History of Light Therapy

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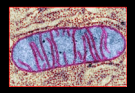
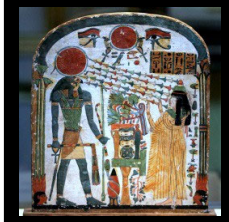


Photobiomodulation and Eye Care

- *The History of Light Therapy*
- *The Basic Science of Photobiomodulation - The effects of FR/NIR light on cells*
- *Photobiomodulation in Eye Disease Dry AMD*
  - *Diabetic Retinopathy*
  - *Inherited Retinopathies*
  - *Glaucoma*
- *The Future of Photobiomodulation*

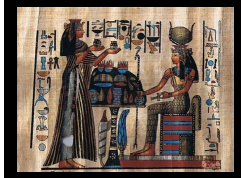
We Evolved Under the Sun

Ancient Times



- Ancient Egyptians are said to have built special temples for healing with sunlight and colored light.
- Pythagorus used color for healing five hundred years before the birth of Christ.
- Reference to color healing can be found in ancient Chinese and Indian texts.

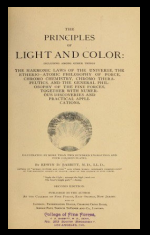
Ancient Times



- Virtually all the major civilizations recognized the importance of light in healing.
- The Assyrians, Babylonians and Egyptians all practiced therapeutic sun-bathing.
- The Greek city of Heliopolis (which means 'City of the Sun') was renowned for its healing temples and light rooms.

1700 – 1800s

- (1876) Augustus Pleasanton used blue light to stimulate secretory glands and the nervous system; he found it to be very effective in treating a variety of diseases, especially those accompanied by pain.
- Edwin Babbitt published The Principles of Light and Color. He developed the Chromodisc for treating patients with specific colors and also Solar Elixirs, made by irradiating water with sunlight and filtering it with special filters. He found that the 'sensitized' water had special healing properties



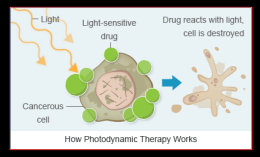
Niels Ryberg Finsen

Red and blue light to treat Lupus Vulgaris

1903 Nobel Prize in Medicine and Physiology

Photodynamic Therapy PDT

- Oscar Raab and Herman von Tappeiner in Germany noted that phototoxic effects on cells could be enhanced with exogenous dyes.
- This field of antimicrobial and, eventually, antitumor phototherapy is termed *photodynamic therapy* (PDT).



Kate Baldwin and Harry Riley Spitler

- Dr. Kate Baldwin, Chief Surgeon at Philadelphia Woman's Hospital: "...after nearly 37 years of active hospital and private practice in medicine and surgery, I can produce quicker and more accurate results with colors than with any or all other methods combined - and with less strain on the patient...".
- Harry Riley Spitler developed the principles of Syntonics (from 'syntony' - to bring into balance) in which light is used to balance the sympathetic and parasympathetic nervous systems. His College of Syntonic Optometry is now at the forefront of developments in ocular phototherapy.
- Spitler is generally considered to be the father of colored light phototherapy

1930s

- (1933) Russian scientist Gurwitsch hypothesised that all cells emitted light. It took until the late seventies before German biophysicists (Popp et al.) proved that every cell emits at least 100.000 light impulses per second at a variety of frequencies.
- Charing Cross Hospital in London used 'sun-lamps' to treat circulatory diseases, anaemia, varicose veins, heart disease and degenerative disorders.

Post – World War II

- Antibiotics

- The Pharmaceutical Industry

- The grip of the *American Medical Association* and the age of the 'clinical trial' had arrived.

AMA
AMERICAN MEDICAL ASSOCIATION

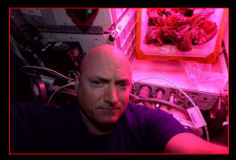
Invention of the LASER

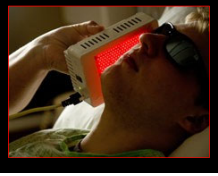
- Einstein postulated stimulated emission of photons in 1917.
- Theodore Maiman built first LASER in 1960
- LASER as precision surgical tool

Endre Mester

- Low-Dose Laser Treatments stimulated wound healing.
- Low-Level Laser Therapy LLLT

NASA: LED Development for Plant Growth and Wound Healing





John Ott

- *John Ott demonstrated that different wavelengths of light have specific influences on cellular function in both plants and animals.*
- *He coined the term 'mal-illumination'*
- *He helped develop the first 'full-spectrum' fluorescent tube and in the early 1970s and undertook a study on the effects of 'full-spectrum' light on school children. Behaviour and academic performance improved markedly.*

Thank You !

