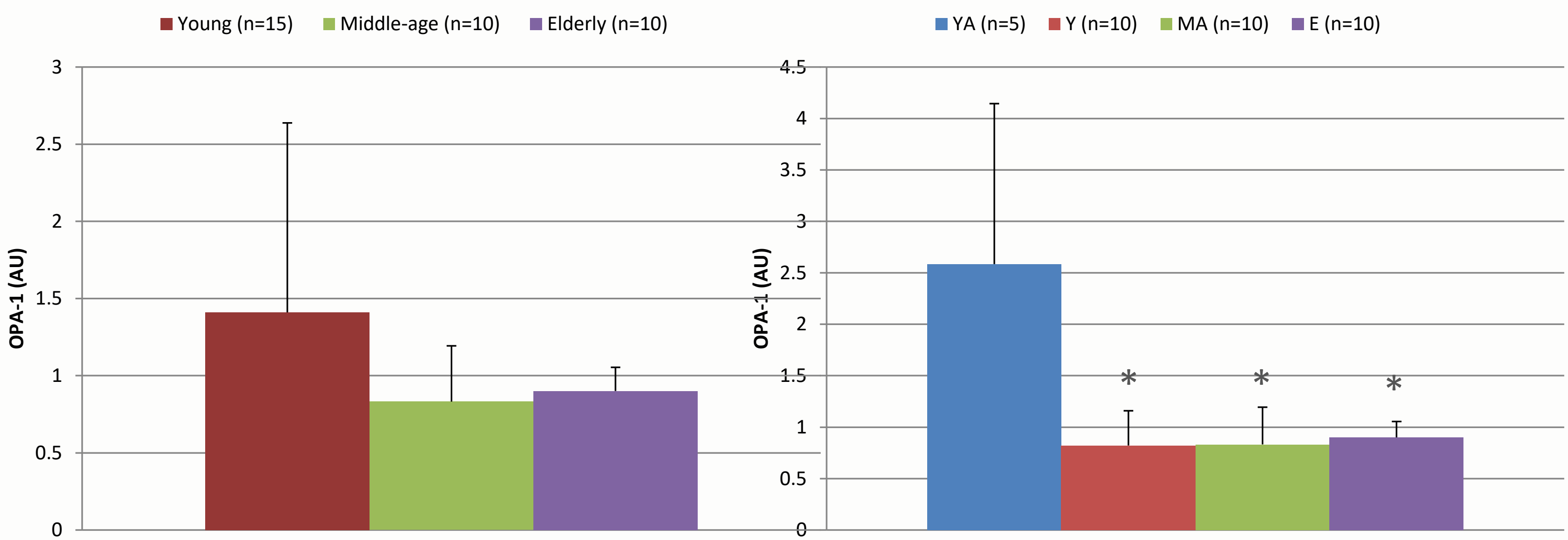
Mitochondrial Dynamics in young and older humans



* Different when compared to YA (p<0.05)

Distefano et al. J Gerontol Med Sci 2016

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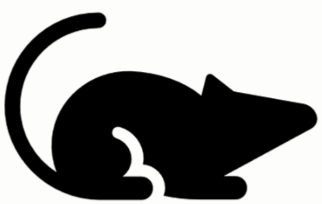
Urolithin A (UA) is a novel ingredient that activates mitophagy

› Metabolite produced by gut bacteria following consumption of foods rich in ellagitannins (polyphenol found in berries, nuts, pomegranate)

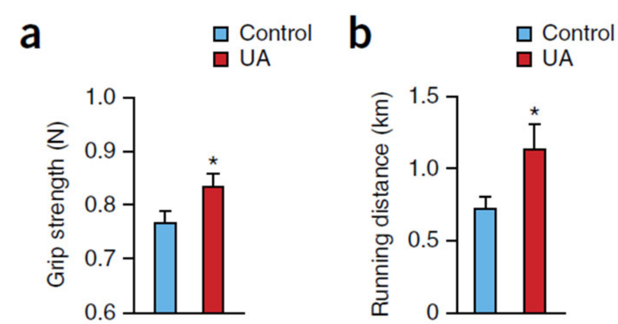
- UA synthesis declines with age
- Only 30-40% of people have gut microbiota for efficient transformation

- Supplementation with UA directly bypasses gut bacteria to improve bioavailabilty



› Preclinical data (aged animals):

- Increased mitophagy
- Improved grip strength
- Increased endurance and exercise capacity



Ryu D et al. *Nature Medicine.* 2016;22(8):879-88.
Tomás-Barberán FA et al. *J Agric Food Chem.* 2014;62(28):6535-6538.

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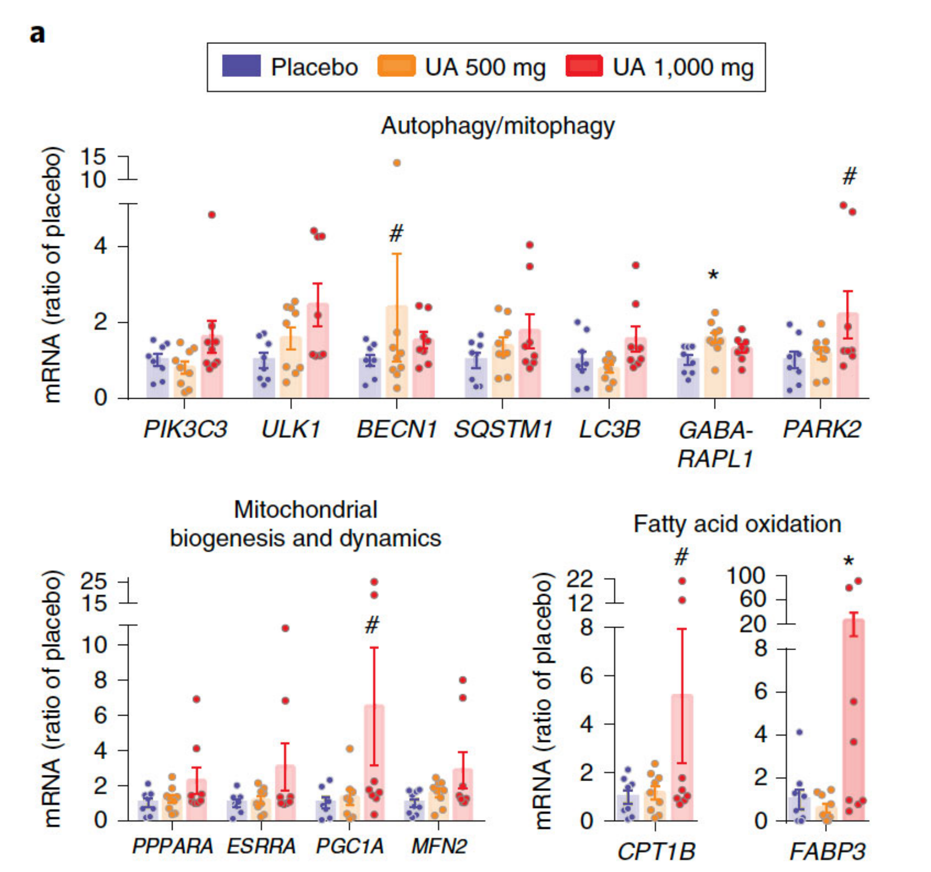
Urolithin A induces a molecular signature of improved mitochondrial and cellular health in humans



Andreux et al., NATURE METABOLISM | VOL 1 | JUNE 2019 | 595–603 | www.nature.com/natmetab

