
NMI
SUMMIT
2024
An Energetic View:
Mitochondrial Nutrition
for Fatigue, the Brain,
& Healthy Ageing
Friday 11th October
Featuring Professor Nick Lane, Dr. Iain Hargreaves, Dr. Joseph Pizzorno,
Dr. Nina Fuller-Shavel, Dr. Deanna Minich and Benjamin Brown
An event by:
Nutritional Medicine Institute
Platinum sponsors:
regenerus labs
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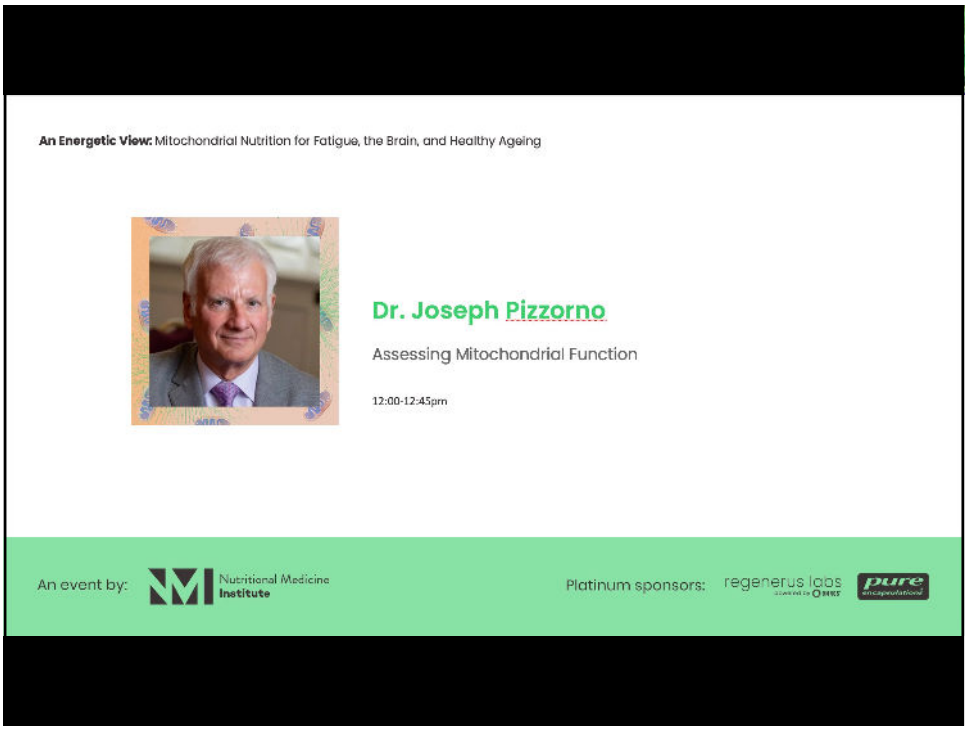
An Energetic View: Mitochondrial Nutrition for Fatigue, the Brain, and Healthy Ageing
Dr. Joseph Pizzorno
Assessing Mitochondrial Function
12:00-12:45pm
An event by:
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Mitochondria: Assessment & Metabolites

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Founding President, Bastyr University
Editor-in-Chief, *Integrative Medicine: A Clinician's Journal*
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Disclosure

Dr. Pizzorno is on the Scientific Advisory Board for Bioclinic Naturals which sells dietary supplements for healthcare professionals. No BCN products are recommended in this lecture.

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Overview

- Mitochondrial Function
- Clinical Assessment
- Laboratory Assessment
  - Direct
  - Indirect
  - Damage
- Insights into mitochondrial metabolites
- Summary

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Assessment of Function

- Clinical
  - Diseases
  - Symptoms
- Laboratory
  - Lactate and pyruvate are elevated when mitochondrial function is substantially impaired—late and indirect measure
  - Direct measurement of ATP production currently only available in research settings
  - 8-OHdG measure of nuclear and mtDNA damage

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Factors Determining Mitochondrial Function

- Genetics
  - mtDNA damage
- Nutritional status
- Toxic load
- Muscle mass
- Age

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Prevalence of Mitochondrial Dysfunction

- “Officially” 1/5,000 worldwide
- Only includes genetic mitochondriopathies
  - Leigh Syndrome
  - NARP (Neuropathy, ataxia, and retinitis pigmentosa)
  - MERRF (Myoclonus epilepsy with ragged red fibers)
  - MNGIE (Mitochondrial neurogastrointestinal encephalomyopathy)
  - MELAS (Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)

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Is Mitochondrial Dysfunction Truly Rare?

- "Fatigue" one of the most common complaints in primary care?
  - 5-7% of visits

Kathryn Nicholson, Moira Stewart, Amardeep Thind - Examining the symptom of fatigue in primary care: a comparative study using electronic medical records: BMJ Health & Care Informatics 2015;22:.

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Clinical Indications of Mitochondrial Dysfunction

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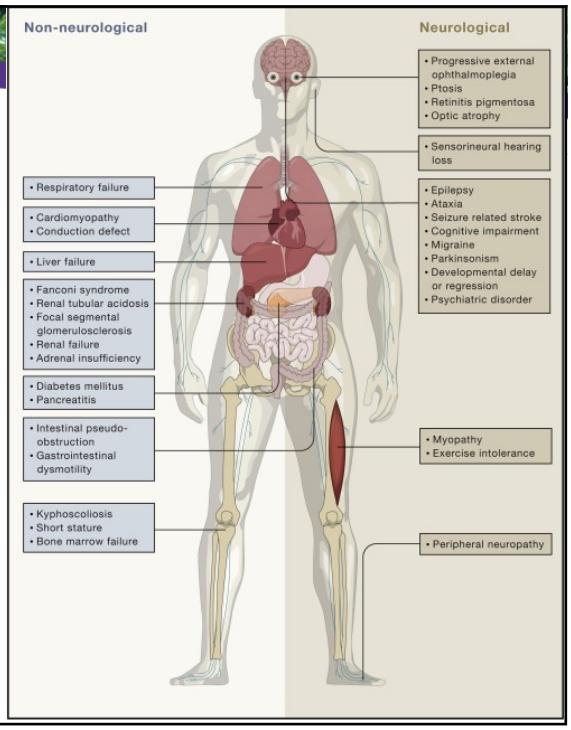
Mitochondrial Diseases



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Acquired Conditions Associated with Mitochondrial Dysfunction

Aging and senescence (Wallace, 2005, Savitha et al., 2005, Skulachev and Longo, 2005, Corral-Debrinski et al., 1992, Ames et al., 1993)
Alzheimer's disease (Stavrovskaya and Kristal, 2005)
Anxiety disorders (Einat et al., 2005)
Atherosclerosis (Puddu et al., 2005)
Bipolar disorder (Stork and Renshaw, 2005, Fattal et al., 2006)
Cancer (Wallace, 2005)
Cardiovascular disease (Fosslien, 2001)
Diabetes (Wallace, 2005, Fosslien, 2001, West, 2000)
Exercise intolerance (Conley et al., 2000)
Fatigue, chronic fatigue syndrome (Fulle et al., 2000, Buist, 1989)
Fibromyalgia (Park et al., 2000, Yunus et al., 1988)
Hepatitis-C virus-associated hepatocarcinogenesis (Koike, 2005)
Huntington's disease (Stavrovskaya and Kristal, 2005)
Myofascial pain (Yunus et al., 1988)
Nonalcoholic steatohepatitis (Lieber et al., 2004)
Parkinson's disease (Stavrovskaya and Kristal, 2005)
Sarcopenia (Bua et al., 2002)
Schizophrenia (Fattal et al., 2006)