DARPA

FIGHT FOR SIGHT

NIH National Eye Institute

NASA

FOUNDATION FIGHTING BLINDNESS

AOIP ADVANCED OCULAR IMAGING PROGRAM

CTSI

McPherson Eye Research Institute UNIVERSITY OF WISCONSIN-MADISON

Mechanisms of Photobiomodulation

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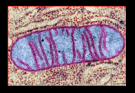
University of Wisconsin-Milwaukee NEUROSCIENCE

UWM UNIVERSITY of WISCONSIN MILWAUKEE



McPherson Eye Research Institute UNIVERSITY OF WISCONSIN-MADISON

Photobiomodulation (aka Low-Level Laser Therapy)

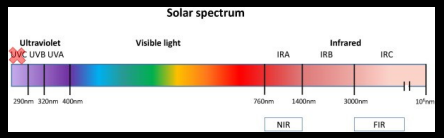
- PBM has been known for nearly 50 years
- *Tiina Karu*
  - Head of Laboratory of Laser Biology and Medicine, Moscow Russia
  - Medical Uses of Lasers

- *Endre Mester*
  - Semmelweis Medical University
  - Ruby laser-induced hair growth

Why has PBM not gained widespread acceptance?

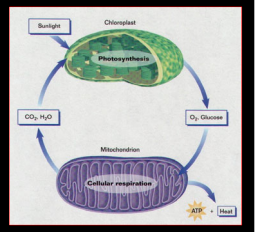
- *Too much like magic*
- *Incomplete understanding of mechanism(s) of action*
- *Pharmaceutical Model of Medicine*

The Solar Spectrum



Photobiomodulation

- *Photobiomodulation* is the process by which a chain of biochemical reactions is triggered by exposure to light
- Photons must be absorbed by a chromophore or photoacceptor molecule
- Photoacceptor molecules include chlorophylls, Vitamin D, rhodopsin, cytochrome c oxidase



PBM in All Life Forms

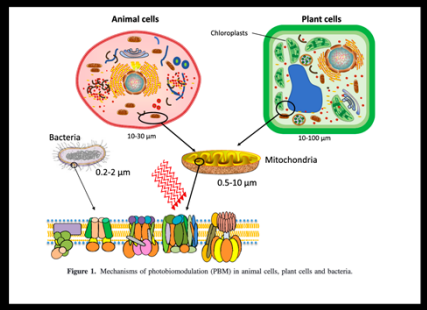


Figure 1. Mechanisms of photobiomodulation (PBM) in animal cells, plant cells and bacteria.

Effect on all Life Forms

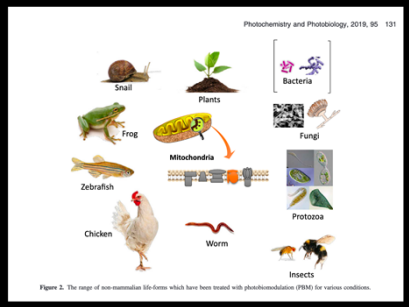
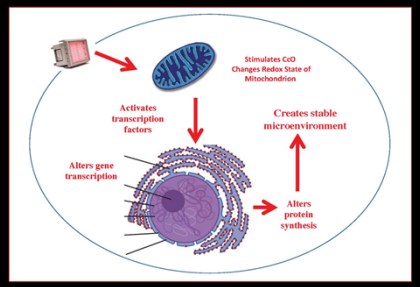


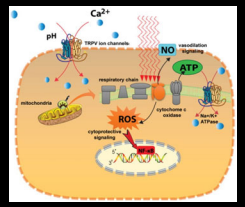
Figure 2. The range of non-mammalian life-forms which have been treated with photobiomodulation (PBM) for various conditions.

FR/NIR Photons Stimulate Mitochondrial Cytochrome c Oxidase and Activate Protective Intracellular Pathways



Chromophores or Photoacceptors

1. Cytochrome c Oxidase
2. Light-Sensitive Ion Channels
3. Direct Actions on Molecules



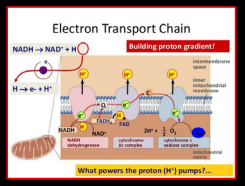
FR/NIR Photons Stimulate Mitochondrial Cytochrome c Oxidase and Activate Protective Intracellular Pathways

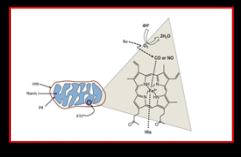
A famous experiment carried out by Otto Warburg uncovered the enzyme responsible for the critical step of cellular respiration which converts the energy conserved in foods to ATP

The enzyme he identified is cytochrome c oxidase (CcO), which is a major player in cellular energy metabolism.