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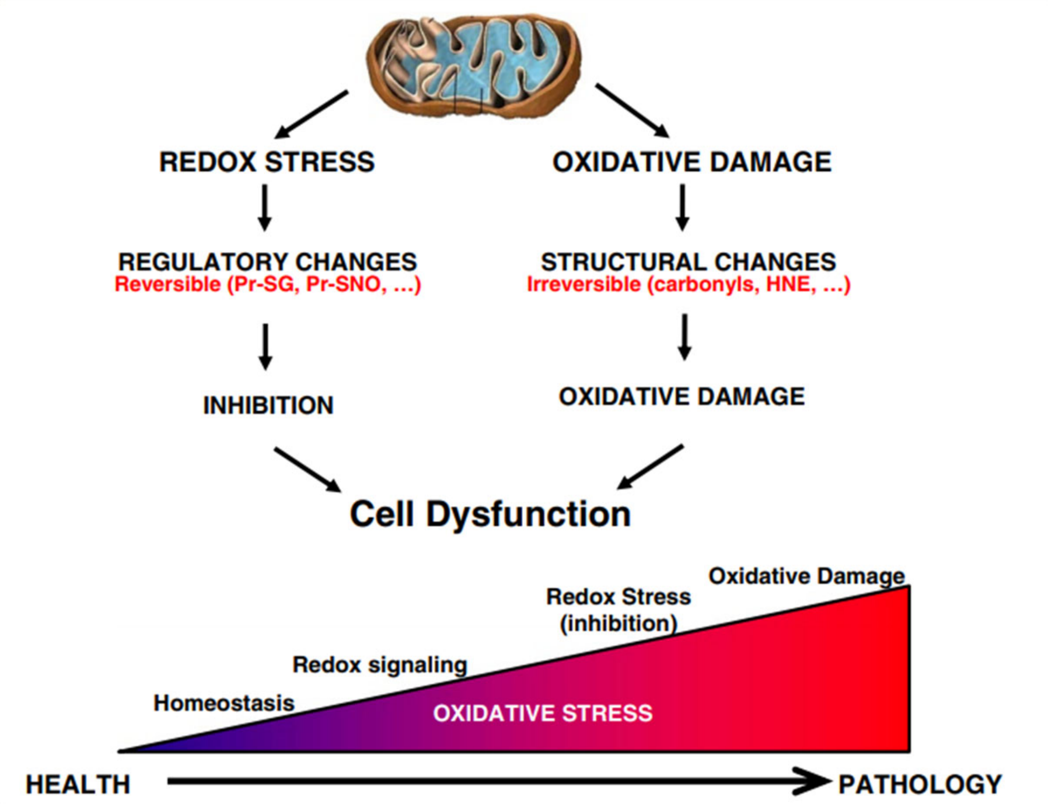
Oxidative stress and aging



Continuum of oxidative stress

Dai DF et al. Longev Healthspan 2014;3:6

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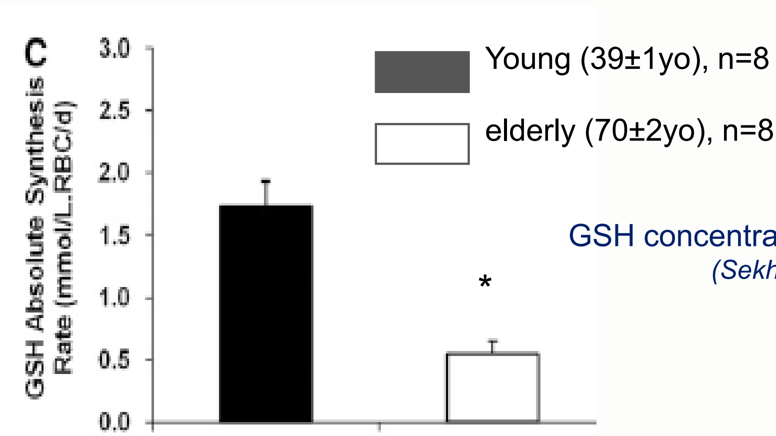
Glutathione is key to cellular protection

- Glutathione synthesis and concentration decreases with age which correlates with increased oxidative stress markers
- GSH decrease correlates with a decreased cellular level of cysteine and glycine with age



GSH concentration reduced by ≈50%
(Sekhar et al 2011)

Original Article

Glutathione Serum Levels and Rate of Multimorbidity Development in Older Adults

Laura M. Pérez, PhD,[1,2,3,*] Babak Hooshmand, PhD,[1,4] Francesca Mangialasche, PhD,[1,5] Patrizia Mecocci, PhD,[6] A. David Smith, PhD,[7] Helga Refsum, PhD,[7,8] Marco Inzitari, PhD,[2,3,9] Laura Fratiglioni, PhD,[1,10] Debora Rizzuto, PhD,[1] and Amaia Calderón-Larrañaga, PhD[1]

J Gerontol Sci Med Sci 2020;75(6):1089-1094

Review

Mitochondrial Glutathione: Recent Insights and Role in Disease

Montserrat Marí [1,*], Estefanía de Gregorio [1], Cristina de Dios [1,2], Vicente Roca-Agujetas [1], Blanca Cucarull [1,2], Anna Tutusaus [1], Albert Morales [1,3,*] and Anna Colell [1,4,*]

Antioxidants (Basel) 2020;9(10):909

Oxidation Damage Accumulation Aging Theory (The Novel Role of Glutathione)

Authors   Authors and affiliations

Rajagopal V. Sekhar M.D.

Encyclopedia of Gerontology and Population of Aging. July 2019.
DOI: https://doi.org/10.1007/978-3-319-69892-2_51-1

Jones DP et al. Free Radic Biol Med. 2002;33(9):1290-300. Sekhar RV et al. Am J Clin Nutr. 2011;94(3):847-53.
McCarty MF et al. Ochsner J. 2018;18(1):81-87.

Glutathione – nutritional strategies

› Amino Acid precursors
- Glutamine
- Glycine
- Cysteine - from N-Acetylcysteine (NAC), whey protein

› Micronutrients – Antioxidants and coenzymes for glutathione synthesis or function
- Vitamin C
- Vitamin E
- Vitamin B6
- Selenium

› Dietary patterns associated with increased glutathione levels
- Mediterranean Diet
- DASH diet

Gould RL and Pazdro R. Nutrients 2019;11:1056; doi:10.3390/nu11051056

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Conclusions

- Aging is only loosely associated with the decline in mitochondrial energetics.
- Obesity and physical inactivity are more powerful drivers of the decrease in mitochondria in aging humans.
- Exercise has much more profound effects on mitochondrial capacity in skeletal muscle than weight loss by calorie restriction
- Promising new dietary interventions are available to improve human health and aging by enhancing mitochondrial energetics.

MITOCHONDRIAL FUNCTION IN DISEASE AND OPPORTUNITIES FOR NUTRITIONAL MODULATION

Eduardo Nunes Chini, MD, PhD

Professor of Pharmacology and Anesthesiology

Co-director Mayo Clinic Mitochondrial Care Center

Kogod Center on Aging, Mayo Clinic College of Medicine

Rochester, Minnesota

Speaker Disclosure

- Holds patents for the use of CD38 inhibitors
- Licenses the use of a CD38 inhibitor to Elysium health
- Holds a patent application for the use of PAPP-A inhibitors in ADPKD
- Consultant for:
  - TeneoBio a biotech company engaged on developing therapeutic antibodies
  - Astellas (Mithobridge), Cytokinetics
  - Nestlé Health Science – Advisory Board
- Dr. Chini has received funding from the following:
  - NIDDK; National Cancer Institute; National Institute on Aging; National Heart, Lung, and Blood Institute; American Federation for Aging Research; Foundation for Anesthesia Education and Research; National Kidney Foundation; American Heart Association; Pfizer; Calico, an alphabet company; Sirtris, a GSK company; TeneoBio; Mayo Clinic; Ted Nash Long Life Foundation

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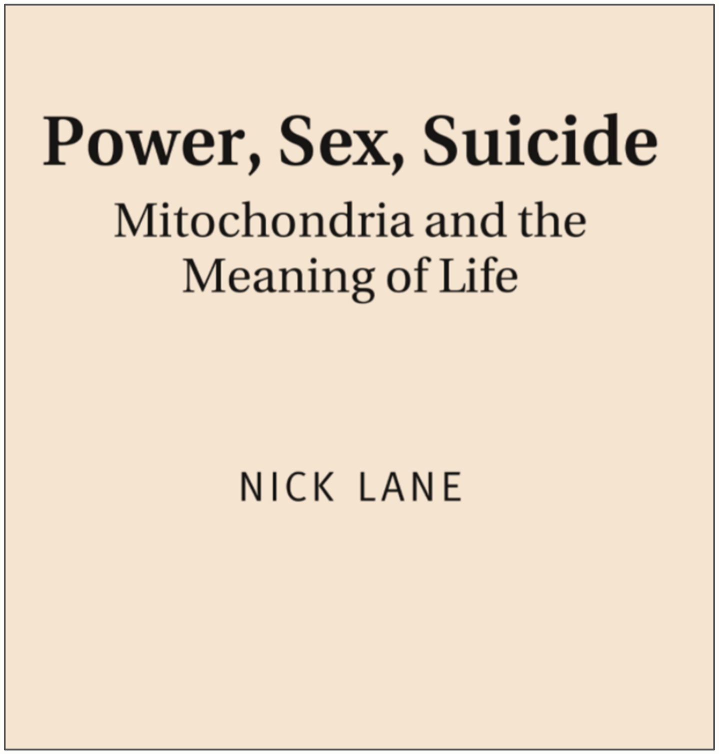
Objectives

