[4/18/2008(Fri) 10:35~11:10/1st FL)]

Mitochondria Control Protein as a Novel Therapeutic Target for Metabolic Syndrome

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Mitochondria biogenesis requires a coordination of two genomes, nuclear DNA (nDNA) and mitochondrial DNA (mtDNA). Disruption of mitochondria function leads to a loss of mitochondrial membrane potential and ATP generating capacity and consequently results in chronic degenerative diseases including insulin resistance, metabolic syndrome and neurodegenerative diseases. Although PPAR-γ coactivator-1α (PGC-1 α) was discovered as a central regulator of mitochondria biogenesis and a transcriptional co-activator of nuclear respiratory factor (NRF) and mitochondrial transcription factor A (Tfam), the expressions of PGC-1α, NRF and Tfam were not significantly altered in tissues showing abnormal mitochondria functions. This observation suggests that there should be another regulator(s) for mitochondria function. Here, we demonstrate microRNAs (miRNAs) can modulate mitochondria function. Overexpression of microRNA dissipated mitochondrial membrane potential and increased ROS production in vitro and in vivo. It will be discussed the target of microRNA and its role in metabolic syndrome.

Mitochondria control protein as a novel therapeutic target for metabolic syndrome

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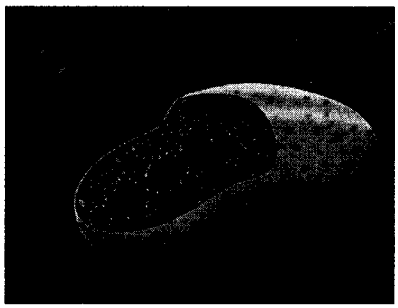
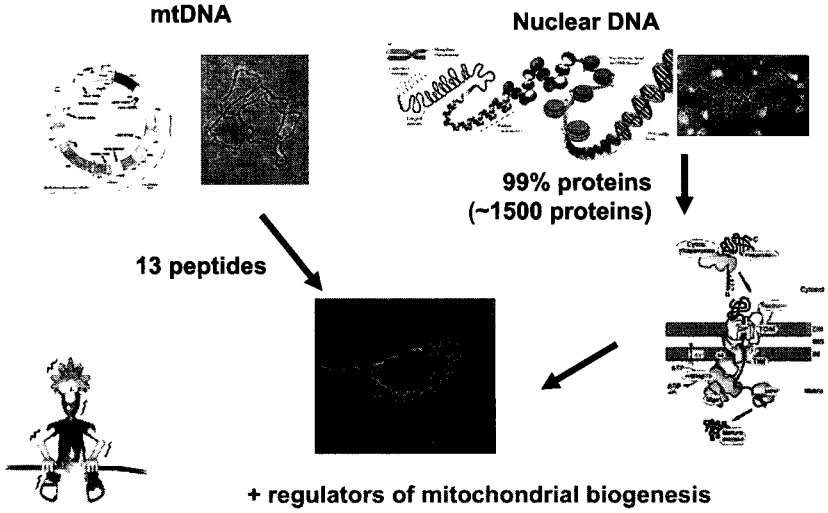
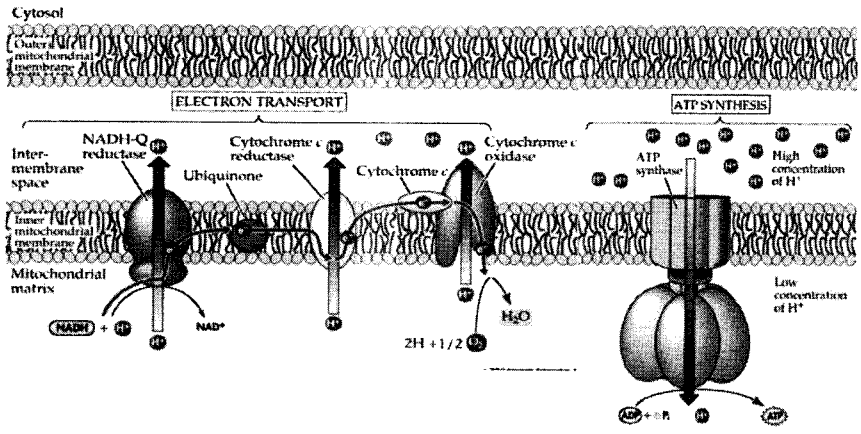