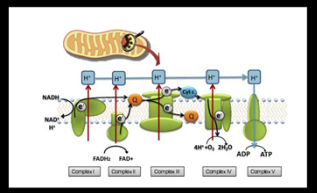
Warburg used a flash of light to displace CO from its binding site on CcO allowing Oxygen to bind and ATP to be made.

Cells frequently use CO and nitric oxide (NO) to block cellular respiration.



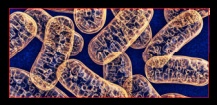


FR/NIR Light Effects on Mitochondrial ETC

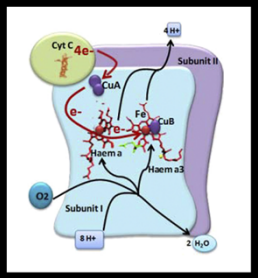


Mitochondrial Dysfunction Plays a Key Role in Cellular Aging and Degenerative Diseases

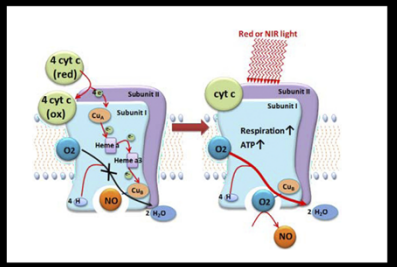
- *Aging*
- *Metabolic Disease*
- *Neurodegenerative Diseases*
- *Cardiovascular Disease and Stroke*
- *Retinal Injury and Disease*



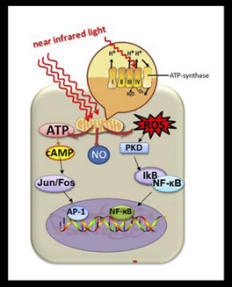
Cytochrome c Oxidase



FR/NIR Light Effect on Cytochrome c Oxiidase



Signaling Mechanisms



Parameters

IRRADIATION PARAMETERS

Irradiation Parameter	Measurement unit	Description
Wavelength	nm	Light is an electromagnetic form of energy with a wave-like behavior. Its wavelength is measured in nanometers (nm), and it is visible within the 400–700 nm range.
Irradiance	W cm^{-2}	It can also be called Power Density or Intensity, and corresponds to the power (in W) divided by the area (in cm^{-2}).
Pulse Structure	Peak Power (W) Pulse frequency (Hz) Pulse width (s) Duty cycle (%)	If the beam is pulsed, the Power should be called Average Power, which is calculated as follows: Average Power (W) = Peak Power (W) x pulse width (s) x pulse frequency (Hz)
Coherence	Coherence length depends on spectral bandwidth	Coherent light produces laser speckle, which is believed to play an important role on photobiomodulation interaction with cells and organelles.
Polarization	Linear polarized or circular polarized	Polarized light is known to lose its polarity in highly scattering media such as biological tissues, therefore this property is not considered very often on the effects of PBM.

LIGHT DOSE PARAMETERS

Irradiation Parameter	Measurement unit	Description
Energy	Joules (J)	It cannot be mistook as dose, as it assumes reciprocity (the inverse relationship between power and time). It is calculated as: Energy (J) = Power (W) x Time (s)
Energy Density	J cm^{-2}	This is a important descriptor of dose, but it could be unreliable when we consider that it assumes a reciprocity relationship between irradiance and time.
Irradiation Time	s	Possibly the best way to prescribe and to record PBM would be to define the four parameters of table 1 and then define the irradiation time as the real "dose".
Treatment Interval	Hours, days or weeks	Different time intervals may result in different outcomes, but more data need to be gathered in order to define the extent of the differences between them.

Thank You !