- 1. Review primary and secondary mitochondrial dysfunction in various disease states
- 2. Discuss the role of Nicotinamide Adenine Dinucleotide (NAD) in cellular metabolism
- 3. Discuss clinical approaches to address mitochondrial dysfunction, including NAD-replacement therapy with vitamin B3 derivatives



Functions:

POWER = Redox-dependent ATP synthesis

SEX = Maternal-inherited mitochondria

SUICIDE = ROS and Apoptosis

› MANY OTHER FUNCTIONS HAVE BEEN DISCOVERED

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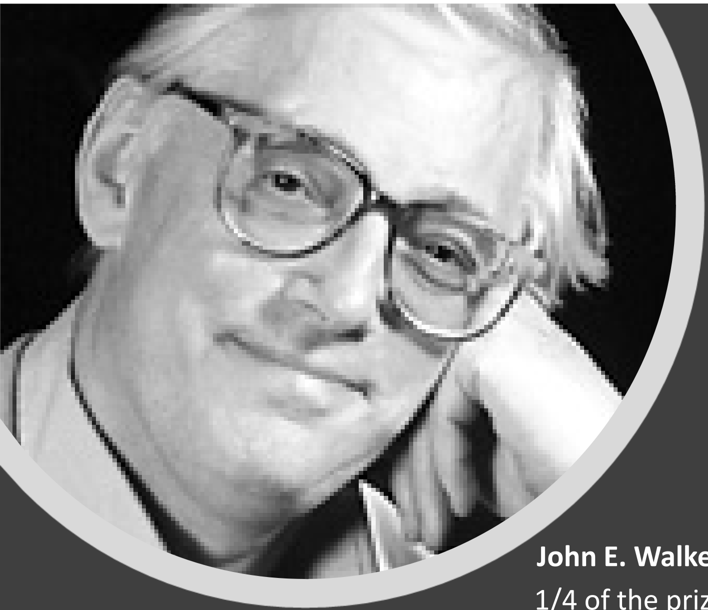
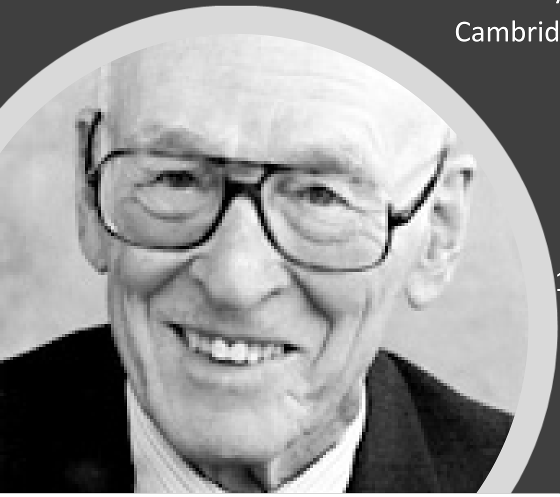


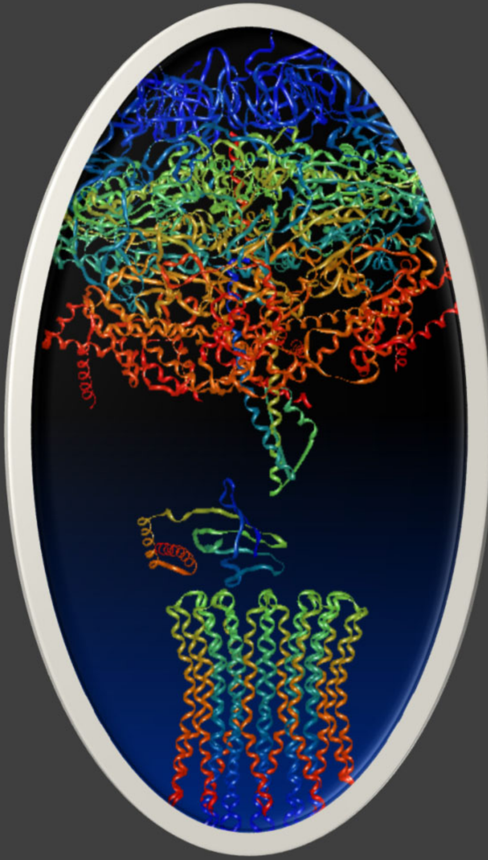
John E. Walker
1/4 of the prize
United Kingdom
Laboratory of Molecular Biology
Cambridge, United Kingdom
b. 1941