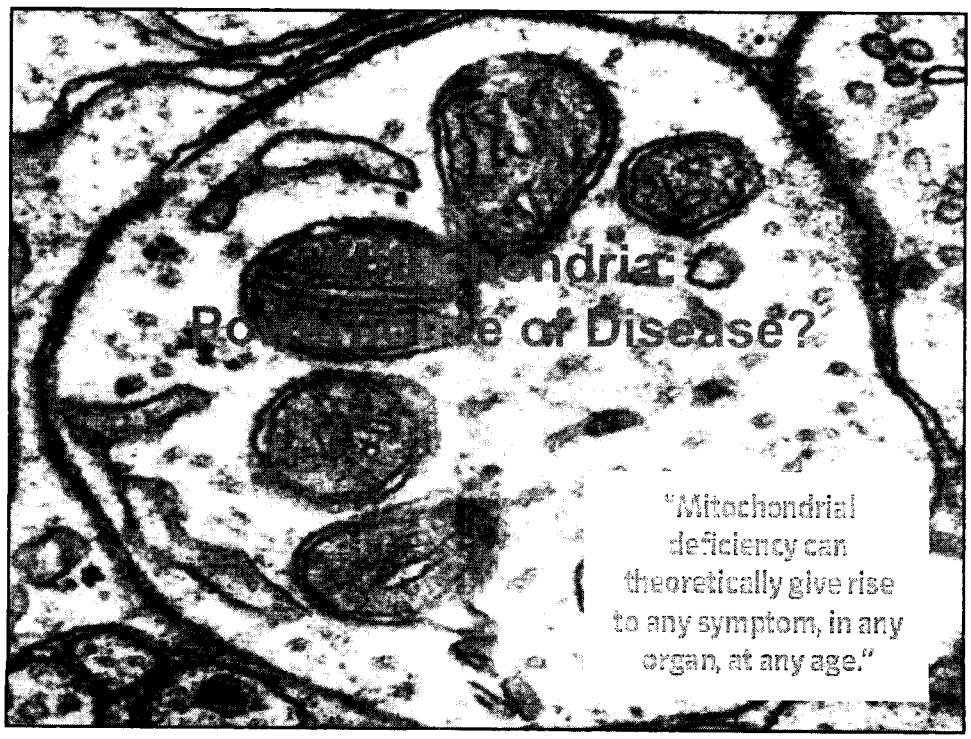
Mitochondria: Two genes, one organelle



Mitochondria : Powerhouse of the cell

oxidative phosphorylation (OXPHOS) reaction



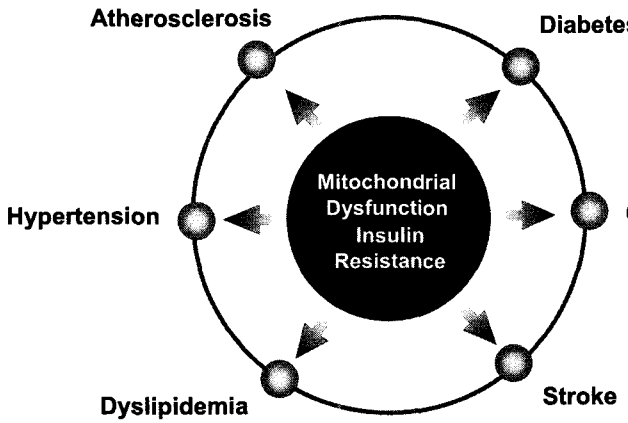


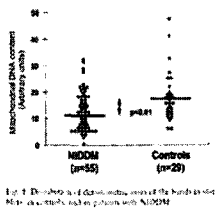
Metabolic Syndrome

- **Syndrome X = Insulin resistance syndrome**
  = Dysmetabolic syndrome
  = Metabolic syndrome
- **Deadly quartet**
  - **Upper body obesity**
  - **Hypertriglyceridemia**
  - **Hypertension**
  - **Hyperglycemia**
- **CHAOS**
  - **Coronary artery disease**
  - **Hypertension**
  - **Adult-onset diabetes mellitus**
  - **Obesity**
  - **Stroke**