Pieczenik SR, Neustadt J. Mitochondrial dysfunction and molecular pathways of disease. Exp Mol Pathol. 2007;83(1):84-92

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Signs and Symptoms Mitochondrial Dysfunction

Organ System	Possible Symptom or Disease
Muscles	Hypotonia, weakness, cramping, muscle pain, ptosis, opthalmoplegia
Brain	Developmental delay, mental retardation, autism, dementia, seizures, neuropsychiatric disturbances, atypical cerebral palsy, atypical migraines, stroke, and stroke-like events
Nerves	Neuropathic pain and weakness (which may be intermittent), acute and chronic inflammatory demyelinating polyneuropathy, absent deep tendon reflexes, neuropathic gastrointestinal problems (gastroesophageal reflux, constipation, bowel pseudoobstruction), fainting, absent or excessive sweating, aberrant temperature regulation
Kidneys	Proximal renal tubular dysfunction (Fanconi syndrome); possible loss of protein (amino acids), magnesium, phosphorus, calcium, and other electrolytes
Heart	Cardiac conduction defects (heart blocks), cardiomyopathy
Liver	Hypoglycemia, gluconeogenic defects, nonalcoholic liver failure
Eyes	Optic neuropathy and retinitis pigmentosa
Ears	Sensorineural hearing loss, aminoglycoside sensitivity
Pancreas	Diabetes and exocrine pancreatic failure
Systemic	Failure to gain weight, short stature, fatigue, and respiratory problems including intermittent air hunger

Pieczenik SR, Neustadt J. Mitochondrial dysfunction and molecular pathways of disease. Exp Mol Pathol. 2007;83(1):84-92

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Examples of Mitochondrial Dysfunction

- ASD
- COVID-19
- Cancer

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Mitochondrial Dysfunction in Autism

- 60% lower NADH oxidase
- 60% lower PDH
- Many dysfunctional Complexes; I most common
  - 60% lower Complex I

Giulivi C, Zhang Y, Omanska-Klusek A, et al. Mitochondrial Dysfunction in Autism. JAMA. 2010;304(21):2389–2396

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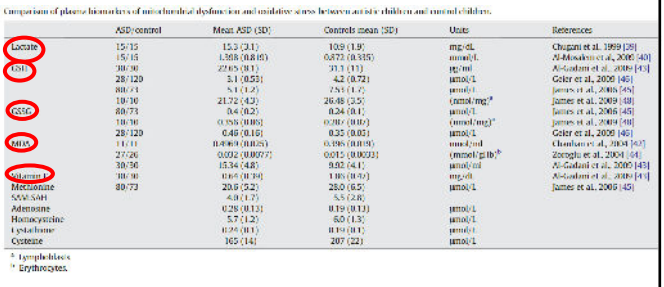
Mitochondrial Dysfunction in Autism

- Lactate: 50% higher
- GSH: 30% lower
  - GSSG: 60% higher
- MDA: 25% higher
- Vitamin E: 66% lower



Palmieri L, Persico AM. Mitochondrial dysfunction in autism spectrum disorders: Cause or effect? Biochimica Biophysica Acta 1797;2010, 1130–7

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Mitochondrial Dysfunction in Autism

- Lactate triple
- Elevated liver enzymes
- Slow Complex I

Table 5 Comparison of mean and SD for biochemical parameters among ASD cases and controls

Biochemical parameters	ASD cases (174)			Control (174) Levels mean ± SD	Chi square X^2	*p* value
	Mild ($n = 57$) Levels mean ± SD	Moderate ($n = 98$) Levels mean ± SD	Severe ($n = 19$) Levels mean ± SD			
Lactate levels	3.5 ± 0.1	3.6 ± 0.1	3.6 ± 0.1	1.2 ± 0.1	2.23	0.5
L:P ratio	13.7 ± 1.8	13.5 ± 1.6	13.4 ± 2.2	19.9 ± 0.2	31.0	< 0.0008*
ALT levels	58.3 ± 1.1	59.6 ± 2.5	58.6 ± 1.2	39.2 ± 6.0	68.9	< 0.0007*
AST levels	38.6 ± 1.5	38.9 ± 1.8	37.9 ± 1.5	19.2 ± 4.9	34.7	< 0.0001*
Serotonin levels	153.5 ± 1.4	153.9 ± 1.5	153.6 ± 1.5	130.1 ± 1.3	222.0	< 0.0007*

Normal levels of lactate, 1.1–2.4 mmol/L; L:P ratio, 20; ALT, 7–56U/L; AST, 5–34U/L; serotonin, 50–149 ng/L
High levels of lactate, > 2.5 mmol/L; L:P ratio, > 20; ALT, > 56U/L; AST, > 35U/L; serotonin, 150–200 ng/L
*p value less than 0.05. *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *L:P ratio*, lactate, pyruvate ratio

Mahalaxmi I, Subramaniam MD, Gopalakrishnan AV, Vellingiri B. Dysfunction in Mitochondrial Electron Transport Chain Complex I, Pyruvate Dehydrogenase Activity, and Mutations in ND1 and ND4 Gene in Autism Spectrum Disorder Subjects from Tamil Nadu Population, India. Mol Neurobiol. 2021;58(10):5303-5311

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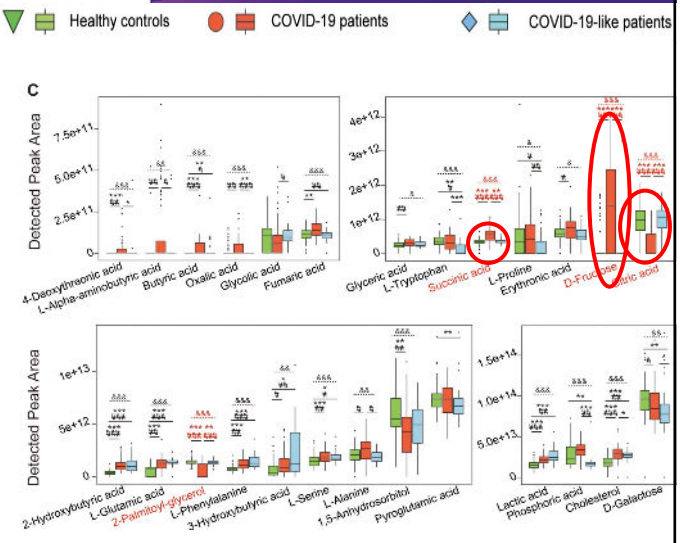
Mitochondrial Dysfunction in COVID

- Elevated:
  - D-fructose
  - Lactate
  - Succinic acid
- Decreased:
  - Citric acid



Shi D, Yan R, Lv L, et al. The serum metabolome of COVID-19 patients is distinctive and predictive. Metabolism. 2021;118:154739. Elsevier COVID free use