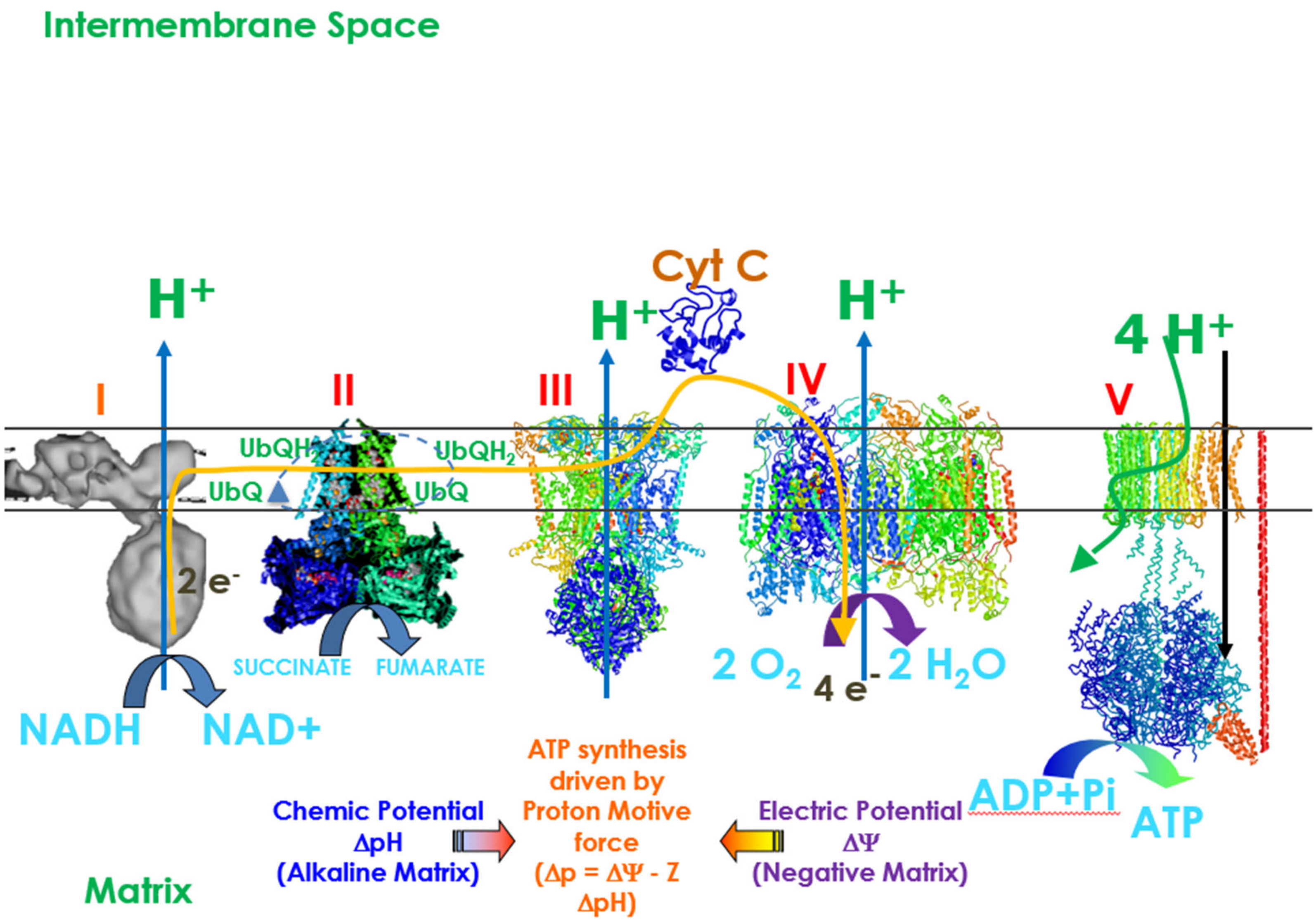


Paul D. Boyer
1/4 of the prize
UCLA, USA
b. 1918

The Nobel Prize in Chemistry 1997

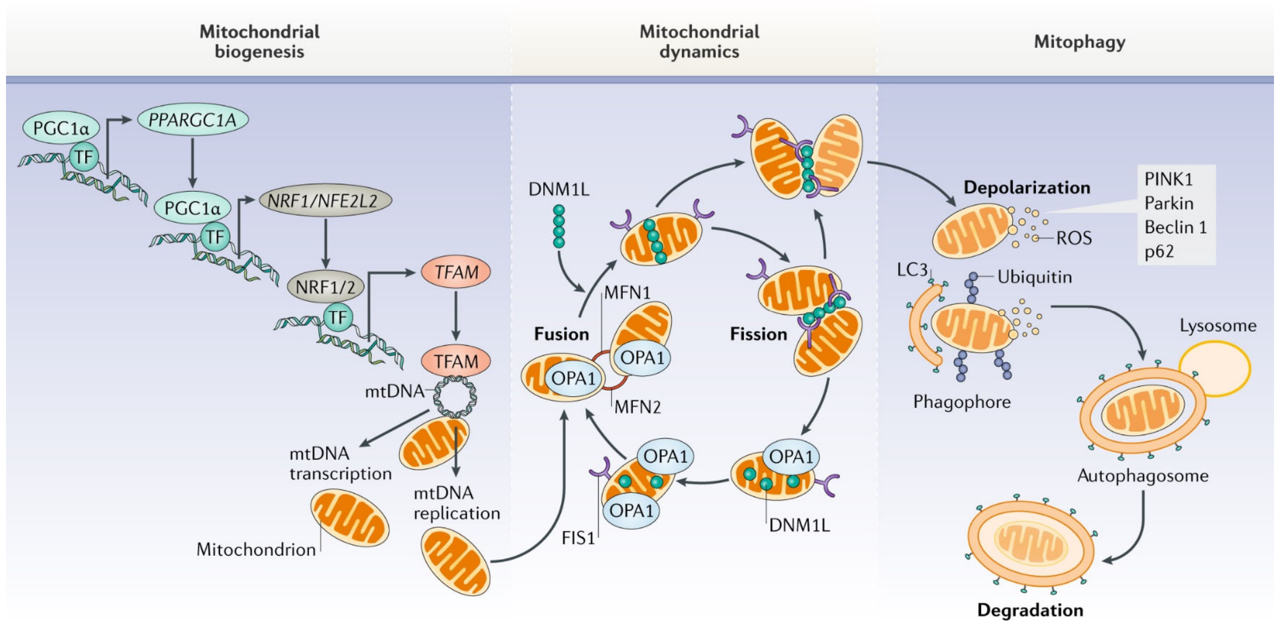
"for their elucidation of the enzymatic mechanism underlying the synthesis of adenosine triphosphate (ATP)"




Intermembrane Space
Cyt C
H+
H+
H+
4 H+
I
II
III
IV
V
UbQH2
UbQH2
UbQ
UbQ
2 e-
SUCCINATE
FUMARATE
2 O2
4 e-
2 H2O
NADH
NAD+
ADP+Pi
ATP
ATP synthesis driven by Proton Motive force (Δp = ΔΨ - Z ΔpH)
Chemic Potential ΔpH (Alkaline Matrix)
Electric Potential ΔΨ (Negative Matrix)
Matrix

The mitochondrial quality control

Mitochondrial biology: not just a powerhouse



Picca A et al. *Nat Rev Cardiol*. 2018 Sep;15(9):543-554.
doi: 10.1038/s41569-018-0059-z.

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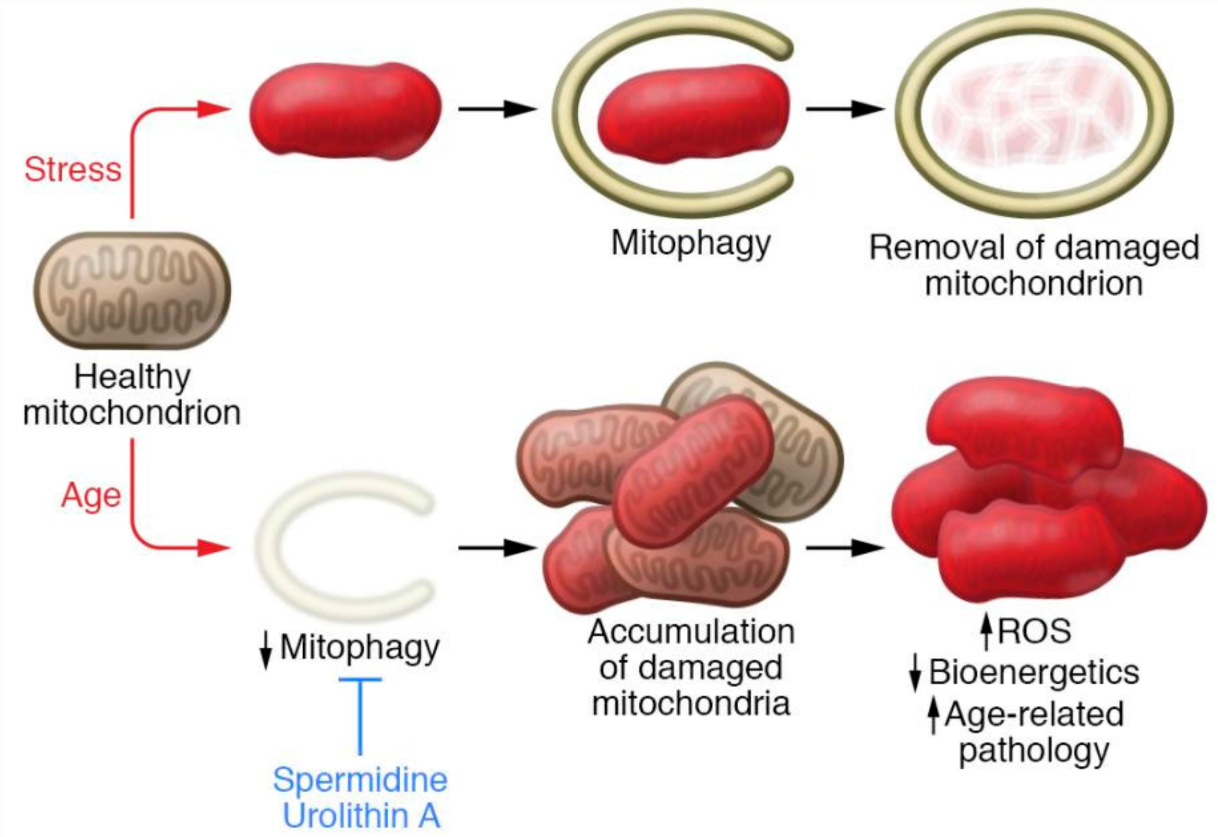
Mitochondria quality control in aging



Jang JY et al. *J Clin Invest.* 2018;128(9):3662-3670.
https://doi.org/10.1172/JCI120842

Where are most of your mitochondria?

- Heart and Kidney: 40% of volume is mitochondria
- Skeletal muscle and liver:10-20%
- Brain: 5%

- From these one can derive signs and symptoms of mitochondrial dysfunction

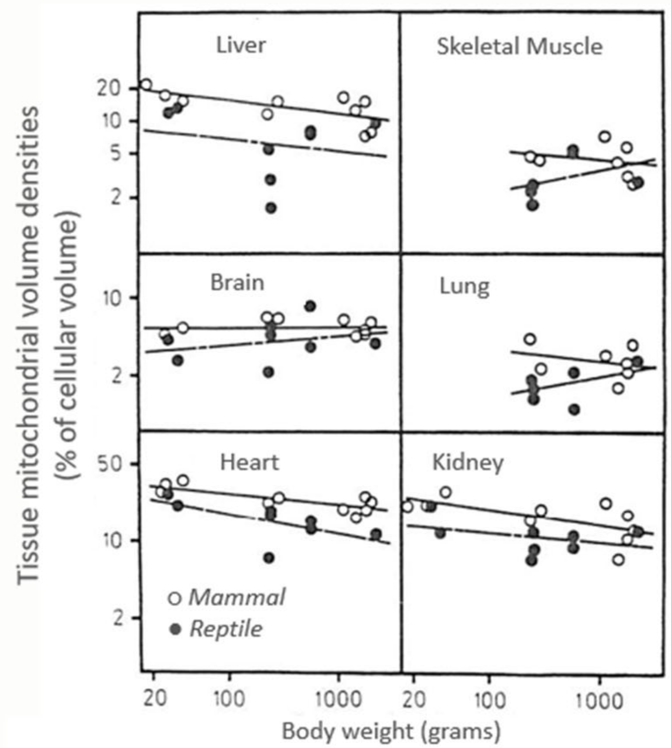


Fig. 2. A comparison of mammalian (○) and reptilian (●) tissue

Else PL and Hulbert *J Comp Physiol B*. 1985;156(1):3-11. doi: 10.1007/BF00692920. PMID: 3836230.