Unblinded by the Light: NIR Photobiomodulation in Retinal Disease

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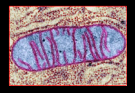

McPherson Eye Research Institute

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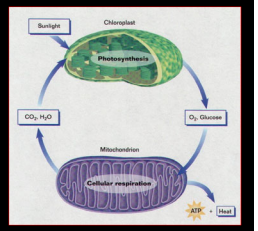
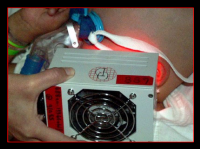


FR/NIR Photobiomodulation From Space Shuttle to Cancer Patients

- NASA funded the development of LEDs for use in plant growth experiments on the space shuttle and international space station

- PBM Improves healing of chemotherapy or radiation-induced mucositis.
  - Frontline Episode



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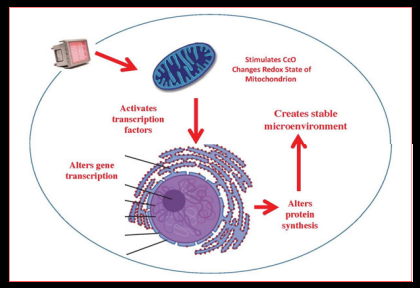

Mitochondrial Dysfunction Plays a Key Role in Cellular Aging and Degenerative Diseases

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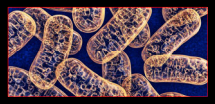
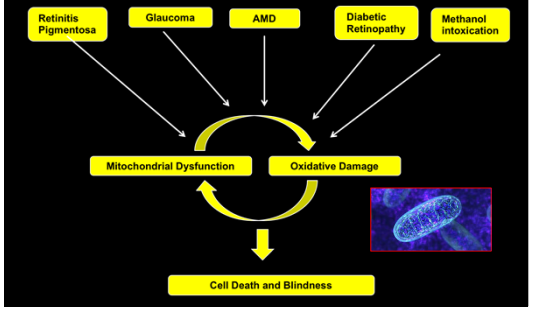
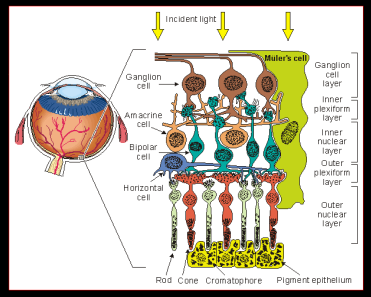


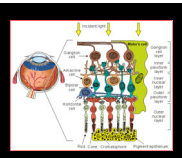
Mitochondrial Dysfunction Plays an Important Role in Retinal Injury and Disease

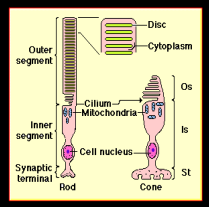


The Retina



Photoreceptors -Vulnerable to Metabolic Inhibition and Oxidative Stress

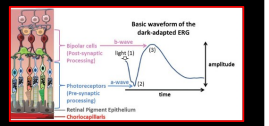




- Most metabolically active cells in body - dark current
- Inner Segment - packed with mitochondria
- Outer segments contain high concentrations of PUFAs subject to lipid peroxidation

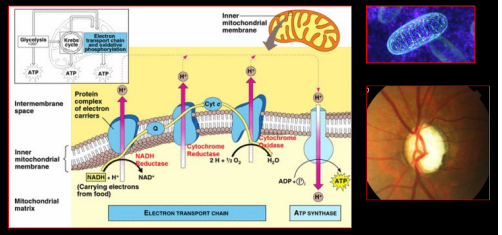
Rodent Models of Retinal Disease

1. Methanol Toxicity
2. Retinitis Pigmentosa
3. Age-Related Macular Degeneration (AMD)

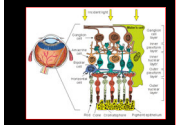


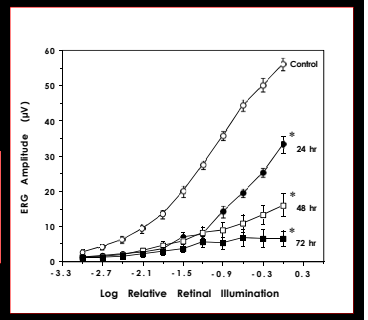
Methanol Intoxication Produces Blindness

Formic Acid, the toxic metabolite in methanol poisoning is a mitochondrial poison



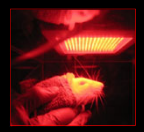
Methanol Intoxication Disrupts Retinal Function

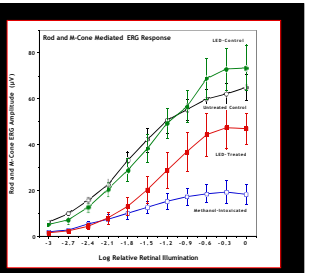


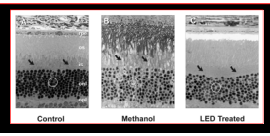


Photobiomodulation Attenuates Methanol Toxicity

670 nm Treatment
At 5 hr, 25hr, 50 hr
25 mW/cm² – 160 sec
4 joules/cm²

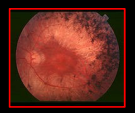


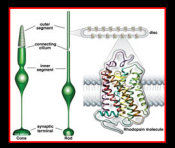




PBM Attenuates Retinal Degeneration in Retinitis Pigmentosa

- Severe retinal degeneration
- Affects 1:4000
- Common cause: Rhodopsin mutations