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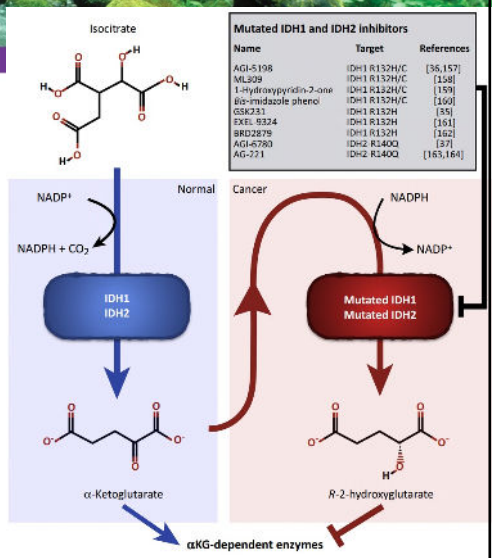
Mitochondrial Dysfunction in Cancer

- Hallmark of cancer
  - Point mutations
  - Copy number changes
- Abnormal
  - Pyruvate dehydrogenase complex
  - Isocitrate dehydrogenase
- Dysfunctional
  - Succinate dehydrogenase
  - Fumarate hydratase



Hsu CC, Tseng LM, Lee HC. Role of mitochondrial dysfunction in cancer progression. Exp Biol Med (Maywood). 2016;241(12):1281-95
M Gagné L, Boulay K, Topisirovic I, Huot MÉ, Mallette FA. Oncogenic Activities of IDH1/2 Mutations: From Epigenetics to Cellular Signaling. Trends Cell Biol. 2017;27(10):738-752.

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Laboratory Assessment of Mitochondrial Dysfunction

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Direct Measures

- Only available in research laboratories
- Several methodologies
  - Staining cells with molecules that fluoresce in proportion to ATP production
  - Measuring mitochondrial membrane potential

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Indirect Measures

- Blood molecules
- Urinary metabolites

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Blood Molecules to Assess Mitochondrial Function

Molecule	Specificity	Sensitivity	Notes
mtDNA copy #/cell	74% in MDDs	100% in MDDs	
Lactate	34–62%	83–100%	Post prandial best
Pyruvate	50–75%	87%	
Lactate:Pyruvate	69-100%	11-82%	
GDF-15	High	78%	

All are measures of patients with genetic mitochondrial dysfunction

Hubens WHG, Vallbona-Garcia A, de Coo IFM, van Tienen FHJ, Webers CAB, Smeets HJM, Gorgels TGMF. Blood biomarkers for assessment of mitochondrial dysfunction: An expert review. Mitochondrion. 2022 Jan;62:187-204. PMID: 34740866

Shayota BJ. Biomarkers of mitochondrial disorders. Neurotherapeutics. 2024 Jan;21(1):e00325. PMID: 38295557

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Lactate:Pyruvate

- Average lactate: 1.0-2.0 mmol/L
- Average pyruvate: 0.08-0.16 mmol/L
- Average lactate:pyruvate: 6.0-33
- Abnormal mitochondrial function starts at 17
- Matched with controls:
  - 17.3 11.4
  - 20.7 15.4

Shayota BJ. Biomarkers of mitochondrial disorders. Neurotherapeutics. 2024 Jan;21(1):PMID: 38295557

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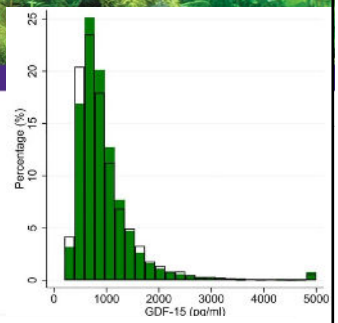
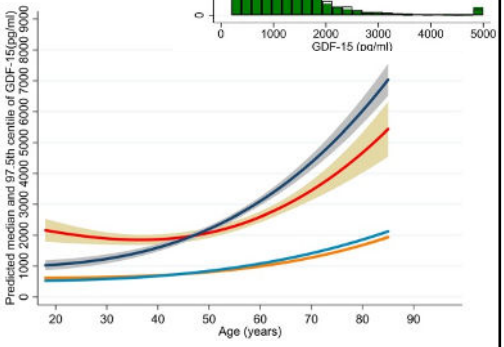
GDF-15

- Growth Differentiation Factor
  - Macrophage inhibitory cytokine-1, placental transforming growth factor-beta, and placental bone morphogenetic protein
- Stress-induced cytokine
- Increased in:
  - Mitochondrial disease
  - Aging
  - Cancer
  - Cardiovascular disease
  - Diabetes
  - Migraine
  - Neurodegeneration





Welsh P, Kimenai DM, Marioni RE, Hayward C, Campbell A, Porteous D, Mills NL, O'Rahilly S, Sattar N. Reference ranges for GDF-15, and risk factors associated with GDF-15, in a large general population cohort. Clin Chem Lab Med. 2022 Aug 18;60(11):1820-1829. PMID: 35976089

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Urine Molecules to Assess Mitochondrial Function

Dispersion of urine Krebs cycle organic acid results

Category	Age	*N*	Citrate	Aconitate	Isocitrate	Oxoglutarate	Succinate	Fumarate	Malate
Unselected	≤1 yr	1117	685±684	119±95	105±75	172±184	52±77	25±36	29±39
	>1 yr	2095	478±440	108±91	93±66	60±86	25±41	9±30	9±23
Mito	≤1 yr	26	663±359	222±162	146±54	250±229	46±39	108±143	87±100
	>1 yr	232	393±341	183±158	120±72	114±166	31±51	44±114	32±67
OA	≤1 yr	52	1143±945	176±131	128±67	275±189	79±67	111±149	93±118
	>1 yr	124	674±601	107±98	84±57	139±255	54±59	119±174	99±121
Normal range			120–675	0–185	4–125	0–152	0–80	0–8	0–13

Values are means±SD expressed in mmol/mol creatinine. The categories of patients relate to diagnosis: mito, mitochondrial/oxidative phosphorylation defect; OA, organic acidemia; unselected, all other patients.

- Fumarate and malate elevated in mito disease
- BUT, must check for organic acidemia

Barshop BA. Metabolomic approaches to mitochondrial disease: correlation of urine organic acids. Mitochondrion. 2004 Sep;4(5-6):521-7 PMID: 16120410.

