Objectives

• Review mitochondrial structure, function and metabolism
• Discuss the pathophysiology of mitochondrial damage, including dietary factors, ROS, and toxins
• Discuss the links between mitochondrial damage and disease
• Review ways to support mitochondria with diet, nutrients, and phytochemicals
Mitochondria
Mitochondrial Distribution

• Approximately 10 million billion total: ~10% of body weight
• Average of 200 to 2000 per somatic cell
  ~5000 in cardiac cells -- 50% of myocardial cytoplasm -- there is complete turnover of myocardial ATP pool every 10 seconds
  ~800 in hepatocytes
  ~300-400 in neurons (filamentous)
• Mitochondria generate and consume the body’s weight in ATP every day
On the origin of mitosing cells. . .

- Mitochondria and chloroplasts contain DNA that is distinct from nuclear DNA
  - Chloroplast genes related to free-living cyanobacteria
  - Mitochondrial genes related to proteobacteria
  - Energetic advantage of oxidative phosphorylation

Mitochondria: Powerhouse of the Cell

- Mitochondria consume about 90% of the oxygen used by the body for oxidative phosphorylation.

- The oxygen serves as the ultimate electron receptor from the electron transport chain, allowing ATP to be generated.
Mitochondrial Anatomy
Functional Mitochondrial Structure

• **Cristae**: invaginations of inner membrane
  – Very large surface area, increases efficiency
  – Cardiolipin (a diphosphatidylglycerol):
    ~20% of inner membrane mass
    allows membrane to bend
  – Studded with enzyme transport chain protein complex, ATP synthase
  – Increased ATP demand → increased cristae
Healthy cristae (left) vs damaged (right)
Mitochondrial Matrix

A mixture of proteins and lipids

- Mitochondrial DNA (mtDNA)
- 70S ribosomes (similar to prokaryote)
- Transfer RNAs
- 1500+ proteins: ~30% of which have no known function
- Ca^{++} accumulation (imported by inner membrane pump)
- mt Nitric oxide synthase – NO production
- Glutathione (15% of total in cell)
Mitochondrial Dynamics—Mitochondrial Fission & Fusion in Human Diseases

• Fission/fusion involved in cell-cycle progression, apoptosis, mitophagy, O₂ sensing
• **Disorders of structure** emerging as major mechanisms of disease – cancer, cardiovascular disease, endocrine disorders, neurodegeneration
• Triggered by changes in the cellular milieu (e.g. oxidative stress) rather than monogenic mutations

NEJM, 2013, Vol 369: 2236-2251
Mitochondrial Genomics

- mt DNA = 37 genes
  (13 proteins, 2 rRNA, 22 tRNA)
- found in circular double-stranded molecules:
  - heavy strand (28 genes)
  - light strands (9)
- 2-10 circles of mtDNA per mitochondria
- Complexed with proteins but not protected by histones—*highly susceptible to oxidative damage*
Mitochondrial Functions
Mitochondrial Functions

• ATP synthesis
• Buffering Ca\(^{++}\) flux (from endoplasmic reticulum & plasma membrane)
• Maintenance of ion gradients (polarized cells)
• Generation of reactive oxygen species (ROS)
Mitochondrial Functions

• Cell signaling
  – ATP is a neurotransmitter

• Regulation of cell growth, cell cycle, metabolism

• Biosynthetic pathways

• Oxidative deamination of monoamines (MAO)
Mitochondrial Bioenergetics

- Catabolism of CHO, fats, & amino acids into carbon skeletons
- Extraction of energy released via catabolism:
  - Glycolysis
  - Citric acid cycle (Krebs)
  - β-oxidation
  - Oxidative phosphorylation
- 36-38 molecules of ATP per molecule of glucose
Net ATP: 30 to 32 ATP per glucose

Glycolysis: +2 ATP via substrate-level phosphorylation
Citric Acid Cycle: +2 ATP via substrate level phosphorylation (1 per pyruvate)
Electron Transport Chain: +26 to 28 ATP via oxidative phosphorylation
Glycolysis

• Ancient metabolic pathway -- in cytosol of most living organisms
• Glucose (6C): initial electron donor
  – Reduces NAD\(^{+}\) into NADH \(\times 2\)
  – Generates ATP \(\times 2\)
    (very rapid but inefficient energy production)
  – Splits into pyruvate \(\times 2\)
Glycolysis

