The dynamic control of mitochondrial function

Mitohealth Workshop, Bergen, Nov 8-9 2008
KJ Tronstad
1. Mitochondrial physiology => Human physiology

2. Modulation of mitochondrial bioenergetics in leukemia cells
Mitochondrial features

Energy production

- Enzyme content and activity (ETC, TCA, β-ox, etc…)
- Metabolite flow
- Membrane potential and integrity
- OXPHOS (ATP synthesis)
Mitochondrial features

Morphology:
- Mass (Biogenesis)
- Structural features
  (size, number, complexity – fission/fusion)
- Localization
Mitochondrial features

Cellular interactions
- Reactive oxygen species (ROS) (by-products or specific?)
- Signalling (Energy status, Stress, Cell death, Ca^{2+}, Oxygen level)
“Mitochondria Make a Comeback”

From special issue: Science, March 1999

"Mitochondria" reports (PUBMED)

Number of reports


Number of reports: 0, 1000, 2000, 3000, 4000, 5000, 6000
Forefront fields:

- Disease/medicine
- Lifestyle
- Cell death
- Evolution
- Forensic science
"Mitomedicine"???

• What is a "good" mitochondrial phenotype?
• Can this be obtained by treatment/lifestyle?
• Is it good to stimulate mitochondrial changes?

Some examples…
Ageing: Blame the damaged mitochondria


Wallace DC. 2005. 

www.uib.no
Resveratrol Improves Mitochondrial Function and Protects against Metabolic Disease by Activating sirt1 and PGC-1α

Marie Lagouge, Carmen Argmann, Zachary Gerhart-Hines, Hamid Meziane, Carles Lerin, Frederic Daussin, Nadia Messaedi, Jill Milne, Philip Lambert, Peter Elliott, Bernard Geny, Markku Laakso, Pere Puigserver, and Johan Auwerx

Resveratrol (in mice)
- enhanced mitochondrial respiration (more mitos)
- enhanced endurance
- higher body temperature during cold test
- related to lifespan extension
Increased substrate oxidation and mitochondrial uncoupling in skeletal muscle of endurance-trained individuals

Douglas E. Befroy*, Kitt Falk Petersen*, Sylvie Dufour†, Graeme F. Mason†, Douglas L. Rothman†, and Gerald I. Shulman*‡‡‡

Endurance training
- increased TCA rates
- unchanged ATP level
⇒ Suggests uncoupling
The pathway to long life

Caloric restriction

Activation of stress pathways

Altered metabolism/O₂ consumption

Altered nicotinamide concentration and/or NAD⁺/NADH ratio

Polyphenols

Activation of Sir2

Prolonged lifespan

“Mitochondrial enhancement”

“Wonder drug”
An agent that simulate lack of energy even if there is enough nutrients

“Metabolic flexibility”

“the capacity to switch from predominantly lipid oxidation and high rates of fatty acid uptake during fasting conditions to the suppression of lipid oxidation and increased glucose uptake, oxidation, and storage under insulin-stimulated conditions”

Kelley and Mandarino, Diabetes, 2000

“Metabolic flexibility is the capacity for the organism to adapt fuel oxidation to fuel availability.”

Patients with type 2 diabetes have normal mitochondrial function in skeletal muscle

R. Boushel • E. Gnaiger • P. Schjerling • M. Skovbro •
R. Kraunsoe • F. Dela

- Reduced oxygen consumption rates
- Reduced mitochondrial content

"Mitochondrial function is normal in type 2 diabetes. Blunting of coupled and uncoupled respiration in type 2 diabetic patients can be attributed to lower mitochondrial content."
MtDNA haplogroup H was a strong independent predictor of outcome during severe sepsis, …
What is "Mitochondrial Function"?
Mitochondrial mass (biogenesis) → Oxidative rates (TCA, β-oxidation, etc) → Respiration (ETC) → OXPHOS → ATP vs ADP and AMP → Energy status → feedback → Energy demand → Mitochondrial mass (biogenesis)
Mitochondrial Function?

What would be an improvement in mitochondrial function...more ATP???

More mitochondria?
(biogenesis)

Increased oxidation?
(fat etc)

Increased respiration?

Increased OXPHOS?

More ATP?
Increased oxidation, steady ATP....???

Mitochondrial mass (biogenesis)

Oxidative rates (TCA, β-oxidation, etc)

Respiration (ETC)

"Uncoupling"

Heat

Energy status

feedback

OXPHOS

ATP vs ADP and AMP
Adjustments in metabolism/signalling…?