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Damage Measures

- 8-OHdG
- CIMP/DMP (place holder)

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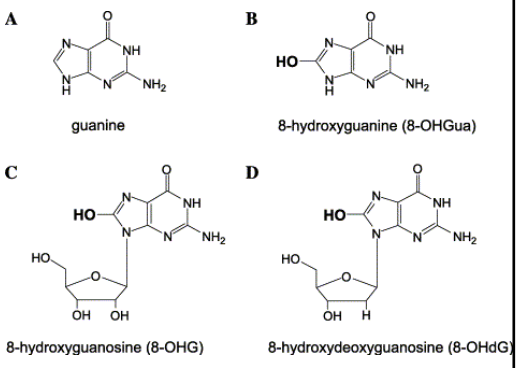
8-OHdG

- Oxidized nucleoside
- Direct measure of DNA damage
- Indirect measure of oxidative stress and toxin load
- Correlates with:
  - Mitochondrial damage
  - Many diseases
  - Multiple cancers
  - Rate of aging
  - Smoking
  - Several toxins



Walter Crinnion "Total Toxic Load," AANP 2015

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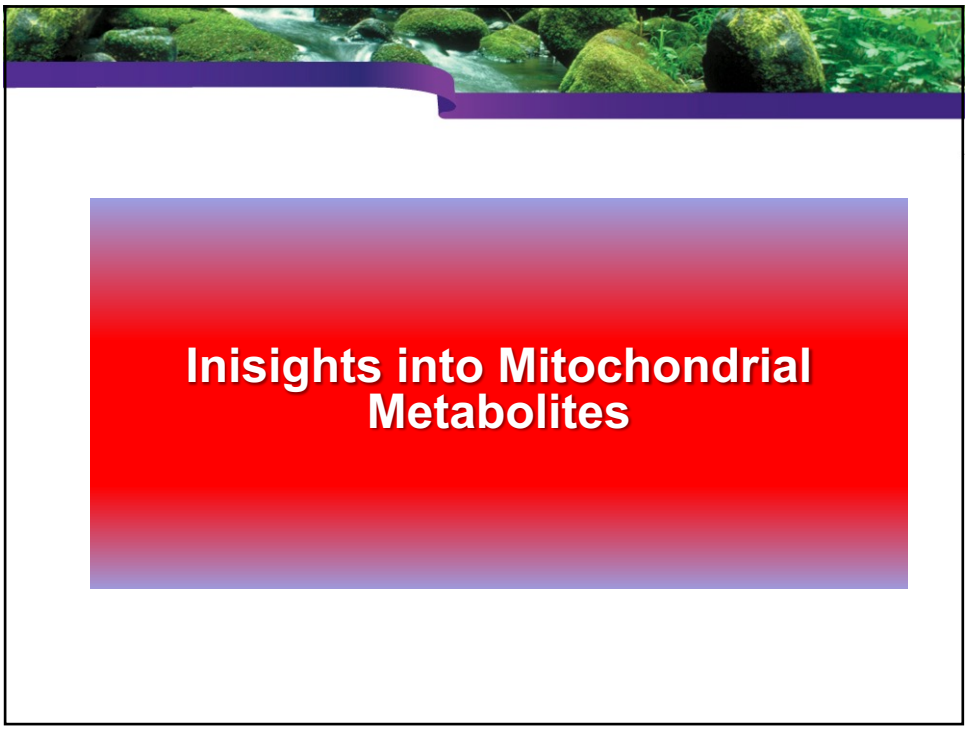
Inisights into Mitochondrial Metabolites

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Mitochondrial Oncometabolites
• Succinate
• Fumarate
• Malate

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SUCCINATE/SUCCINIC ACID

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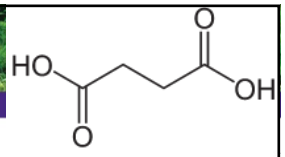

Succinate/Succinic Acid

- Dicarboxylic acid
  - Historically also called amber acid or butanedioic acid
- Converted into fumarate by succinate dehydrogenase, which is complex 2 of the electron transport chain
- Involved in ATP production, epigenetics, tumorigenesis, signal transduction, endo- and paracrine modulation and inflammation
- Signaling molecule reflecting the cellular metabolic state
- Used as a food additive for acidity control
- Primarily produced in citric acid cycle, but significant other sources
- Succinic acid readily ionizes to succinate

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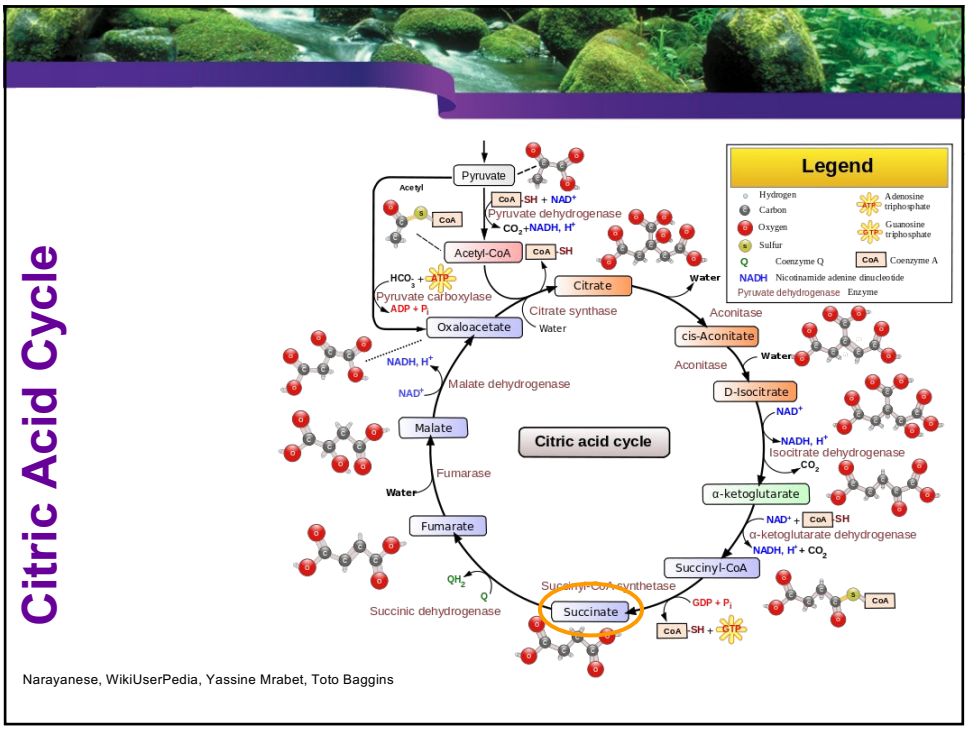
Citric Acid Cycle
Pyruvate
Acetyl
CoA
Pyruvate dehydrogenase
Acetyl-CoA
Pyruvate carboxylase
Citrate
Citrate synthase
Water
Oxaloacetate
Aconitase
cis-Aconitate
D-Isocitrate
NADH, H+
NAD+
Malate dehydrogenase
Malate
Citric acid cycle
Isocitrate dehydrogenase
CO2
Fumarase
α-ketoglutarate
α-ketoglutarate dehydrogenase
Fumarate
Succinyl-CoA
Succinyl-CoA synthetase
Succinate
GDP + Pi
Succinic dehydrogenase
Legend
Hydrogen
Carbon
Oxygen
Sulfur
Coenzyme Q
Adenosine triphosphate
Guanosine triphosphate
Coenzyme A
Nicotinamide adenine dinucleotide
Pyruvate dehydrogenase
Enzyme
Narayanese, WikiUserPedia, Yassine Mrabet, Toto Baggins