Pyruvate (3C)
- Actively transported into matrix for aerobic respiration by mitochondrial pyruvate carrier
- When mitochondrial metabolism inhibited (anaerobic conditions, etc.), converted into lactate by LDH, which regenerates NAD⁺
Oxaloacetic Acid

Malic Acid

Fumaric Acid

Succinic Acid

Citric Acid Cycle

Citric Acid

cis-Aconitic Acid

Isocitric Acid

α-Ketoglutaric Acid

NADH / FADH$_2$

Electron Transport and Oxidative Phosphorylation

(2) H + $\frac{1}{2}$ O$_2$ $\rightarrow$ H$_2$O

KEY

Green = cofactor

Red = inhibitor
Conventional wisdom has been that mitochondria prefer carbohydrates (glucose) as the primary source of energy, however, fatty acids (ketones), and amino acids can also be readily utilised by mitochondria.
Acetyl-CoA

• Primary substrate for TCA cycle - essential to balance between carbohydrate (CHO) & fat metabolism
• Produced in mitochondrial matrix from coenzyme A combined with acetyl group (2C) from
  – CHO: Pyruvate decarboxylation
  – Fatty acids (beta oxidation) / Ketone bodies
  – Amino acids
Tricarboxylic Acid (Krebs) Cycle

• Final common catabolic pathway for all nutrients (protein, fat, carbohydrates)
• Enzymes located in mt matrix (except for complex II - succinate dehydrogenase)
• Acetyl-CoA oxidized to CO₂
• Produces
  – Metabolic byproducts: amino acid precursors
  – NADH, FADH₂, GTP
Long Chain Fatty Acids: Mitochondrial Metabolism

• Most dietary fatty acids undergo β-oxidation in mitochondria
• High carbohydrate intake impairs β-oxidation, resulting in accumulation of intracellular lipid intermediates and triglycerides, causing insulin resistance
• Fasting, starvation, and low carbohydrate/high fat diets increase hepatic β-oxidation, resulting in ketogenesis
Ketone Bodies

- Ketones soluble in water—no protein carriers required
- Plasma levels increase with fasting, high fat/low CHO diets, and uncontrolled diabetes
- Ketones are preferred fuel (vs glucose) for cardiac muscle and renal cortex
- Used in brain (after crossing blood brain barrier) proportionate to concentration in blood, provide energy when glucose availability is limited
Amino Acids as Fuel Sources

• Can be oxidised, degraded into pyruvate, used as citric acid cycle intermediates, or converted into ketone bodies

• Oxidative degradation of AAs produces 10-15% of total metabolic energy

• Act as precursors for gluconeogenesis when glucose supply is low
Amino acid precursors for TCA cycle

Leucine  
Lysine  
Phenylalanine  
Tryptophan  
Tyrosine

Acetyl-CoA

Acetoacetyl-CoA

Isocitrate

Glutamate

α-Ketoglutarate

Succinyl-CoA

Succinate

Phenylalanine  
Tyrosine

Isoleucine  
Methionine  
Threonine  
Valine

Arginine  
Glutamine  
Histidine  
Proline

Citrate

Oxaloacetate

Fumarate

Aspartate

Malate

Pyruvate

Alanine  
Cysteine  
Glycine  
Serine  
Tryptophan

Asparagine
**Mitochondrial Matrix**

*FIG. Mitochondrial Respiratory Chain.* Protons (H\(^+\)) are pumped from the mitochondrial matrix to the intermembrane space through complexes I, III, and IV. Complex V utilizes the proton gradient as a source of energy to produce ATP. Coenzyme Q\(_{10}\) transfers electrons from complexes I and II to complex III. Riboflavin is a precursor of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). The amide form of niacin, (nicotinamide) is a precursor for nicotinamide adenine dinucleotide (NAD). Vitamin K\(_{1}\) in combination with vitamin C serve as electron acceptors to bypass a deficiency in complex III. Carnitine function to transfer long chain fatty acids across the mitochondrial membrane.
Introducing: The Electron Transport Chain
Mitochondrial Energy Production
Stressors:
- Aging/Senescence
- Wounding
- Xenobiotics
- Radiation/Light
- Heat & Cold
- Pathogens
- Biotoxins
- Drought
- Heavy Metals
- Air Pollutants \((\text{O}_3; \text{SO}_2)\)
- Hormones