Venus of Willendorf
c. 24,000-22,000 BCE
Oolitic limestone
11.1 cm high
(Naturhistorisches Museum, Vienna)

Insulin Resistance & Mitochondria





Insulin Resistance & Mitochondria

From Science 300, 1140-1142, 2003

Mitochondrial Dysfunction in the Elderly: Possible Role in Insulin Resistance

Kitt Falk Petersen,[1] Douglas Befroy,[1,7] Sylvie Dufour,[1,7] James Dziura,[1] Charlotte Ariyan,[3] Douglas L. Rothman,[4] Loretta DiPietro,[5,6] Gary W. Cline,[1] Gerald I. Shulman[1,2,7]*

Table 2. Metabolic rates and tissue lipid content of participants (*24*).

	Basal rates of glucose production (mg/kg of LBM/min)	Clamp peripheral glucose metabolism rate (mg/kg of LBM/min)	Intramyocellular lipid content (%)	Intrahepatic lipid content (%)	Mitochondrial TCA flux rate (nmol/g of muscle/min)	Mitochondrial ATP synthesis rate (μmol/g of muscle/min)
Young	2.3 ± 0.1	6.2 ± 0.6	0.96 ± 0.08	0.49 ± 0.10	96 ± 10	7.50 ± 0.77
Elderly	2.4 ± 0.1	4.0 ± 0.4	1.39 ± 0.15	1.61 ± 0.38	62 ± 5	4.06 ± 0.65
P value	0.34	<0.002	0.035	0.036	<0.006	<0.004

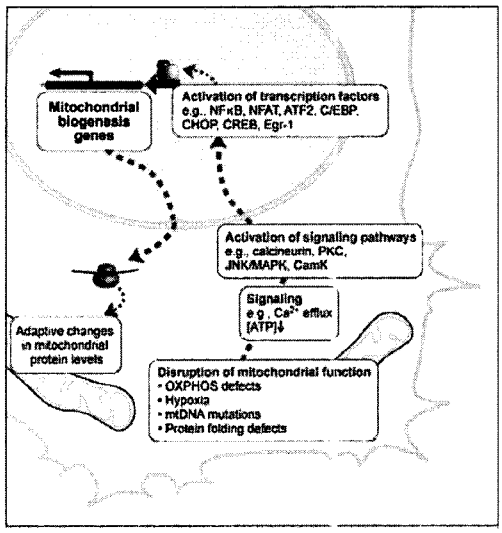
Hypothesis

The mitochondrial dysfunction causes metabolic syndrome

"Faulty mitochondria may well be the cause of diabetes, but we still don't know what makes them faulty."

Mitochondrion is the novel therapeutic target for metabolic syndrome

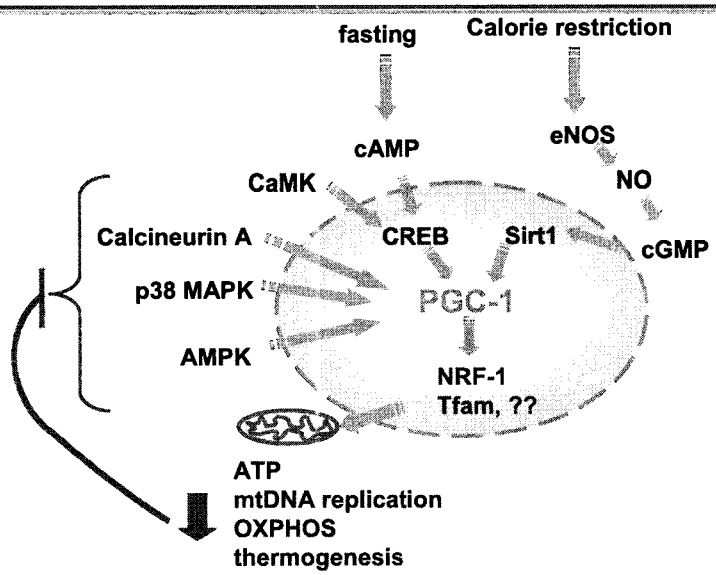
Model for retrograde signaling in mitochondrial stress pathways