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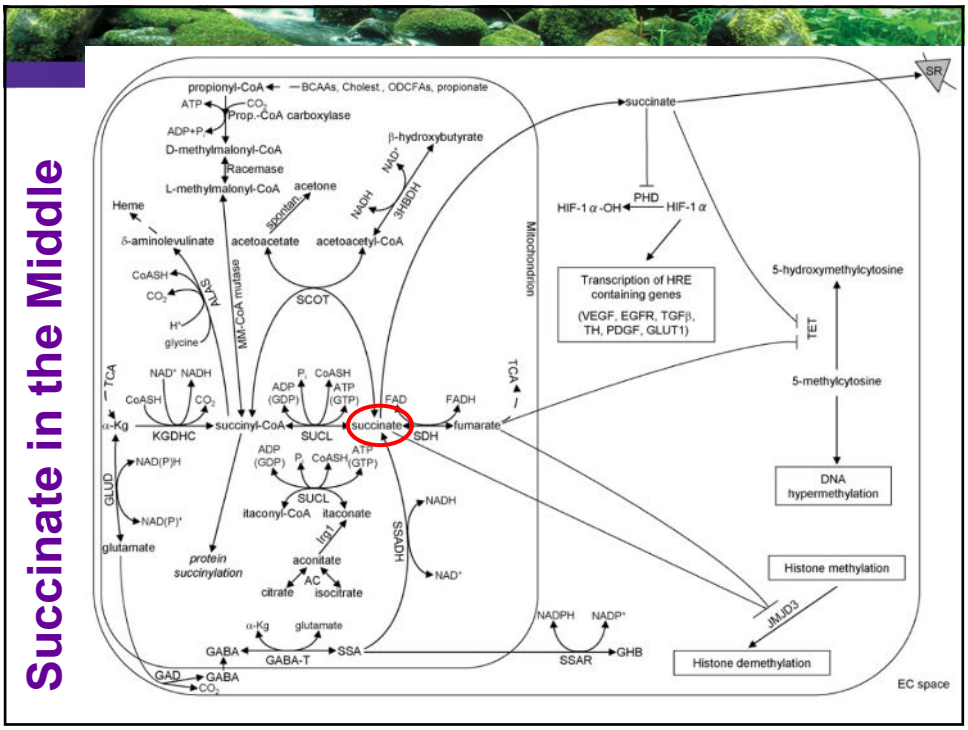
Succinate in the Middle
propionyl-CoA
BCAAs, Cholest., ODCFAs, propionate
Prop.-CoA carboxylase
D-methylmalonyl-CoA
Racemase
L-methylmalonyl-CoA
MM-CoA mutase
succinyl-CoA
KGDHC
α-Kg
SUCL
succinate
SDH
fumarate
FADH
FAD
NAD+ NADH
CoASH
CO2
ADP (GDP)
ATP (GTP)
Pi
TCA
GLUD
NAD(P)H
NAD(P)+
glutamate
itaconyl-CoA
itaconate
Irg1
aconitate
AC
citrate
isocitrate
protein succinylation
SSADH
NADH
NAD+
α-Kg
glutamate
GABA
GABA-T
SSA
SSAR
NADPH
NADP+
GHB
GAD
CO2
Heme
δ-aminolevulinate
ALAS
glycine
acetoacetate
acetoacetyl-CoA
SCOT
spontan.
acetone
3HBDH
β-hydroxybutyrate
Mitochondrion
succinate
SR
HIF-1α-OH
PHD
HIF-1α
Transcription of HRE containing genes
(VEGF, EGFR, TGFβ, TH, PDGF, GLUT1)
5-hydroxymethylcytosine
TET
5-methylcytosine
DNA hypermethylation
Histone methylation
JMJD3
Histone demethylation
EC space

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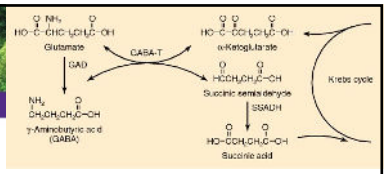

Succinate Production

- Mostly synthesized from succinyl-CoA by the enzyme succinyl-CoA synthetase in a GTP/ATP-producing step
  - Genetic diseases: Leigh syndrome and Melas syndrome
- Smaller amounts synthesized through the GABA shunt, which is found in neurons, glial cells, macrophages and pancreatic cells
- Plants and microorganisms can also create through the Glyoxylate cycle, an anaerobic pathway
- **Gut dysbiosis can be a major source**

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The Many Roles of Succinate

- Important metabolite at the cross-road of several metabolic pathways
- Involved in the formation and elimination of reactive oxygen species.
- Involved in epigenetics, tumorigenesis, signal transduction, endo- and paracrine modulation and inflammation.
- Huge in cancer
  - Promotes the excessive glycolysis (Warburg Effect)
  - Promotes angiogenecis
  - Moves immune system from cancer killing Th1 to cancer tolerant Th2

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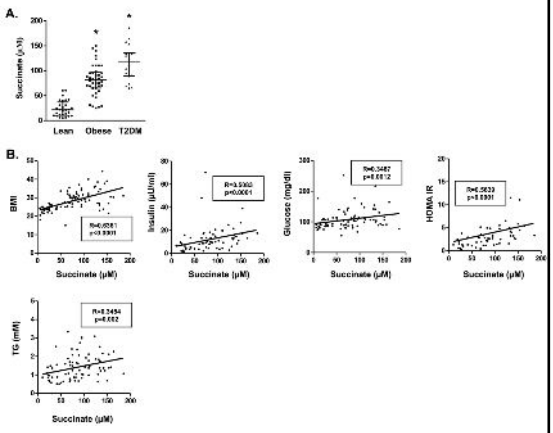
Serum Succinate Levels Correlate with Common Disorders

- Correlates with:
  - BMI
  - Cancer
  - Diabetes
  - Glucose levels
  - Insulin levels
  - Obesity
  - Triglyceride levels
- Serum and urine levels poorly correlate



Serena, Carolina et al. "Elevated circulating levels of succinate in human obesity are linked to specific gut microbiota." The ISME journal vol. 12,7 (2018): 1642-1657

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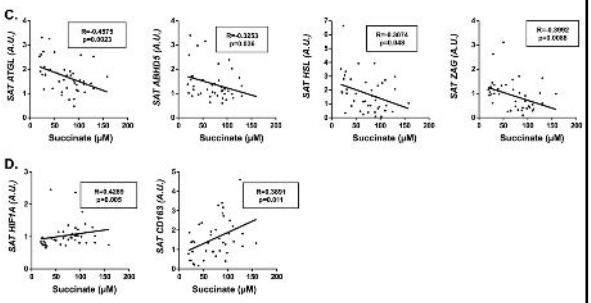
Succinate is Anti-lipolytic

- Inhibits release of fatty acids from adipocytes (SAT ATGL)
- Increases hypoxia-inducible factor HIF-1α, a key transcription factor underlying chronic inflammation
- Subcutaneous fat more susceptible than visceral



Serena, Carolina et al. "Elevated circulating levels of succinate in human obesity are linked to specific gut microbiota." The ISME journal vol. 12,7 (2018): 1642-1657

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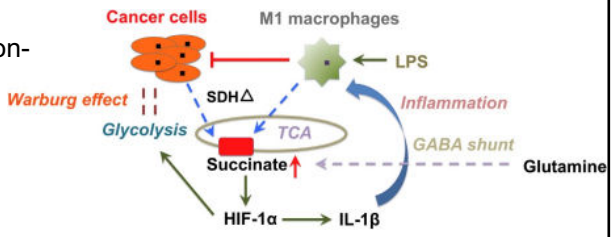
Succinate in Cancer

- Succinate is 1 of 3 oncometabolites, metabolic intermediates whose accumulation causes metabolic and non-metabolic dysregulation implicated in tumorigenesis
- Succinate and fumarate accumulation occur in tumors driven by inactivating mutations in SDH and FH, Elevated succinate increases cancer cell glycolysis



Jiang S, Yan W. Succinate in the cancer-immune cycle. Cancer Lett. 2017;390:45-47
Yang M, Soga T, Pollard PJ. Oncometabolites: linking altered metabolism with cancer. J Clin Invest. 2013;123(9):3652-3658.