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MITOCHONDRIAL DYSFUNCTION: PRIMARY AND SECONDARY

Mitochondria

Neurodegenerative disorders
- Alzheimer
- Parkinson
- Huntington
- Friedreich ataxia

Cancer
Heart Disease
Sepsis
Osteoporosis
Aging Process
Diabetes
Multiple Sclerosis
Lupus
Rheumatoid Arthritis

Genetic Diseases
- Pearson’s syndrome
- Kearns-Sayre syndrome
- Chronic progressive external ophthalmolplegia (CPEO)
- MELAS (Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes)
- MERRF (myoclonus epilepsy with ragged-red fibers)
- LHON (Leber hereditary optic neuropathy)
- NARP (neuropathy, ataxia, and retinitis pigmentosa)

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Mitochondrial diseases

1) Every 30 minutes a child is born in the US who will develop a mitochondrial disease by age 10.

2) At least 1 in 200 individuals in the general public have a mitochondrial DNA mutation that may lead to disease.

3) Mitochondrial disease is a relatively newly diagnosed disease – first recognized in an adult in the 1960s and in the 1980s for pediatric onset cases. It is greatly under diagnosed and the true prevalence is difficult to determine.

Source: www.UMDF.org

Mitochondrial dysfunction occurs as part of daily life

- Mitochondrial dysfunction can be induced by viral infections such as Influenza A, SARS-Cov-2, Dengue virus and more…
- High caloric diets can cause mitochondrial dysfunction
- Prolonged inactivity and immobilization lead to mitochondrial dysfunction
- Physiological stress also impacts metabolism and mitochondrial function

Tiku V, Tan MW, Dikic I. *Trends Cell Biol*. 2020;30(4):263-275
de Mello AH et al. *Life Sci*. 2018;192:26-32
Buso A et al. *Front Physiol*. 2019;10:474

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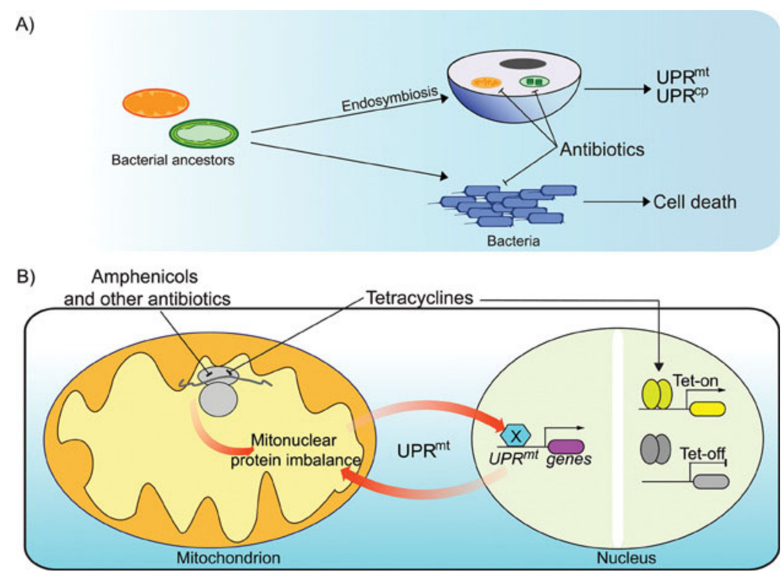
Common antibiotics induce mitochondrial dysfunction & oxidative damage in mammalian cells

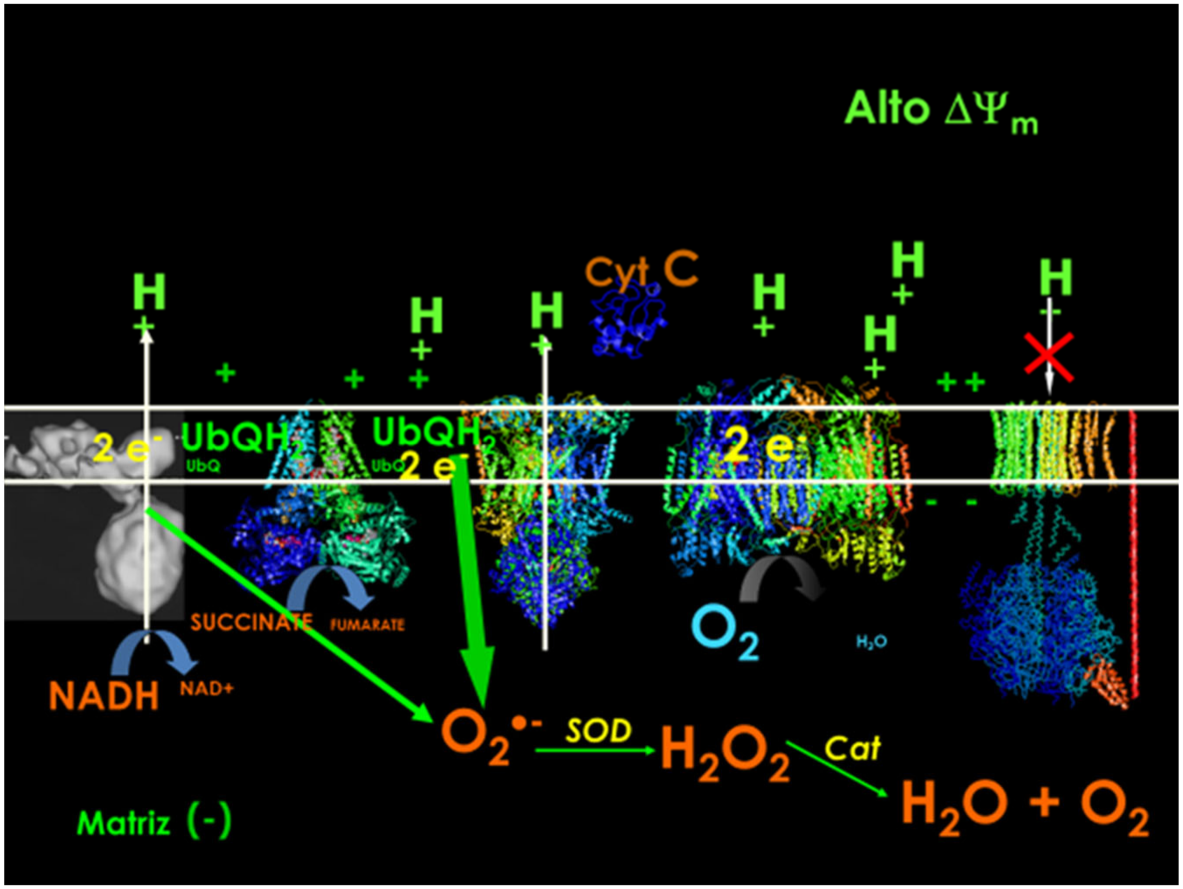
Dqwlelrwlfv# diihfwlqj# edfwhuld# surwhlq# v|qwkhvlv#dqg# kxpdq#khdowk#

Class	Name	Target	Reported side effects
Aminoglycosides	Amikacin, Dibekacin, Gentamicin, Kanamycin, Neomycins, Streptomycin, Tobramycin	Peptide elongation at the bacterial 30S ribosomal subunit	Kidney injury, ototoxicity, and vestibular toxicity
Amphenicols	Chloramphenicol, Thiamphenicol	Protein elongation by overlapping with the binding site at the A-site of 50S ribosomal subunit	Aplastic anemia, bone marrow suppression, neurotoxicity
Macrolides	Azithromycin, Carbomycin A, Clarithromycin, Erythromycin	Peptide-bond formation and ribosomal translocation	Myopathy, QT prolongation, nausea
Oxazolidinones	Eperezolid, Linezolid, Posizolid, Radezolid, Sutezolid	Peptide-bond formation by blocking tRNA binding at the A-site of 50S ribosome	Nausea, bone marrow suppression, lactic acidosis
Streptogramins	Pristinamycin, Quinupristin/dalfopristin, Virginiamycin	Protein elongation at the A- and P-sites of 50S ribosome	Nausea, myalgia, arthralgia
Tetracyclines	Doxycycline, Chlortetracycline, Lymecycline, Meclocycline, Minocycline, Tetracycline	Polypeptide synthesis by sterically blocking the recruitment of the aminoacyl-tRNA at the A-site of the bacterial 30S ribosomal subunit	Phototoxicity, secondary intracranial hypertension, teeth discoloration, steatosis, liver toxicity



Kalghatgi S et al. *Sci Transl Med. 2013;5(192):192ra85.*
Wang X, Ryu D, Houtkooper RH, Auwerx J. Bioessays. 2015 Oct;37(10):1045-53.