Oxidative Stress

Molecular Damage
- Lipids & Fatty Acids
- Amino Acids
- Proteins
- Nucleic Acids
- Pigments

Cellular Effects
- Membrane Damage
- Loss of Organelle Functions
- Reduction in Metabolic Efficiency
- Reduced Carbon Fixation
- Electrolyte Leakage
- Chromatid Breaks
- Mutations

Cell Death
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The Mighty Mitochondria

Hydrogen Peroxide

Superoxide

The Mighty Mitochondria
An individual produces about 1 kg of oxygen radicals per year. The consequence is about 100,000 oxidative attacks on mDNA per cell per day.
Causes of Increased Mitochondrial ROS

- Caloric excess
- Hyperglycaemia (endothelial)
- Inflammatory mediators (TNFα)
- Hypoxia
- Environmental pollutants & toxicants
- Toxic metals (mercury, arsenic)
- Ionizing radiation
Denham Harman

• First proposed the idea of “free radicals” in 1956 and postulated that these compounds play a role in aging through cross-linking reactions.
• Free radicals covalently modify lipids, proteins, cellular and mitochondrial DNA.

Harman D. Free radical theory of aging: consequences of mitochondrial aging
Free Radical Theory of Aging

- Increased oxidant generation
- Declining defenses and repair
- Accumulation of the end products of oxidative damage
  - Advanced Glycosylated End Products (AGEs)
  - Protein Oxidation (NitroTyrosine)
  - Oxidised LDL, Isoprostanate F2, Lipid Peroxides, MDA
  - DNA damage (8-OH dG)
Free Radicals, ROS, and RNS…

React with and damage structural and functional components of cells

- Membranes & Receptors
- Enzymes & other proteins
- Cellular DNA & RNA
- Mitochondrial DNA & Membranes
Mitochondria & Free Radicals

• About 1-2% of oxygen consumed by our mitochondria is converted to superoxide and hydrogen peroxide.
• One rat liver mitochondrion produces \( \sim 3 \times 10^7 \) superoxide radicals per day.
• Each liver cell contains \( \sim 1000 \) mitochondria.
NK-kB Mediated Cellular Damage

↑ Oxidative Stress

Activation of NF-KB

Up-regulation of stress and inflammation genes including inducible NOS (iNOS)

↑ RNS, NO, *ONO2−

Increased Cellular Damage
How Does the Body Protect Itself From ROS?

1. Enzymes
   - Catalase \((Fe)\)
   - Superoxide dismutase-SOD \((Zn, Cu, Mn)\)
   - Glutathione peroxidase \((Se)\) and glutathione reductase

2. Dietary Anti-Oxidants
   - Vitamin C for aqueous compartments
   - Vitamin E for lipid compartments
   - Carotenoids, flavonoids, etc.

3. Endogenous Anti-Oxidant Molecules
   - Glutathione, cysteine, CoQ\(_{10}\), lipoic acid, uric acid, cholesterol.
Understanding Oxidative Stress

To have a comprehensive understanding of the body’s red-ox potential and level of total oxidative stress, you need to know:

1. What is the antioxidant reserve or total antioxidant capacity?
2. What is the throughput of reactive oxygen species and free radicals?
3. What damage to cellular components is being done?
Oxidative Stress Blood/Urine

Total Antioxidative Capacity (TAC) Overview:

TAC Breakdown:

- SOD (Superoxide enzymes): 21
- CAT (catalase): 16
- GSH (glutathione): 11
- GS-SG (glutathione): 17.33
- CYS-SH (cysteine): 16
- CYS-S-S-CYS (cystine): 14.2
- Sulphate: 8
- Cysteine/Sulfate Ratio: 11.69

Effects:

- Lipids: 12
- Proteins: 34
- DNA: 22

Adverse Effects:

- GSH (glutathione)
- GS-SG (glutathione)
- CYS-S-S-CYS (cystine)
- Sulphate

Anti Oxidant

CAT (catalase)

GPx (controls GSH/G S-S-G pathway)
Glutathione Formation and Recycling
Antioxidant Enzymes

**Superoxide Dismutase:**

\[2O_2^- + 2H^+ \rightarrow H_2O_2 + O_2\]