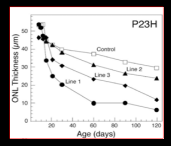


830 nm PBM Ameliorates RP in the P23H Rat

P23HRat Model of RP

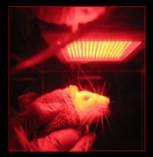
Mutation in Rhodopsin Gene - same as human mutation. – P23H

Rod photoreceptors begin to die during early in development. Death slows into adulthood



Treatment Protocol

Critical Period
From p10 - p25
830nm LED Array
180 sec
25mW/cm² 4.5 J/cm²



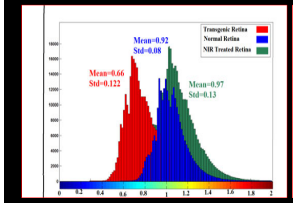
Outcomes at P30

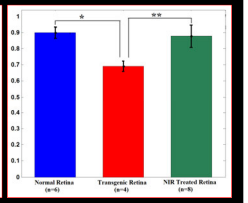
Retinal Metabolic State
Retinal Function
Retinal Morphology

830nm PBM Normalizes Retinal Mitochondrial Function

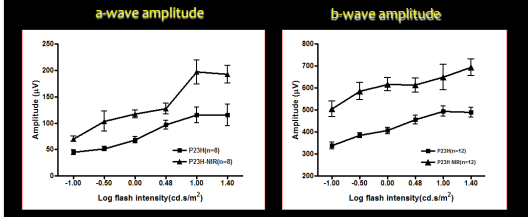
Assessed by NADH/FAD Mitochondrial Redox Cryoimaging

Detects changes in the oxidation state of the mitochondrial respiratory chain

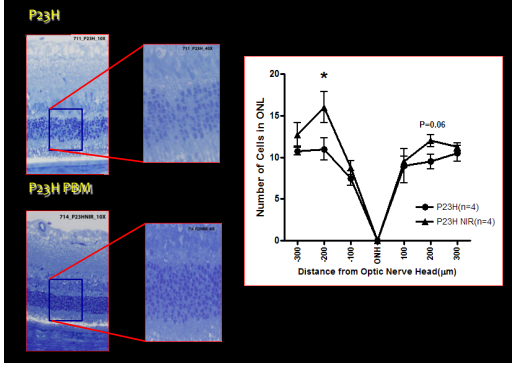




830 nm PBM Protects Retinal Function Assessed by Scotopic ERG

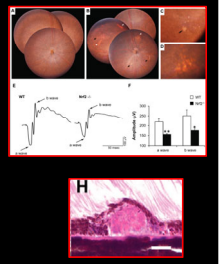


830 PBM Attenuates Photoreceptor Cell Death

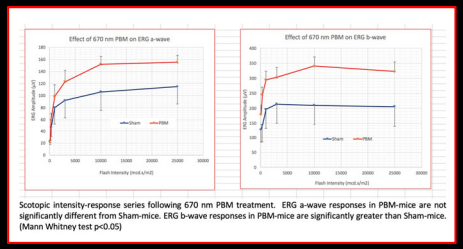


Effect of PBM in Nrf2 knockout Mouse Model of AMD

- Nrf2 knockout mouse
- Nrf2 is a transcription factor that plays a key role in retinal antioxidant and detoxification responses
- *Nrf2 ko Mouse Exhibits AMD-like pathology*
  - RPE degeneration
  - ERG reductions
  - Drusen-like deposits
- PBM daily (4.5 J/cm²) for 12 weeks



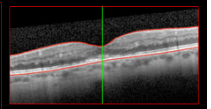
670nm PBM Attenuates Retinal Dysfunction in the Nrf2 ko Mouse Model of AMD



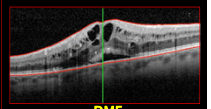
Scotopic intensity-response series following 670 nm PBM treatment. ERG a-wave responses in PBM-mice are not significantly different from Sham-mice. ERG b-wave responses in PBM-mice are significantly greater than Sham-mice. (Mann Whitney test p<0.05)

PBM Attenuates Diabetic Macular Edema

- Complex Pathophysiology of DME
  - Oxidative Stress
  - Elevated VEGF
  - BRB breakdown
- Resulting in extracellular fluid accumulation in macula and decreased vision.
- Treatment : Anti-VEGF injections