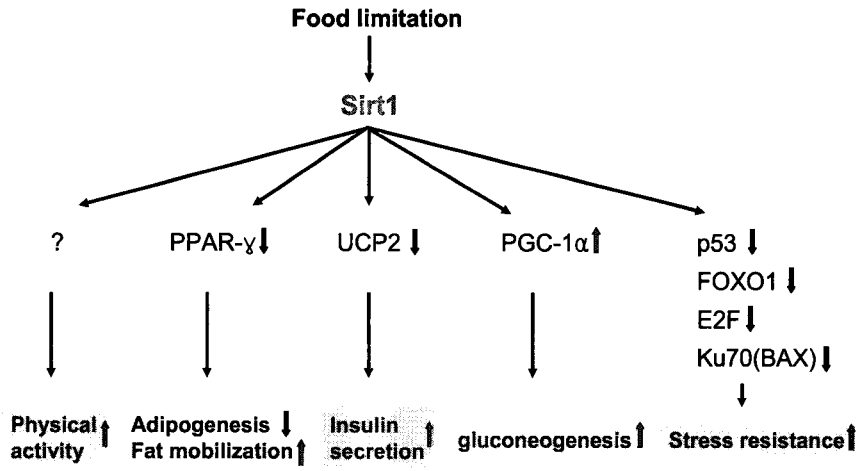
Ryan MT, Hoogenraad NJ. 2007.
Annu. Rev. Biochem. 76:701–22

Mitochondria dysfunction
(loss of $\Delta\Psi_m$ and ATP)
↓
Release of Ca^{2+}
from mito to cyto
↓
Calcium sensitive signaling
↓
Activation of TFs
↓
Nuclear gene transcription

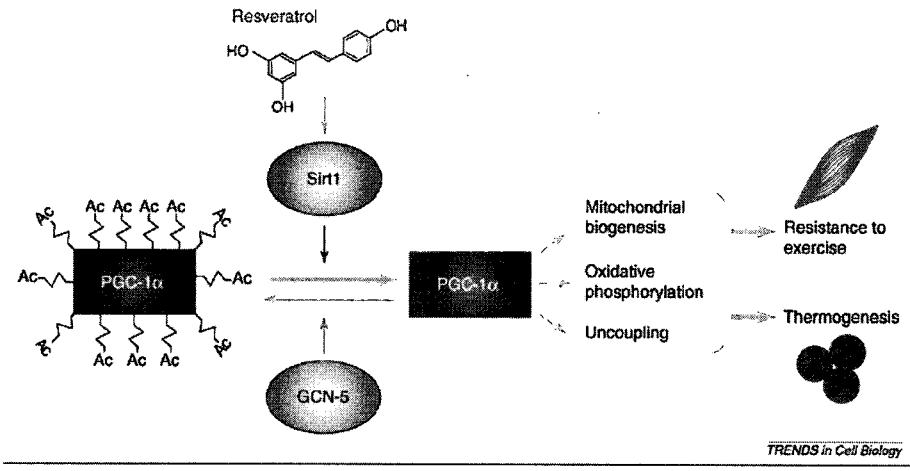
Mitochondria modulator(s)



SIRT1 is implicated in many mammalian CR responses



Resveratrol promotes mitochondrial functions through Sirt-1-mediated deacetylation of PGC-1α



Is there any other novel mitochondria modulator(s)?

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