NAD metabolism and function in mitochondrial biology



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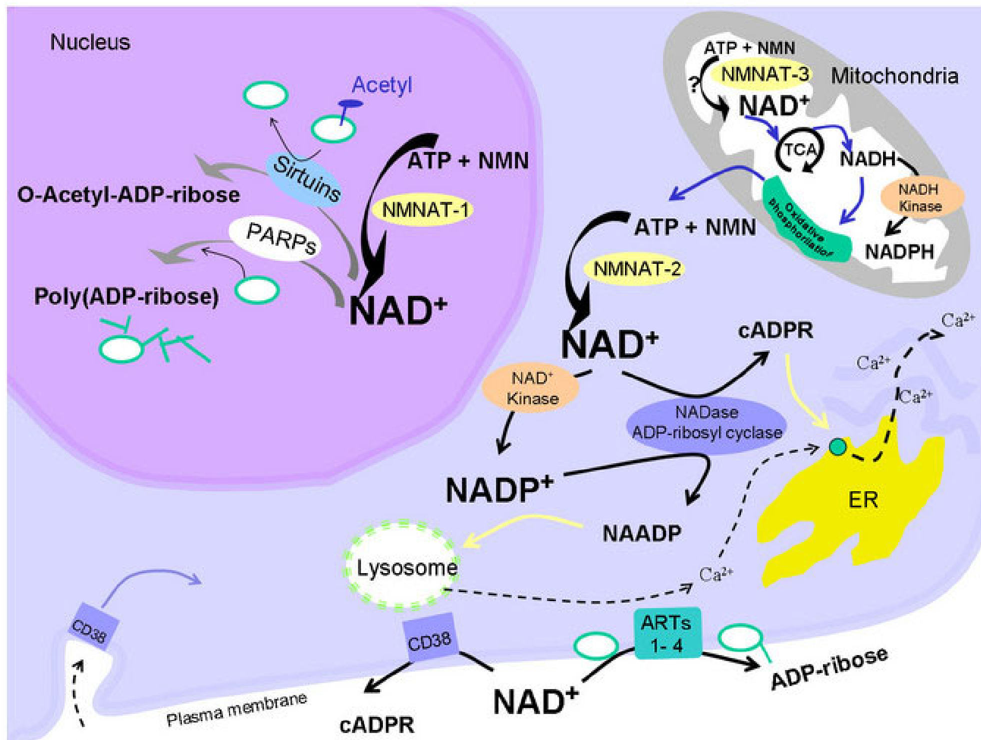
NAD biology



Berger F, Ramírez-Hernández MN, Ziegler M. Trends Biochem Sci. 2004;29(3):111-8.

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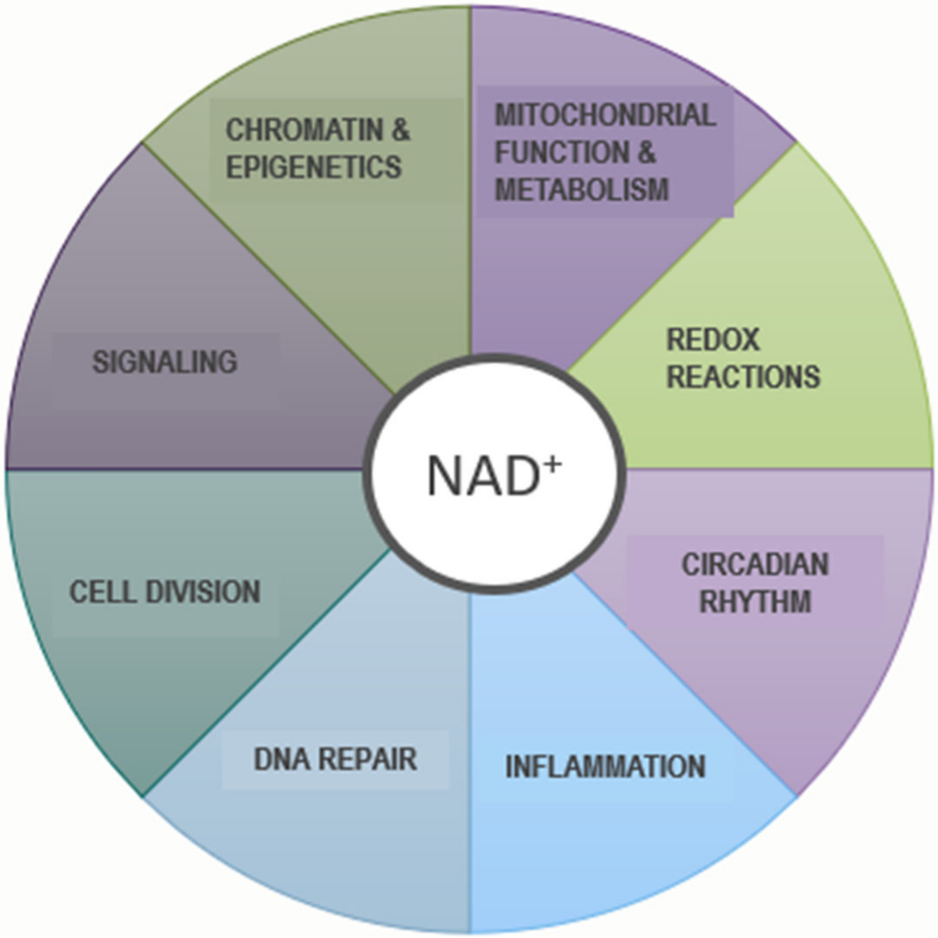
NAD Functions: Mitochondria and More