- Cytosolic SOD1 (Zn & Cu)
- Mitochondrial SOD2 (Mn)

**Glutathione Peroxidase (GPx) (Se)**

\[H_2O_2 + 2GSH \rightarrow 2 H_2O + GSSG\]

**Catalase:**

\[2H_2O_2 \rightarrow 2 H_2O + O_2 (Fe)\]
Mitochondrial ROS
Experimental and Molecular Pathology 83 (2007) 84–92

• Superoxide (O$_2^-$) primarily generated by electrons escaping from complex I and complex III
• 0.4 to 4% of all O$_2$ consumed is converted to O$_2^-$
• Dismutation of O$_2^-$ into H$_2$O$_2$ by MnSOD2
• H$_2$O$_2$ reduced to water by glutathione peroxidase or peroxiredoxin
• H$_2$O$_2$ also participates in mitochondrial and intracellular redox signaling
Mitochondrial function

Generation of ROS

Oxidative damage mtDNA mutations

Mitochondrial dysfunction

Ageing

«The vicious cycle»
What’s The Damage?

Oxidative stress from free radicals, ROS, and RNS can damage many cellular components

- Damaged Fats
- Damaged Sugars
- Damaged Proteins
- Damaged DNA
One can evaluate with:

- Damaged Fats -- Lipid Peroxides, oxidized LDL, Isoprostane F2
- Damaged Sugars -- HgbA1c, AGEs
- Damaged Proteins -- 3-Nitrotyrosine
- Damaged DNA -- 8-OH Deoxyguanosine
Therapies for ↓ Lipid Peroxides

Consider fat-soluble antioxidants:

- Vitamin E (interrupts rapid propagation of lipid peroxides)
- CoQ10
- Lipoic Acid

For lowering serum lipid peroxides, the combination of Curcumin, cayenne, and garlic is effective.

8-OHdG as a Marker of Oxidative Stress

“The biomarker 8-OHdG has been a pivotal marker for measuring the effect of endogenous oxidative damage to DNA and as a factor of initiation and promotion of carcinogenesis.”

Damaged DNA (8-OHdG)

8-hydroxy-deoxyguanosine

- When an activated oxygen species reacts with the nucleotide guanosine, 8-hydroxy-deoxyguanosine is created.
- 8-OHdG is the most frequent mutagenic lesion in our DNA.
- Damage can be triggered by chemical toxicity, inflammation, or radiation.
Treating Damaged DNA

• Carotene supplementation has been found to decrease DNA oxidation.
• Reduce iron overload, if present.
• Combination antioxidant support is most effective.
• Methylation is critical for DNA synthesis.

Effective Treatment

The effectiveness of any given antioxidant in the body depends on which free radical is involved, how and where it is generated, and the location of the target damage.
Effective Treatment

- Nutritional Anti-Oxidants (Vit A, C, E)
  - Glutathione, alpha-Lipoic Acid
  - CoEnzyme Q-10 (CoQ-10)
- Plant-based Anti-Oxidants
  - Resveratrol
  - EpiGalloCatechinGallate (EGCG)
  - Many, many, many others
- Proper Methylation Function (B-Vitamins)
- Mineral Co-Factors (Mg, Mn, Fe, Zn)
- Amino Acid Balance and Protein Digestion
- Eat Your Vegetables!
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Mitochondrial Dysfunction & Disease

- Metabolic syndrome: insulin resistance, type 2 diabetes, obesity, non-alcoholic fatty liver disease
- Cardiovascular disease (congestive heart failure)
- Cancer
- Neurodegenerative & neuromuscular disorders
- Mood disorders; bipolar disorder
- Chronic fatigue; fibromyalgia
- Multiple chemical sensitivity
- Premature aging
The Brain is Uniquely Vulnerable to Oxidative Damage

- Intolerance for blood flow interruptions
- Limited regeneration—although neurogenesis and gliogenesis can be stimulated
- Circuit-based functions: small deficits have huge impact
- Aging sensitive
- PUFAs
The Brain is Uniquely Vulnerable to Oxidative Damage

- Multiple sources of ROS generation (e.g. NOx, Complex I, p450s, neurotrophic factor withdrawal)
- Redox active metal-rich (catalytic iron)
- Auto-oxidation of monoamines
- Glutamate excitotoxicity
- Limited antioxidant and repair capacity (low catalase, mitochondria lack catalase)
- Resident immune cells (microglia) produce ROS and cytokines
Common Mediators of Neurodegeneration