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GUT DYSBIOSIS THROWS A MONKEY WRENCH INTO THE MIDDLE OF MITOCHONDRIAL METABOLISM

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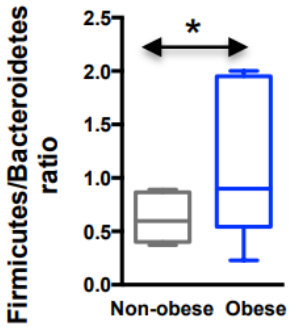
Some Gut Organisms Produce Succinate

- Increase in the Firmicutes/Bacteroidetes ratio in obese subjects
- Decreased richness and biodiversity at the phylum and genus level
- Both species important!
- The problem is imbalance



Serena, Carolina et al. "Elevated circulating levels of succinate in human obesity are linked to specific gut microbiota." The ISME journal vol. 12,7 (2018): 1642-1657

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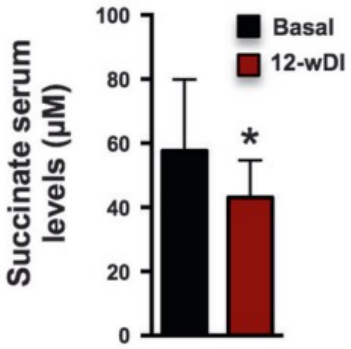
Weight Loss

- Decreases succinate levels
- Improves gut flora



Serena, Carolina et al. "Elevated circulating levels of succinate in human obesity are linked to specific gut microbiota." The ISME journal vol. 12,7 (2018): 1642-1657

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SUCCINATE DEHYDROGENASE (SDH)

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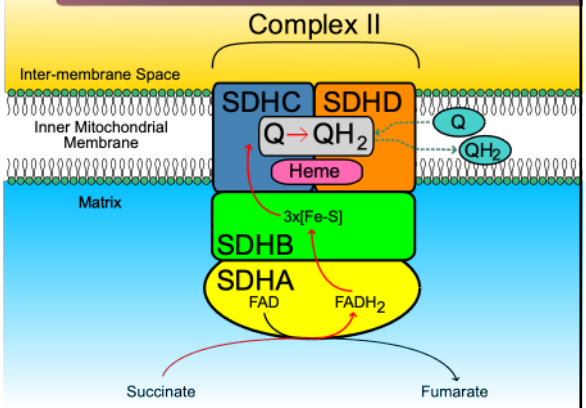
Succinate Dehydrogenase

- 4 subunits
- Both CAC and OXPHOS
- Succinate is a carcinogen
- SDH is a tumor suppressor
- Contains iron and sulfur



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By Jawahar Swaminathan and MSD staff at the European Bioinformatics Institute - http://www.ebi.ac.uk/pdbe-srv/view/images/entry/1puz600.png, displayed on http://www.ebi.ac.uk/pdbe-srv/view/entry/1puz/summary, Public Domain, https://commons.wikimedia.org/w/index.php?curid=5929813

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SDH Mutations

- SdhA mutations
  - Leigh syndrome, mitochondrial encephalopathy, and optic atrophy.
- SdhB mutations
  - Tumorigenesis in chromaffin cells, causing hereditary paraganglioma, hereditary pheochromocytoma, renal carcinoma and gastrointestinal stromal tumor (GIST)
- SdhC mutations
  - Secreased life-span, increased production of superoxide ions, hereditary paraganglioma, hereditary pheochromocytoma.
- SdhD mutations
  - Hereditary paraganglioma and hereditary pheochromocytoma

Succinate dehydrogenase - Wikipedia

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Succinate Dehydrogenase Deficiency

- Mitochondrial myopathies:
  - 23% have SDH dysfunction
  - Activity only 34% of normal
- COVID
  - Succinate levels increase during COVID
  - In an animal model, increasing succinate dehydrogenase activity protects lungs from acute respiratory distress syndrome (ARDS).
- Neurodegenerative disease
  - Alzheimer's, Parkinson's and Huntington's
  - Mutations in SDH correlate with onset of neurodegenerative disorders
- Increased production of superoxides

Vladutiu GD, Heffner RR. Succinate dehydrogenase deficiency. Arch Pathol Lab Med. 2000;124(12):1755-1758
Vohwinkel, Christine U et al. Targeting alveolar-specific succinate dehydrogenase A attenuates pulmonary inflammation during acute lung injury. FASEB journal : official publication of the Federation of American Societies for Experimental Biology vol. 35,4 (2021): e21468
Jodeiri Farshbaf M, Kiani-Esfahani A. Succinate dehydrogenase: Prospect for neurodegenerative diseases. Mitochondrion. 2018;42:77-83.

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SDH is Impaired By

- Deficiencies of: iron, riboflavin, vitamin E
  - Riboflavin deficiency common: 26% of adolescents not taking supplements
- Methyl malonic acid ⇒ adenosyl B12 deficiency
- Fumarase deficiency
- Environmental toxins

- CANCER!

Lopez R, Schwartz JV, Cooperman JM. Riboflavin deficiency in an adolescent population in New York City. Am J Clin Nutr. 1980;33(6):1283-1286.

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Many Environmental Toxins Poison SDH

- Arsenic
- Fungicides
- DDT/DDE
- BPA
- PAHs

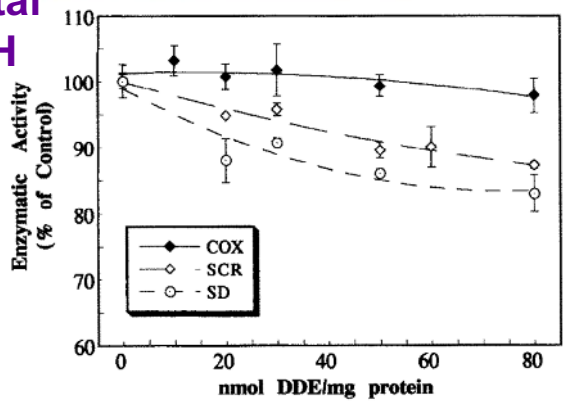

FIG. 3. Effect of DDE on succinate dehydrogenase (SD), succinate cytochrome c reductase (SCR) and cytochrome c oxidase (COX). Values are means ± SD of three to six independent experiments (when the error bars are absent, SD is encompassed by the size of the symbols).

Lopez R, Schwartz JV, Cooperman JM. Riboflavin deficiency in an adolescent population in New York City. Am J Clin Nutr. 1980;33(6):1283-1286.