Adapted from Rajman L et al. *Cell Metab.* 2018;27(3):529-547

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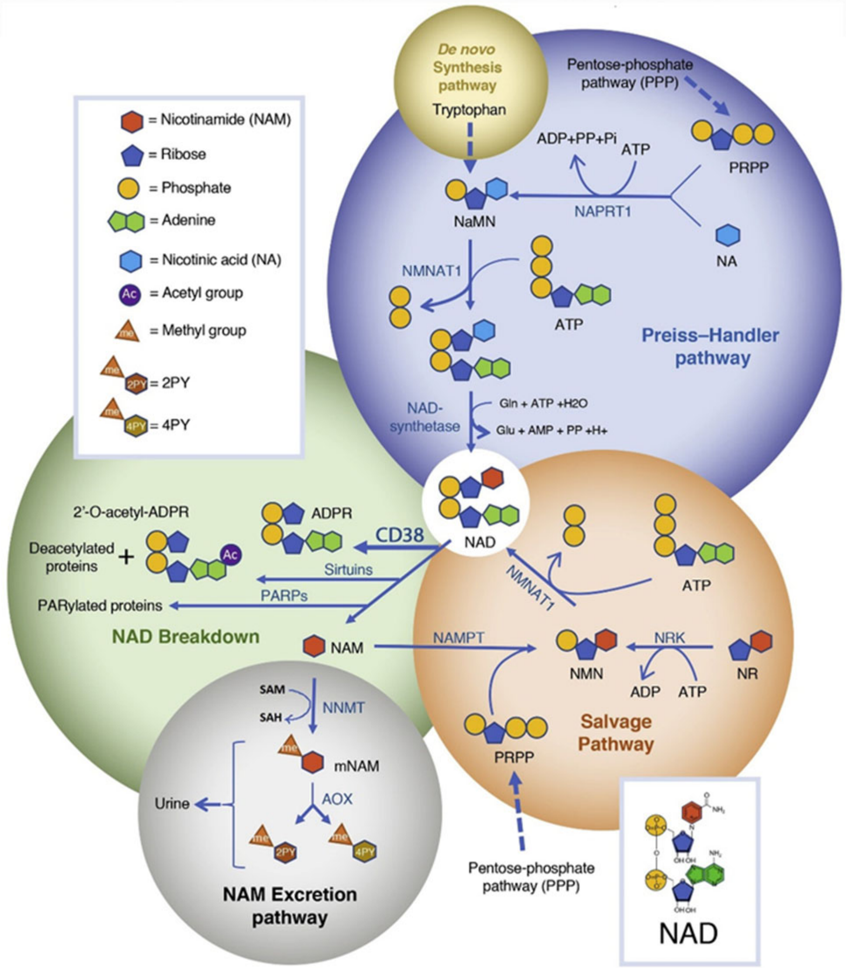
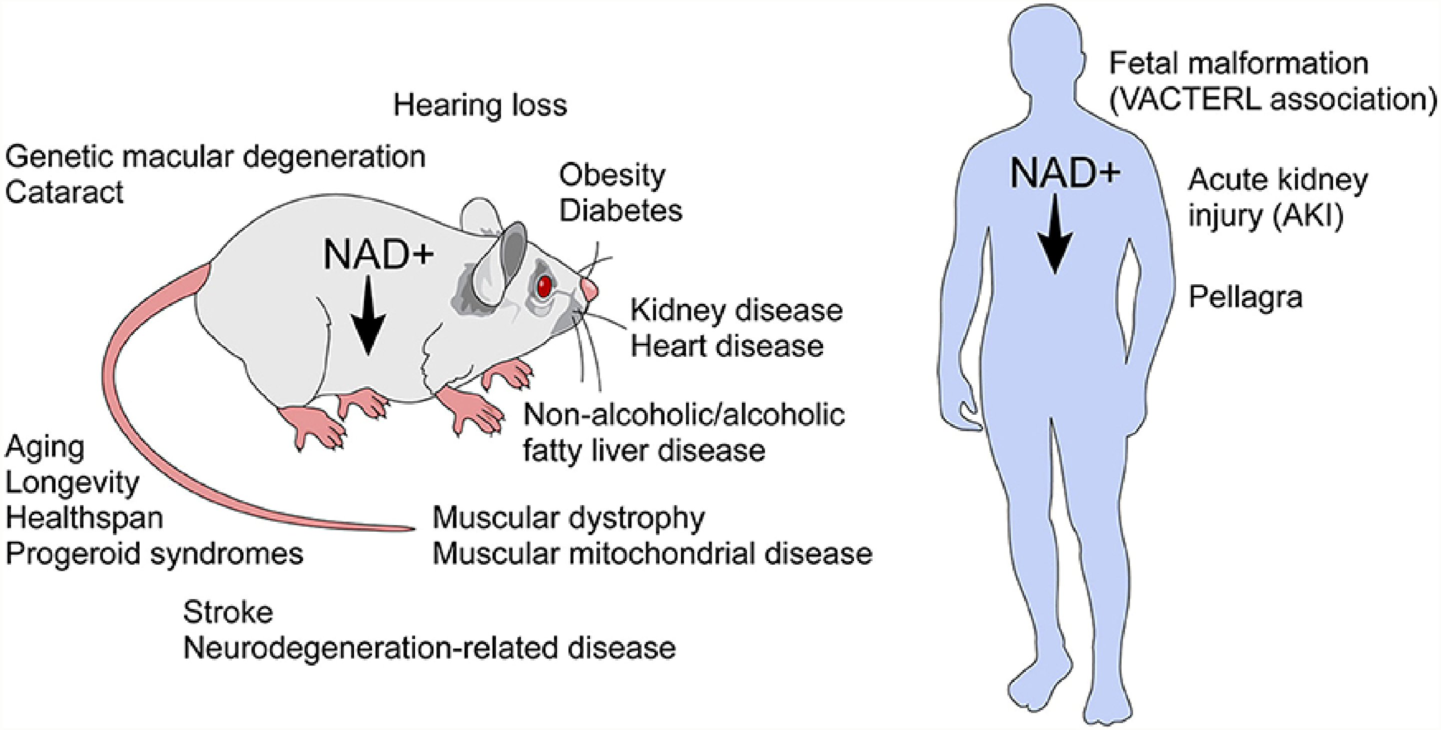
NAD metabolism: role of vitamin B3 derivatives



Chini EN. *Cell Metabolism* 2020;31(6):1041-1043 DOI: 10.1016/j.cmet.2020.05.013

NAD$^+$ decline has been implicated in several diseases and age-related conditions



Hogan KA, Chini CCS, Chini EN. Front Immunol. 2019 May 31;10:1187.
doi: 10.3389/fimmu.2019.01187.

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Image source: clipart-library.com

The concept of NAD "boosting" therapy

Chini EN, Chini CCS, Espindola Netto JM, de Oliveira GC, van Schooten W.

The Pharmacology of CD38/NADase: An Emerging Target in Cancer and Diseases of Aging. Trends Pharmacol Sci. 2018 Apr;39(4):424-436.

Boosting NAD

Trends in Pharmacological Sciences

Volume 39, Number 4

April 2018

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Is there any evidence of NAD-deficiency causing disease and of the benefits of NAD-boosting and NAD-replacement therapy in human evidence?

- Vitamin B3 deficiency leads to pellagra.
- Pellagra can lead to the four "Ds": dermatitis, diarrhea, dementia and death.
- Pellagra can be primary and secondary

Photo: Waring Historical Library, Medical University of South Carolina, Charleston, SC.

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The puzzle: increased longevity after nicotinic acid administration for secondary cardiac prevention?

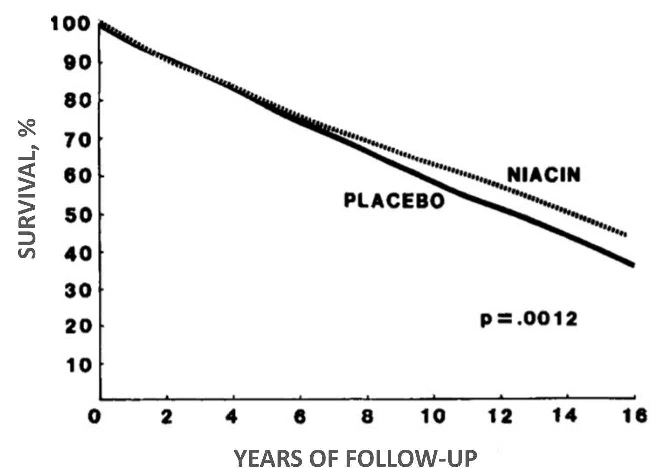
JACC Vol. 8, No. 6
December 1986:1245–55

COOPERATIVE STUDIES

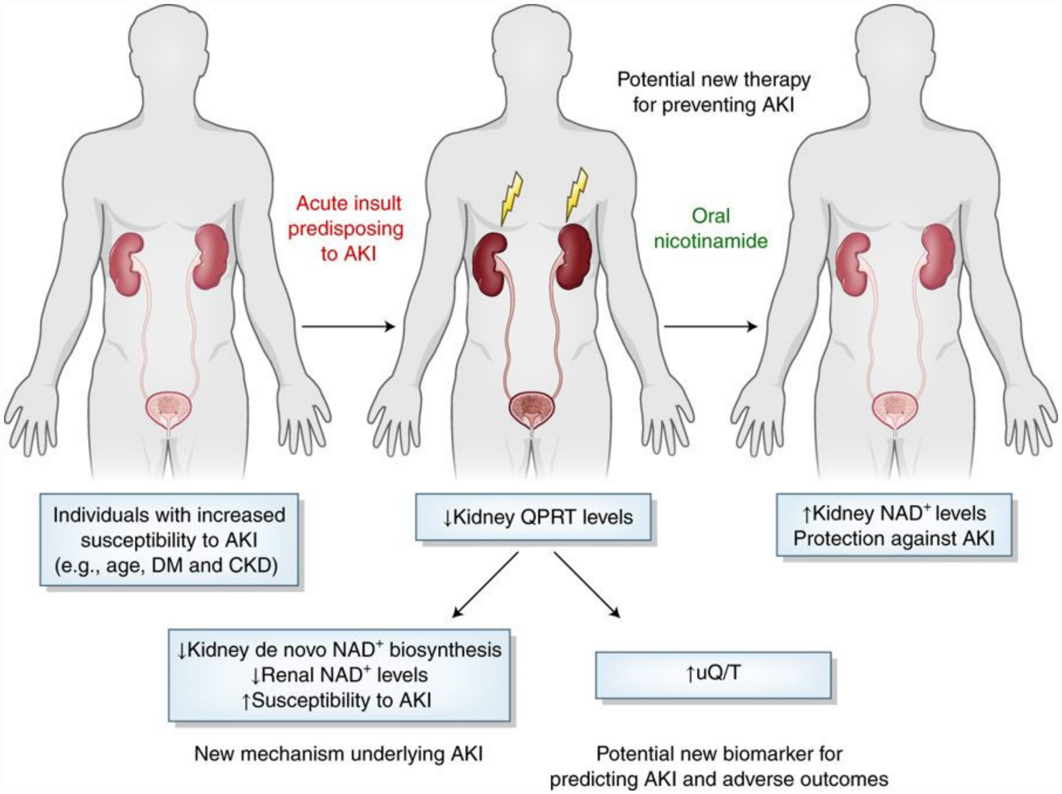
Fifteen Year Mortality in Coronary Drug Project Patients: Long-Term Benefit With Niacin

PAUL L. CANNER, PHD,* KENNETH G. BERGE, MD,† NANETTE K. WENGER, MD, FACC,‡ JEREMIAH STAMLER, MD, FACC,§ LAWRENCE FRIEDMAN, MD,‖ RONALD J. PRINEAS, MD, FACC,** WILLIAM FRIEDEWALD, MD,‖ FOR THE CORONARY DRUG PROJECT RESEARCH GROUP††

Figure 2. Survival curves for niacin and placebo treatment groups.