Cellular Interactions:
- Nutrient flow
- Other ATP sources
- ROS production
- Signalling events
Mitochondrial manipulation

- **Diet Restriction**
  - metabolic adaptation/compensation
  - glucose deprivation
  - respiratory substrates

- **Targeted Strategies**
  - inhibition/activation (OXPHOS, glycolysis)
  - activation of mitochondrial biogenesis (AMPK, PPARs)
Energy state and uncoupling

Fatty acid oxidation  Oxygen consumption  Energy charge

Grav et al, JBC, 2003
Mitochondria and cancer

Glucose → Pyruvate (secr.) → CO₂ + H₂O

Tumor cell mitochondria

High in tumors → FDG-PET imaging

Low in tumors (?) → implications?
Low respiration may support:

- Adaptation to hypoxic environment
- Abnormal expression of metabolic enzymes
- Reactive oxygen species (ROS)
- Acidification of tumour microenvironment
HIF-1 mediates expression of pyruvate dehydrogenase kinase: A metabolic switch required for cellular adaptation to hypoxia
Jung-whan Kim, Irina Tchernyshyov, et al
Cell Metabolism, Vol 3, 177-185, March 2006

HIF-1 mediates adaptation to hypoxia by actively downregulating mitochondrial oxygen consumption
Ioanna Papandreou, Rob A. Cairns, et al
p53 Regulates Mitochondrial Respiration

Satoaki Matoba,¹ Ju-Gyeong Kang,¹ Willmar D. Patino,¹ Andrew Wragg,¹ Manfred Boehm,¹ Oksana Gavrilova,² Paula J. Hurley,³ Fred Bunz,³ Paul M. Hwang³,*

The energy that sustains cancer cells is derived preferentially from glycolysis. This metabolic change, the Warburg effect, was one of the first alterations in cancer cells recognized as conferring a survival advantage. Here, we show that p53, one of the most frequently mutated genes in cancers, modulates the balance between the utilization of respiratory and glycolytic pathways. We identify Synthesis of Cytochrome c Oxidase 2 (SCO2) as the downstream mediator of this effect in mice and human cancer cell lines. SCO2 is critical for regulating the cytochrome c oxidase (COX) complex, the major site of oxygen utilization in the eukaryotic cell. Disruption of the SCO2 gene in human cancer cells with wild-type p53 recapitulated the metabolic switch toward glycolysis that is exhibited by p53-deficient cells. That SCO2 couples p53 to mitochondrial respiration provides a possible explanation for the Warburg effect and offers new clues as to how p53 might affect aging and metabolism.

Science 16 June 2006:
Vol. 312. no. 5780, pp. 1650 - 1653
mtDNA and metastasis

ROS-Generating Mitochondrial DNA Mutations Can Regulate Tumor Cell Metastasis

Kaori Ishikawa,1,2,3* Keizo Takenaga,4,5* Miho Akimoto,5 Nobuko Koshikawa,4 Aya Yamaguchi,1 Hirotake Imanishi,1 Kazuto Nakada,1,2 Yoshio Honma,5 Jun-Ichi Hayashi1†

“We used cytoplasmic hybrid (cybrid) technology to replace the endogenous mtDNA in a mouse tumor cell line that was poorly metastatic with mtDNA from a cell line that was highly metastatic, and vice versa.”

“These results indicate that mtDNA mutations can contribute to tumor progression by enhancing the metastatic potential of tumor cells.”

Science, 2008: Vol. 320. no. 5876, pp. 661 - 664
Mitochondria and cancer

*Mitochondrial dysregulation appears to parallel the high glucose requirements in tumor cells*

=> *mitochondrial properties may be potential biomarkers of cancer and/or unique targets for novel and selective anti-cancer therapy*
Energy sensor systems

Mitochondrial effects:
- biogenesis
- function
- signalling
- permeability transition

Nutritional status

Hypoxia

HIF-1 → TSC → Akt → LKB1 → HK → PPARs

mTOR → p53

Cellular energy status

Autophagy
Protein synthesis
Angiogenesis
Cell cycle
Proliferation
Cell death

"Proof of principle?"

TTA – tetradecylthioacetic acid

Stimulates mitochondrial energy metabolism

Leukaemia

Diets:
- Lard
- n-3 PUFA
- TTA

Berge RK et al. 2001
Iversen PO et al. 2006

Glioma

% survival

Days after implantation

0 20 40 60 80 100
10 12 14 16 18 20 22

Palmitic acid
- TTA

Berge RK et al. 2001
TTA-induced apoptosis

Cytochrome c

Glutathione

ΔΨ

Caspase-3

TTA

Tronstad et al., Chemistry & Biology, 2003
Glucose \rightarrow \text{Pyruvate} \rightarrow \text{Lactate (secr.)}

\text{High in tumors} \rightarrow \text{FDG-PET imaging}

\text{Low in tumors (?)} \rightarrow \text{implications ?}

\text{Tumor cell energy metabolism}

\text{Mitochondria and cancer}
Multiparameter image analysis

### Mitoch. parameters (arbitrary units)

- **Number**: 32, 59, 44
- **Total mitochondrial mass**: 2145, 4043, 3143
- **Degree of mitochondrial branching**: 1.89, 2.23, 2.15
- **Integrated cellular intensity (Δψ)**: 6595.5, 11593.5, 8955.3
- **Average mitochondrial intensity (Δψ)**: 206.1, 196.5, 203.5

Connection? - function and structure
Some remaining questions

- Mechanisms of mitochondrial adaptations to nutrient overload?
- Signals and modulators of mitochondrial biogenesis?
- Geno/phenotypes - function - disease?
- Targets for mitochondrial modulation?
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