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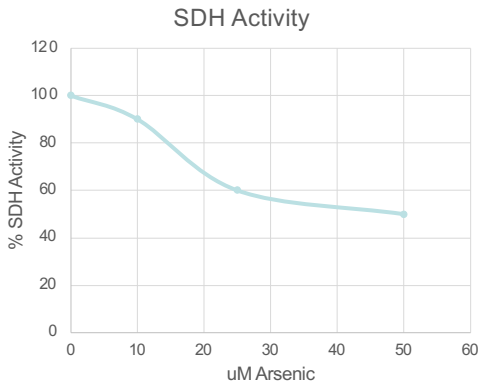
Arsenic

- Cell culture
- **Average** person has 1.3-7.5 uM arsenic in various tissues



Hosseini MJ, Shaki F, Ghazi-Khansari M, Pourahmad J. Toxicity of Arsenic (III) on Isolated Liver Mitochondria: A New Mechanistic Approach. Iran J Pharm Res. 2013;12(Suppl):121-138.
Yamauchi H, Yamamura Y. Concentration and chemical species of arsenic in human tissue. Bull Environ Contam Toxicol. 1983;31(3):267-270

49

BPA Impairs Complex II (SDH)

- Prenatal rat study shows dose-dependent decrease in SDH activity
- Cell study shows carcinogenic effect inhibited by ginger

Jiang Y, Liu J, Li Y, et al. Prenatal exposure to bisphenol A at the reference dose impairs mitochondria in the heart of neonatal rats. J Appl Toxicol. 2014;34(9):1012-1022
Lei D, Hong T, Li L, Chen L, Luo X, Wu Q, Liu Z. Isobaric tags for relative and absolute quantitation-based proteomics analysis of the effect of ginger oil on bisphenol A-induced breast cancer cell proliferation. Oncol Lett. 2021 Feb;21(2):101. doi: 10.3892/ol.2020.12362.

50

Indications of SDH Dysfunction

- Exercise intolerance
- Elevated urinary succinic acid
- Many diseases: Cancer, COVID, diabetes, obesity, neurodegeneration

Brière JJ, Favier J, El Ghouzzi V, et al. Succinate dehydrogenase deficiency in human. Cell Mol Life Sci. 2005;62(19-20):2317-2324.

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Restoring Normal Succinate Levels

- Address causes of SDH inhibition
  - Arsenic, BPA (bisphenols), etc.
  - Deficiencies of vitamins B2 and C, CoQ10
- Address over production
  - Gut dysbiosis
  - Decrease weight if overweight
  - Normalize blood sugar control
- Retest if on a ketogenic diet or taking supplemental amino acids

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FUMARATE

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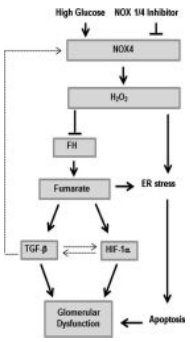
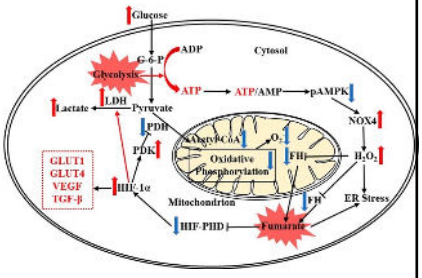
Fumarate Is a "Disease-promoting Metabolite"

- Excess fumarate stimulates
  - Endoplasmic reticulum stress
  - HIF-1α and TGF-β production
- FH inhibited in diabetic kidney disease
- Diabetes may promote FH inhibition





You YH, Quach T, Saito R, et al. Metabolomics Reveals a Key Role for Fumarate in Mediating the Effects of NADPH Oxidase 4 in Diabetic Kidney Disease. J Am Soc Nephrol. 2016 Feb;27(2):466-81.
Zhang G, et al. The Warburg Effect in Diabetic Kidney Disease. Semin Nephrol. 2018 Mar;38(2):111-120.

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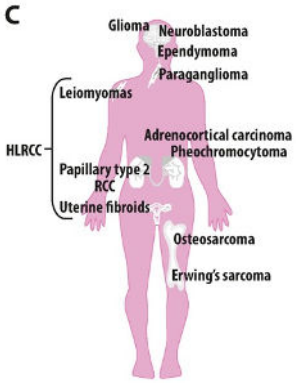
Fumarate hydratase (FH)

- FH catalyzes conversion of fumarate to malate – FH is considered a tumor suppressor
- Germline mutations in FH (heterozygous) –
  - Hereditary leiomyomatosis-renal cell carcinoma syndrome (HLRCC)
  - Increased risk of cutaneous and uterine leiomyomas, renal cancer
  - Risk for multiple other cancer types
- FH loss results in multiple cellular adaptations to accommodate fumarate accumulation

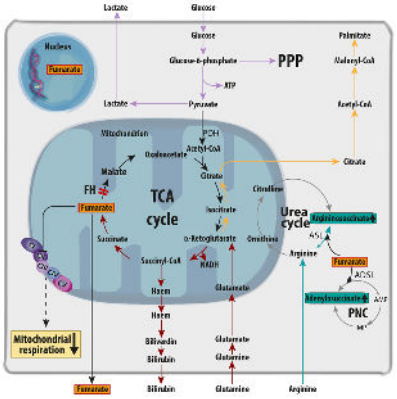


Schmidt C, Sciacovelli M, Frezza C. Fumarate hydratase in cancer: A multifaceted tumour suppressor. Semin Cell Dev Biol. 2020 Feb;98:15-25.

55

FH Deficiency Rewires Cellular Metabolism

- Inhibition of Succinate Dehydrogenase
- Shift towards anaerobic glycolysis & lactate production
- Glucose diverted to pentose phosphate pathway to supply NADPH for GSH synthesis
- Cells rely on external arginine and glutamine
- Succination of many proteins (ex: GSH) – covalent binding to cysteine residues, impaired function
- FH alteration ~ 1/1000 in pop



Schmidt C, Sciacovelli M, Frezza C. Fumarate hydratase in cancer: A multifaceted tumour suppressor. Semin Cell Dev Biol. 2020 Feb;98:15-25.
Shuch B, Li S, Risch H, et al. Estimation of the carrier frequency of fumarate hydratase alterations and implications for kidney cancer risk in hereditary leiomyomatosis and renal cancer. Cancer. 2020 Aug 15;126(16):3657-3666.

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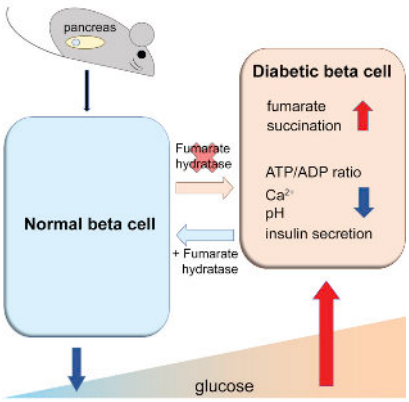
Fumarate Hydratase and Diabetes

- In animal model, deletion of FH causes
  - Progressive deterioration of β cell function & severe diabetes
  - Impaired oxidative metabolism ATP production, intracellular calcium handling, and cytosolic acidification
  - Progressive loss with only slight glucose elevations early
  - Succination of proteins marker for mitochondrial dysfunction



Adam J, et al. Fumarate Hydratase Deletion in Pancreatic β Cells Leads to Progressive Diabetes. Cell Rep. 2017 Sep 26;20(13):3135-3148.