- Reactive species and oxidative/nitrative damage
  – which offending species?
- Mitochondrial dysfunction
- Abnormal protein aggregates
- Inflammation
Common Types of Neurodegeneration

- Alzheimer’s Disease
  - (a.k.a. Senile Dementia of the Alzheimer’s Type – SDAT)
- Cognitive Impairment
- Memory Loss
- Parkinson’s Disease
- Stroke/ CVA
Damage to Lipids, Proteins, DNA, & RNA in Mild Cognitive Impairment

“These studies establish oxidative damage as an early event in the pathogenesis of Alzheimer disease that can serve as a therapeutic target to slow the progression or perhaps the onset of the disease.”

Markesbery, W., Arch Neurol. 64(7):954-956; July, 2007
Oxidative Stress Response

ROS/RNS

Adaptation Responses

Oxidation of proteins, lipids and DNA

Failure to adapt

Organelle dysfunction

Calcium dysregulation

Apoptosis

Necrosis

e.g. Neurotrophic factors, Neurogenesis, DNA repair etc
Metabolic Regulation of Cognitive Dysfunction

• Diabetes aggravates, and energetic challenges attenuate, CNS inflammation.
• Exercise and caloric restriction ameliorate, and diabetes exacerbates, Alzheimer’s disease models.
• Cognitive impairment associated with trauma or ischemia can be modified by caloric intake and exercise.
Is oxidative stress a useful target for brain disorders?

Dual roles of ROS:
Signaling vs damage → Xenohormesis
– Are ROS merely associated with the disease process or play a causative role?
– Do antioxidant compounds interfere with physiological processes?
– Does redox signaling role interfere with antioxidant efficacy?

Goal of antioxidant therapy in disease states is to normalise elevated ROS levels and decrease oxidative damage
Xenohormesis

All substances are poisons; there is none that is not a poison. The right dose differentiates a poison and remedy.

Paracelsus (1493–1541)
Xenohormesis

Figure 1. Activation of Nrf2-Keap1 signaling by xenohormetic phytochemicals with cancer chemopreventive potential.

The Ketogenic Diet (KD)

• Mimics fasting state – switches from metabolism of glucose to metabolism of ketones
• Clinically-used treatment for intractable seizures in children and adolescents
• High fat – low carbohydrate (4:1, fat:non-fat)
• Efficacy appears to be independent of seizure type
• Mechanism of action unknown but attributed to ketone bodies, glycolysis, and mitochondrial metabolism
• Research direction: clinic to bench
Mitochondrial Neurologic Disorders Treated with Ketogenic Diets

- Drug-resistant epilepsy: proven long-term anticonvulsant effects
- Alzheimer’s disease: protects against β-amyloid
- Parkinson’s disease: increased mitochondrial efficiency
- Brain tumors
- Autism spectrum disorders
- Migraines
- Traumatic brain injury and stroke (theoretical)
Overnight fast

- Glucose
- Glycogen
- Amino acids
- Ketones
- Fatty acids
- CO₂
- Muscle
- Liver
- Fat

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Starvation

- glucose
- glycogen
- amino acids
- ketones
- fatty acids
- CO₂
- muscle
- liver
- fat

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Ketogenic Diet

- reduces inflammation (NFκB)
- enhances mitochondrial biogenesis
- enhances ATP production
- reduces ROS production
- reduces apoptosis
- increases insulin sensitivity
- increases leptin sensitivity
Activation of the Nrf-2 Adaptive Response in the Ketogenic Diet

Ketogenic Diet

Mild oxidative/electrophilic stress (H$_2$O$_2$, 4-HNE)

Protein kinase cascade

Keap1

Nrf2

Keap1

Nucleus

~ 1 week

Target gene transcription (Gclc, Gclm, Nqo1, Ho-1)

Nrf2

ARE

Antioxidant Response

> 3 weeks

ROS

Milder and Patel, Epilepsy Res. 2011
Major Sources of Mitochondrial Dysfunction:

• Oxidative stress
• Macronutrient overload
  • Glucotoxicity (glycation)
  • Lipotoxicity
• Environmental toxins
Mitochondrial hormesis [mitohormesis]

- Increased oxidative stress promotes longevity and metabolic health.
- In contrast with Denham Harman’s free radical theory of aging, increased formation of ROS within the mitochondria cause an adaptive response (mitohormesis) that culminates in increased stress resistance and long-term reduction in oxidative stress.