NAD-boosting with nicotinamide decreases the risk of perioperative Acute Kidney Injury?



Heerajnarain Bulluck & Derek J. Hausenloy. Nature Medicine 2018;24:1306–1307

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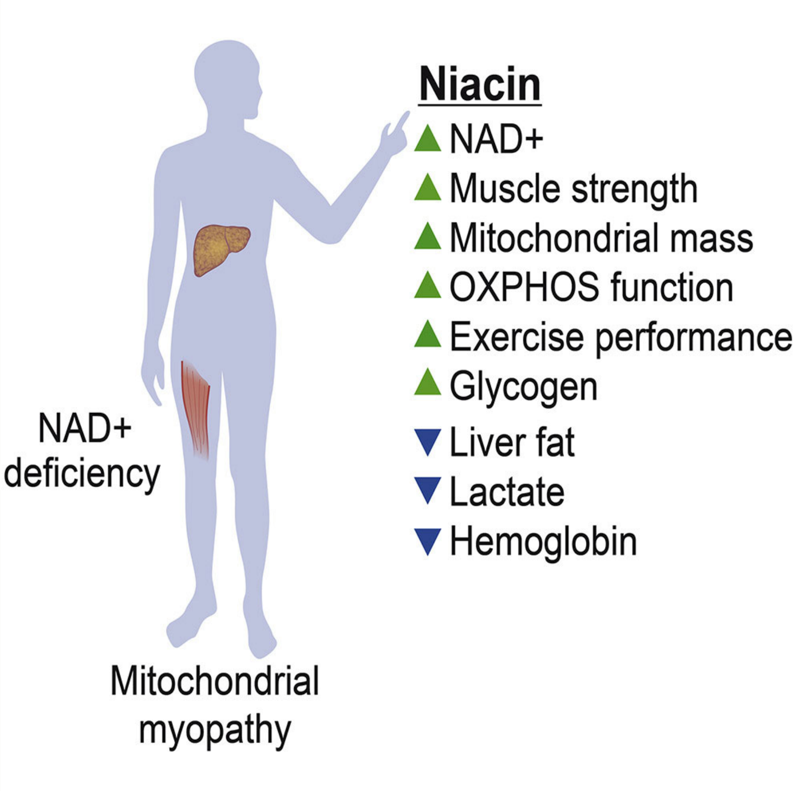
Niacin Cures Systemic NAD+ Deficiency and Improves Muscle Performance in Adult-Onset Mitochondrial Myopathy



Pirinen E, et al. *Cell Metabolism* 2020;31(6):1078-1090.e5

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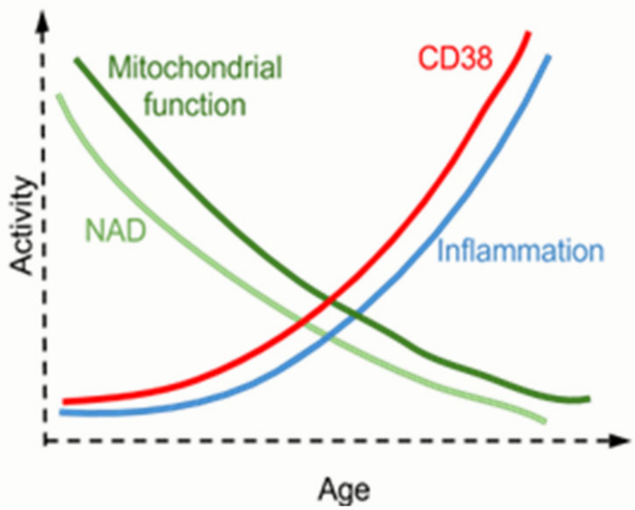
NAD levels decrease during aging in animal models.
Data in humans is needed.



CD38 Dictates Age-Related NAD Decline and mitochondrial Dysfunction through an SIRT3-Dependent Mechanism

Camacho-Pereira J, Tarragó MG, Chini CC, Nin V, Escande C, Warner GM, Puranik AS, Schoon RA, Reid JM, Galina A, Chini EN. Cell Metab. 2016 Jun 14;23(6):1127-39.

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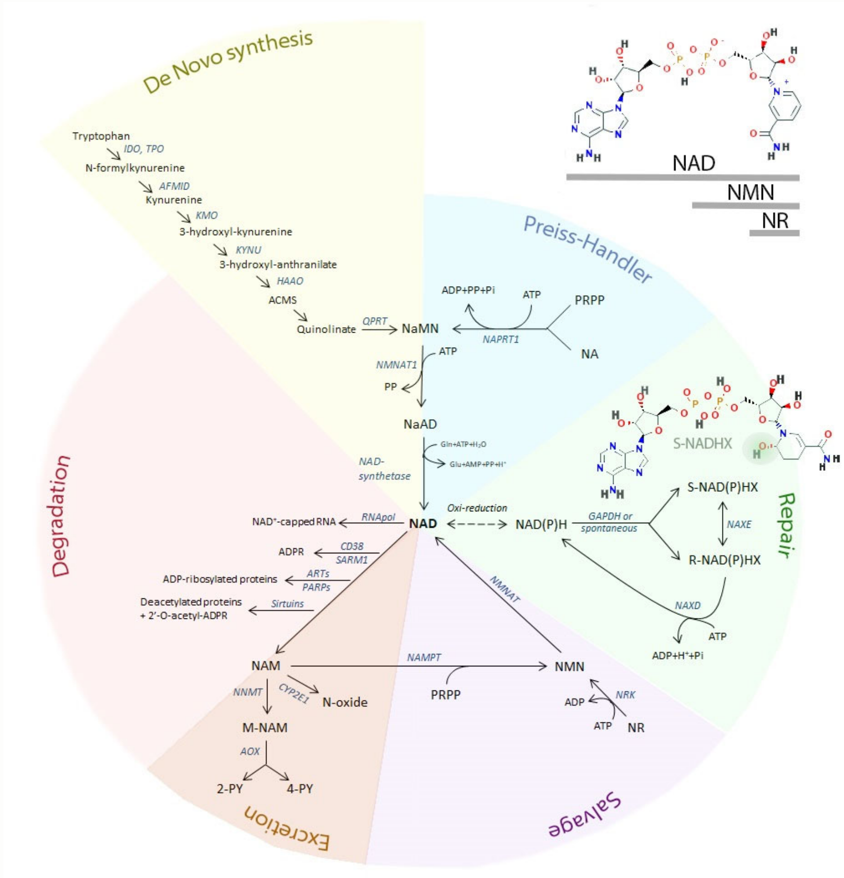
Nutritional Interventions to optimize mitochondrial biology

NAD-boosting with vitamin B3 derivatives, inhibition of NAD degradation or activation of its synthesis



There are multiple forms of vitamin B3 Including NAM, NA, NR and NMN

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Other interventions have been proposed to induce mitochondrial health

- Caloric restriction preserves mitochondrial function during aging
- Future research is needed to investigate dietary interventions that prevent or reverse mitochondrial dysfunction

Conclusions

- Mitochondrial function is complex
- Mitochondrial quality control is very important
- NAD is key for the function of mitochondria and cells
- NAD metabolic dysregulation plays a role in pre-clinical models of human diseases and in a growing number of human conditions.
- NAD metabolism can be manipulated in vivo by NAD-boosting with high doses of vitamin B3
- Research is ongoing to define the safety and efficacy of NAD boosting therapy in various human conditions

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Questions?

- Access the webinar recording on the Nestlé Medical Hub & Nestlé Nutrition Institute

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