Normal Macula

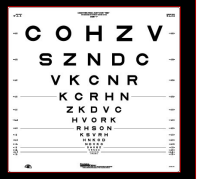


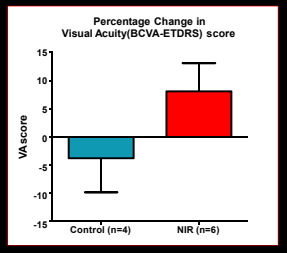
DME
20/200 vision

670 nm Photobiomodulation as a Therapy for Diabetic Macular Edema

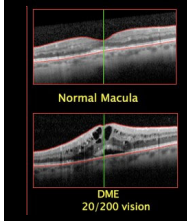
- Treatment Resistant Diabetic patients with clinically significant DME
  - Control:Standard of Care (n = 4)
  - Treated: Standard of Care plus PBM (n = 6)
- PBM Treatment Protocol:
  - LED Array given to patient for treatment
  - Treatment - 90 sec 3 x per week for 8 weeks
- Assessments at Baseline, 8 weeks and 24 weeks
  - Visual Acuity
  - OCT

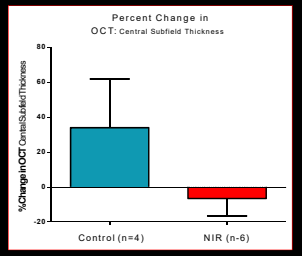
670 nm PBM Improves Visual Acuity in DME





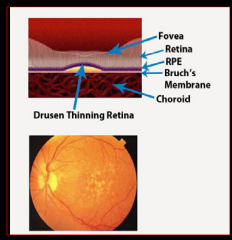
670 nm PBM Decreases Retina Edema in DME



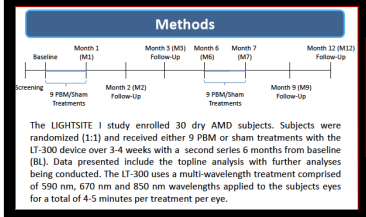


PBM Ameliorates Dry AMD
Age-Related Macular Degeneration

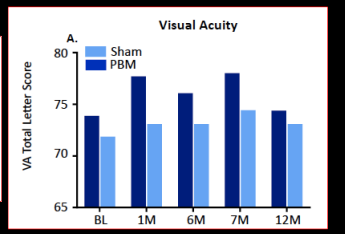
- Leading cause of age-related vision loss
- Complex Pathogenesis
  - Mitochondrial Dysfunction
  - Immune Dysregulation
  - Oxidative Stress



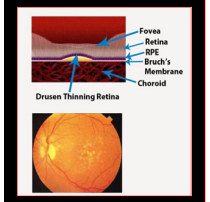
PBM Ameliorates Dry AMD

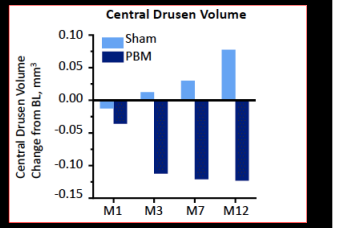


PBM Improves Visual Acuity in AMD

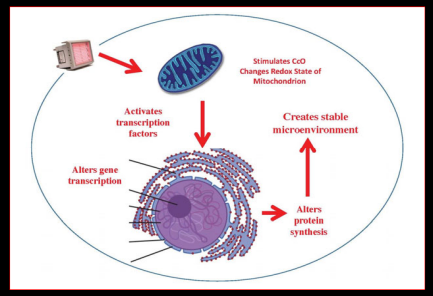


PBM Decreases Drusen Volume in AMD

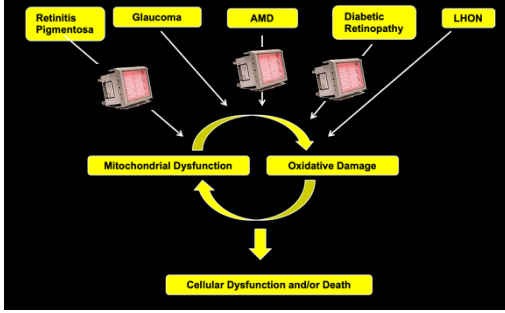




FR/NIR Photons Stimulate Mitochondrial Cytochrome c Oxidase and Activate Protective Intracellular Pathways