Exp Gerontol. 2010 Jun;45(6):410-8
Mitochondrial hormesis
[mitohormesis]

- ROS are essential signaling molecules which are required to promote health and longevity.
- Abrogation of this mitochondrial ROS signal by antioxidants impairs the lifespan-extending & health-promoting capabilities of reduced calorie uptake, glucose restriction & physical exercise.

Exp Gerontol. 2010 Jun;45(6):410-8
“What doesn’t kill you, makes you stronger!”

Figure 2. Differential responses to rising oxidative stress.

- Oxidative stress
  - Priming
  - Mild to moderate
- Inflammation
- Apoptosis
  - Extreme

- Nrf2
- NFκB
- AP-1
Mitochondrial Poisons: Cigarette Smoke!

- Cyanide
- Carbon Monoxide
- First identified as mitochondrial toxins in 1940s
- Block mitochondrial energy production by displacing oxygen from heme (hemoglobin, cytochrome c)
- Both are found in cigarette smoke!
Mitochondrial Toxins: Environmental Chemicals

- 2,4 Dinitrophenol: uncouples OXPHOS – causes weight loss but potentially fatal
- Atrazine: inhibits complexes I & II
- Organochlorines (eg dioxin): disrupt signaling
- Bisphenol A: inhibits complex II
- Organophosphates
Mitochondrial Toxins: Metals

- Iron (overload)
- Manganese (overload)
- Mercury
- Lead
- Arsenic
Mitochondrial Toxins: Pharmaceuticals

- Acetaminophen: irreversibly inhibits β-oxidation
- Aminoglycoside antibiotics
- Anti-retroviral drugs (NTRIs)
- Aspirin: inhibits & uncouples OXPHOS
- Cancer chemotherapy agents (platinum)
- Metformin: complex I inhibitor
- Tamoxifen: inhibits complexes III & IV
- Valproic acid: inhibits complex IV
- Statins

Simvastatin Impairs Exercise Training Adaptations

- 37 sedentary overweight or obese adults at risk for metabolic syndrome, randomised to 12 wks of aerobic exercise, vs exercise plus 40 mg simvastatin

- Exercise only: CV fitness increased by 10% in exercise, along with 13% increase in skeletal muscle mitochondrial citrate synthase (from biopsy)

- Exercise plus statin: CV fitness blunted to 1.5% increase, with 4.5% decrease in citrate synthase
Mitochondrial Dysfunction & Diet

- Caloric excess
  numerous studies
- Fructose: Lustig, “Fructose: it's "alcohol without the buzz”
- Alcohol: Cellular and Mitochondrial Effects of Alcohol Consumption
Mitochondrial Dysfunction & Diet

- Saturated fat: Dietary fat, fatty acid saturation and mitochondrial bioenergetics.
  

- Advanced glycation end products (preformed & hyperglycemic): Pathological Significance of Mitochondrial Glycation
  
  International Journal of Cell Biology, 2012, Article ID 843505
Obesity, T2DM & Mitochondrial Function

• Obese individuals tend to tire more easily and have decreased physical endurance than those with low BMIs, *in spite of increased food intake*
Obesity, T2DM & Mitochondrial Function

- Skeletal muscle mitochondria in obese individuals with T2DM, are...
  - small
  - have reduced contents and
  - impaired electron transport activity
Mitochondrial dysfunction
Inefficiency of ETC and β oxidation

- mtDNA mutations (A3243G, A8344G)
- Imbalanced acetylation status of mitochondrial proteins
- Environmental toxins, POPs

Overproduction of ROS
Accumulation of lipids
Disruption of insulin signaling pathway

Insulin resistance

- Anti-diabetic drugs
- Regular exercise
- Natural products
- Antioxidants
- Pyruvate
The Perfect Storm (Insulin Resistance)

- Glucose unable to enter cell
- β oxidation is inhibited leading to lipid accumulation in skeletal muscle, liver, & heart
- Gluconeogenesis is inhibited
- Krebs cycle intermediates are depleted
- Only one option remains: break down muscle and replace it with fat
- All these conditions are intracellular energy deficits (obesity, CHF, cachexia, diabetes, fatty liver)
Nrf2, the Oxidant ‘Thermostat’ of the Cell: The ‘Oxidant-stat’

Antioxidant Response Elements
ARE: GSH, GST’s, GPx, Catalase and others

GSH

Nucleus

OxStress

Released to travel to nucleus

KEAP1
Nrf2
Cul3

IFM

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Nrf2 activation

- Oxidative stress
- Caloric restriction
- Curcumin
- Green tea extract
- Pterostilbene
- Sulforaphane
- Garlic (allicin)
- DHA

- Catalase
- Glutathione
- SOD
- GST (Phase II detox)
- Inhibits NF-κB
- Inhibits microglial activation
• Oxidative stress
• Caloric restriction
• Curcumin
• Green tea extract
• Pterostilbene
• Sulforaphane
• Garlic (allicin)
• DHA
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Exercise Increases Mitochondrial Numbers

Moderate intensity exercise 4 months:

- 67% increase in mitochondrial density
- 55% increase in cardiolipin content
- Increase in mitochondrial oxidation enzymes
- All linked to improvement in hemoglobin A1c and fasting plasma glucose
Pharmacological Intervention → Mitochondrial Function → Mitochondrial Biogenesis → ROS↓ → Insulin Sensitivity↑ → Normal Metabolism

Exercise → Mitochondrial Function → Mitochondrial Biogenesis → ROS↓ → Insulin Sensitivity↑ → Normal Metabolism

Calorie Restriction → Mitochondrial Function → Mitochondrial Biogenesis → ROS↓ → Insulin Sensitivity↑ → Normal Metabolism
ATP depletion:

Calorie restriction, Exercise
Cold temperatures

- AMPK
  - SIRT1
  - PGC-1alpha
    - (muscle, brain, liver, brown adipose tissue)
    - Gene regulation (numerous)
    - Mitochondrial biogenesis
      - ↑ATP
      - ↑Fatty acid oxidation, ↑Energy, Endurance, Weight loss, Longevity
Phytochemicals

Alpha Lipoic Acid, Berberine, Curcumin, Quercetin, Resveratrol, Pterostilbene, Green tea Polyphenols

AMPK

PGC-1alpha
(muscle, brain, liver, brown adipose tissue)

Gene regulation (numerous)

Mitochondrial biogenesis
↑Fatty acid oxidation, ↑Energy, Endurance, Weight loss, Longevity

SIRT1

↑ATP
Phytochemicals that support Mitochondrial Function

- Curcumin (turmeric)
- Sulforaphane (broccoli)
- Berberine
- Quercetin
- Resveratrol (red wine)
- Pterostilbene (purple berries)
- Green tea polyphenols
Nutrients that support Mitochondrial Function

- Acetyl-L-carnitine: 1500-3000 mg
- Alpha lipoic acid: 300-900 mg
- Coenzyme Q10 (ubiquinone): 50-200 mg
- Magnesium: 100-500 mg

Neurobiol Aging. 2013, pii: S0197-4580(13)00525-3
Nutrients that support Mitochondrial Function

- N-acetylcysteine: 500-3000 mg
- Creatine: 5-15 grams
- Melatonin: 3-20 mg
- Ketogenic & branched chain amino acids
- Nicotinamide riboside: 250-1000 mg

Neurobiol Aging. 2013, pii: S0197-4580(13)00525-3
Benefits of Enhanced Mitochondrial Function

- ↓ ROS / Oxidative Stress
- ↑ Metabolic Function
- ↑ Energy Level
- ↑ Exercise Performance
- ↓ Body Fat / ↑ Lean Muscle Mass
- ↓ Age-Related Deterioration
- ↑ Increased Lifespan (?)
- Cancer suppression
Treatment:
a TO DO list to support your mitochondrial function

- Get adequate nutrition
- Stay cool and hydrate
- Prevent infections
- Exercise (physical & mental)
- Avoid toxins
Treatment:
a TO DO list to support your mitochondrial function

Supplements:
- CoQ-10
- Omega-3 Fatty Acids
- B-Vitamins [particularly B2 & B3]
- Alpha-Lipoic Acid
- Nrf2 Activators
- Rhodiola