Photobiomodulation is Therapeutically Effective in Retinal Disease

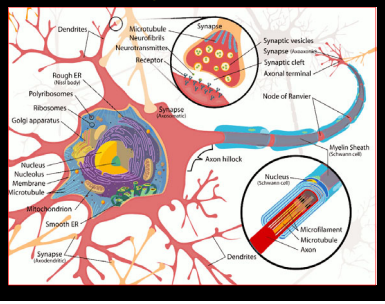


The Pivotal Role of Mitochondrial Dysfunction in Aging and Disease

Janis T. Eells, Ph.D.
Biomedical Sciences
University of Wisconsin-Milwaukee

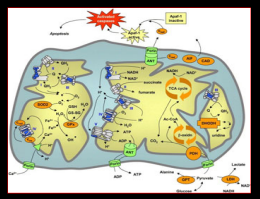
McPherson Eye Research Institute

Population Differences of Mitochondria in a Single Neuron



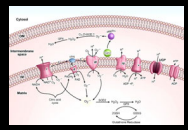
Multiple Roles of Mitochondria

- Energy production
- Generation of ROS
- Metabolic Pathways
- Cell Signaling
- Role in Cell Death

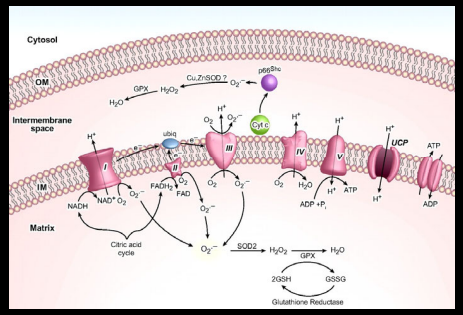


OXPHOS major endogenous source of ROS

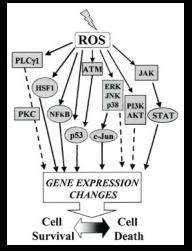
- ROS are toxic byproducts of respiration
- When ETC inhibited electrons accumulate in early stages of ETC and generate superoxide
- Mitochondrial detoxification systems
  - MnSOD
  - GSH and GPx
  - No catalase except in cardiac mito
- Chronic ROS exposure can result in oxidative damage to mito and cellular proteins, lipids and nucleic acids
- Acute ROS exposure can inactivate the Fe-S centers in ETC complexes I, II and III and aconitase resulting in a shutdown of mito energy production.

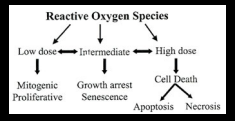


Oxidative phosphorylation, superoxide production, and scavenging pathways in mitochondria



H_20_2 and other ROS are Fundamental Signaling Molecules





Dose determines the effect

Martindale and Holbrook. J Cell Phys 192:1-15, 2002

Mitochondrial H_2O_2 – ROLE IN SIGNALING

- Stimulates Ca^{2+} release
  - ER, Mitochondria
- Activates Transcription Factors
  - AP1 (*fos, jun*), NFκB
- Activates Inflammatory Mediators
  - MCP-1, TNF-α, IL1-β, IL6, IL8.STAT1-α
- Activates Adhesion Molecules
  - ICAM-1, VCAM-1, E-Selectin
- Changes Cell Shape--Mechanotransduction

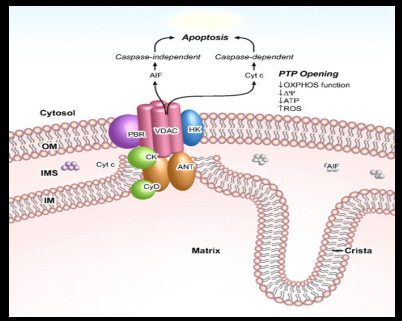
Mitochondrial Dysfunction

1. Mitochondrial dysfunction may be inherited, spontaneous, age-acquired, physiologically regulated, or drug-induced
2. Mitochondrial dysfunction may be transient, fixed, or progressive
3. Mitochondrial dysfunction can cause "any disease, in any organ, at any age"

Mitochondria – major switch for initiation of apoptosis

- switch involves opening of mtPTP
- mito inner membrane contains death promoting factors
  - cyt c
  - AIF – a flavoprotein
  - Caspases
- opening of mtPTP causes collapse of mito membrane potential, swelling of inner membrane and release of death factors
- cyt c activates cytosolic caspase cascade
- AIF – translocates to nucleus - chromatin destruction
- Initiation signals for mtPTP
  - excessive uptake of Ca
  - increased exposure to ROS
- decline in energetic capacity – loss of membrane potential

Mito PTP and Apoptosis



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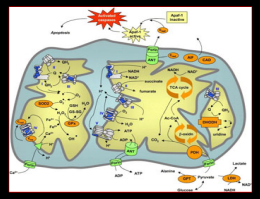
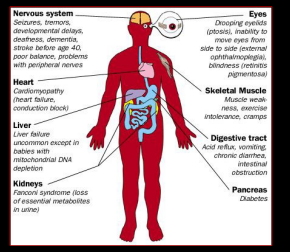


Mitochondrial Disease

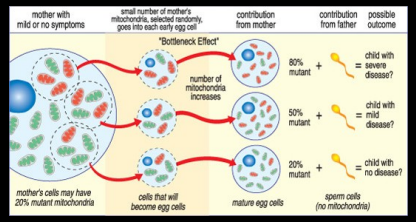
- Mitochondrial defects occur in wide variety of degenerative diseases, aging and cancer
- Commonly involve tissues with high energy requirements
- Genetic and molecular complexity – bewildering array of inheritance patterns



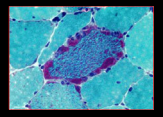
Unique Mitochondrial Features Contributing to Disease

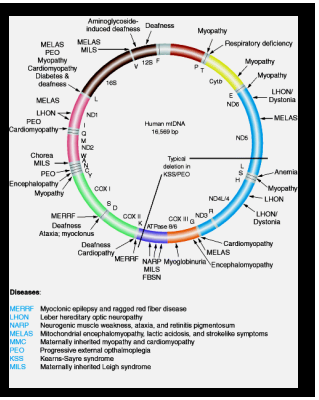
- Polyplasmy - cells contain multiple mitochondria with multiple genomes
- Heteroplasmy – wt mtDNA and mutant mtDNA
- Threshold Effect – critical number of mutant mtDNAs for tissue to become dysfunctional
- Mitotic Segregation – at cell division proportion of mutant mtDNA in daughter cells may vary
- Maternal Inheritance – at fertilization all mtDNA derives from oocyte

Maternal Inheritance of Mitochondrial DNA Mutations



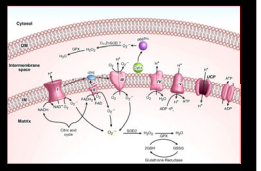
Mitochondrial Mutations Known to Cause Disease

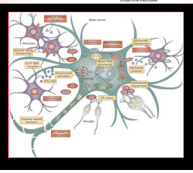




Mitochondrial Theory of Neurodegenerative Disease

- During respiration a small fraction of the oxygen is incompletely reduced by the ETC to form reactive oxygen species (ROS)
- ROS causes oxidative damage to mitochondrial DNA, lipids and proteins.
- These damaged mitochondria with defective respiratory enzymes produce less energy (ATP) and also generate more ROS.
- This vicious cycle operates in an age-dependent manner.





Mitochondrial Theory of Age-Related Degenerative Diseases

- The electron transport chain (ETC) in the inner membrane is actively involved in ATP synthesis coupled respiration.
- During respiration a small fraction of the oxygen is incompletely reduced by the ETC to form reactive oxygen species (ROS) which may cause oxidative damage to mitochondrial DNA, lipids and proteins.
- These damaged mitochondria with defective respiratory enzymes produce less energy (ATP) and also generate more ROS.
- This vicious cycle operates in an age-dependent manner.
- Environmental toxins also contribute to mitochondrial damage.

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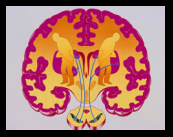
- This vicious cycle operates in an age-dependent manner.
- Environmental toxins also contribute to mitochondrial damage.

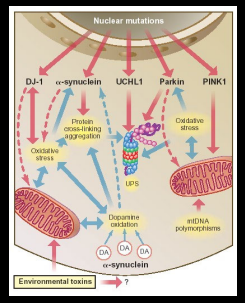
Parkinson's Disease

- clinical characteristics – bradykinesia, rigidity, tremor
- pathology – degeneration of Dopaminergic neurons in SN
- Genetic component
- Mitochondrial involvement
  - complex I deficiency in SN
  - not known if neurons more affected than glia
  - GSH depletion
  - Complex I deficiency
- Environmental Factors
  - MPTP story
  - TIQ
  - Rotenone



Pathogenesis of PD

- *Genetic Mutations*
  - *Alpha-synuclein*
- *Environmental Toxins*
  - *MPTP*
  - *Pesticides*
- *Common theme:*
  - *Protein mishandling*
  - *Oxidative stress*
  - ***Mitochondrial dysfunction***



Greenamyre et al., (2004) Science 304, 1120-1122.

The end