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Fumarate Elevation

- High-intensity exercise – until >1hr post-exercise
- Overactive bladder
  - Elevated and correlated with urinary frequency and symptoms
- Mitochondrial dysfunction
  - Fumarate & malate highly correlated with mitochondrial disease – no good correlation with other Kreb's intermediates or lactate.
  - A cutoff value of about 90 mmol/mol creatinine for fumarate or malate in infants, or a value of 25 for older individuals, distinguished 25–30% of mitochondrial disease patients

Sun T, et al. Metabolomic profiles investigation on athletes' urine 35 minutes after an 800-meter race. J Sports Med Phys Fitness. 2017 Jun;57(6):839-849.
Mossa AH, et al. Urinary metabolomics predict the severity of overactive bladder syndrome in an aging female population. Int Urogynecol J. 2020 May;31(5):1023-1031.
Barshop BA. Metabolomic approaches to mitochondrial disease: correlation of urine organic acids. Mitochondrion. 2004 Sep;4(5-6):521-7.

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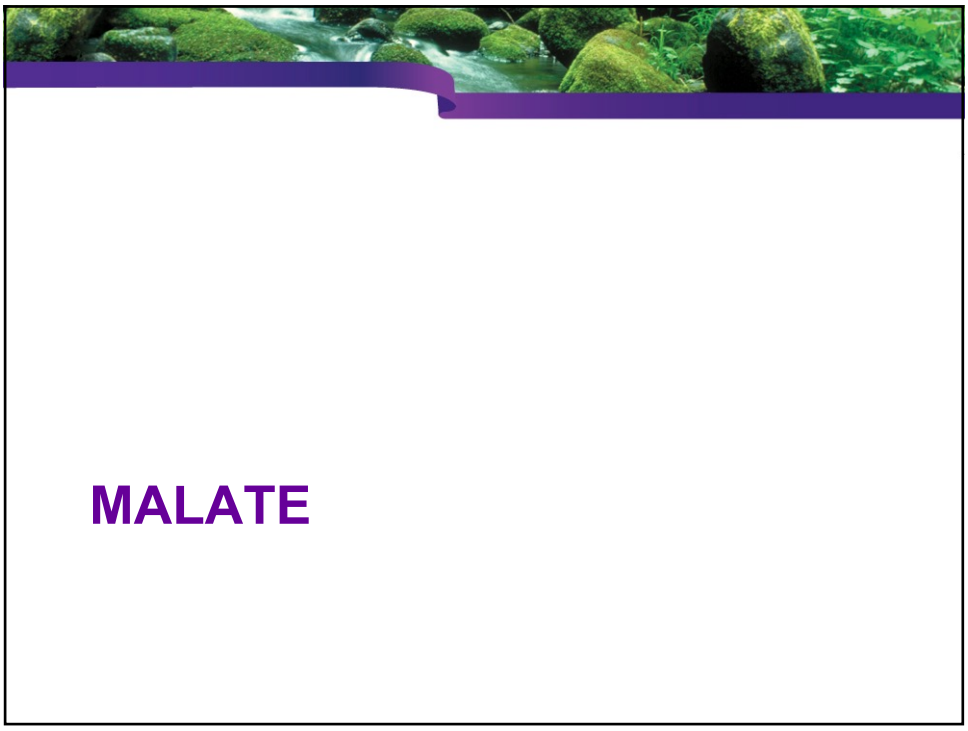
MALATE

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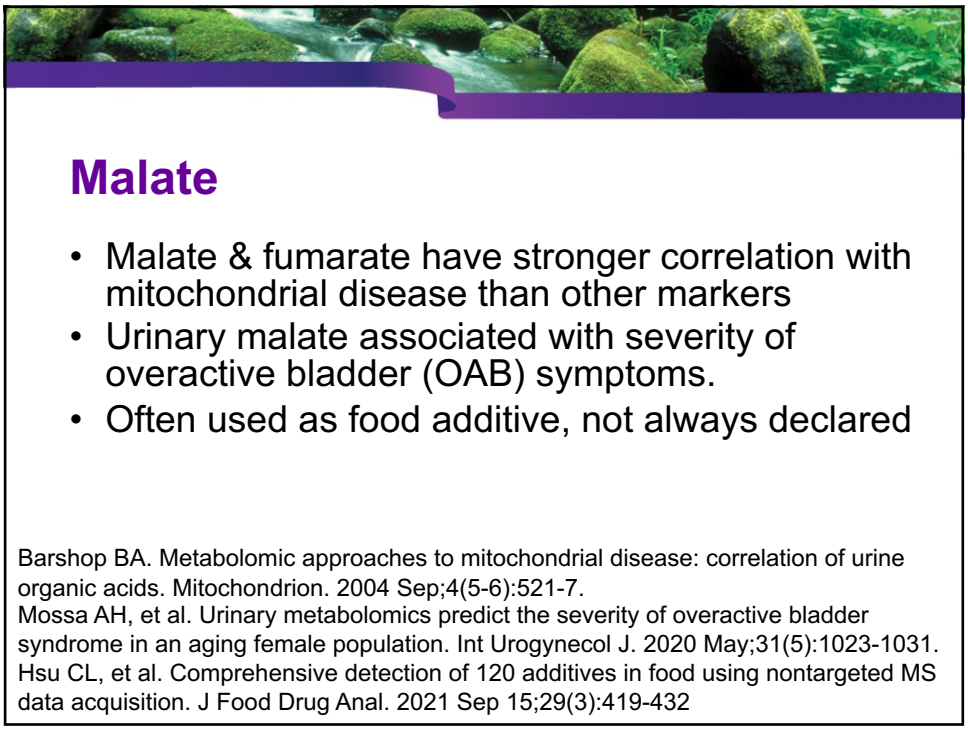
Malate
• Malate & fumarate have stronger correlation with mitochondrial disease than other markers
• Urinary malate associated with severity of overactive bladder (OAB) symptoms.
• Often used as food additive, not always declared
Barshop BA. Metabolomic approaches to mitochondrial disease: correlation of urine organic acids. Mitochondrion. 2004 Sep;4(5-6):521-7.
Mossa AH, et al. Urinary metabolomics predict the severity of overactive bladder syndrome in an aging female population. Int Urogynecol J. 2020 May;31(5):1023-1031.
Hsu CL, et al. Comprehensive detection of 120 additives in food using nontargeted MS data acquisition. J Food Drug Anal. 2021 Sep 15;29(3):419-432

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MDH2 – Cancer biomarker

- Urinary levels of MDH2 may be cancer biomarker
- Retrospective and prospective cohorts including 1091 NSCLC patients and 736 healthy controls
  - Urinary MDH2 concentration discriminated patients with stage I NSCLC from healthy participants
  - AUC was 0.7234 in a prospective cohort
  - MDH2 was highly expressed in lung cancer tissue and knockdown of MDH2 markedly reduced cell proliferation in lung cancer cells

Ma YC, et al. Urinary malate dehydrogenase 2 is a new biomarker for early detection of non-small-cell lung cancer. Cancer Sci. 2021 Jun;112(6):2349-2360

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Conclusion

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Bottom Line

- Mitochondrial dysfunction is very common in chronic disease
- GDF-15 currently best single marker
  - Available from Mayo Clinic, more labs expected
- Lactate:Pyruvate
  - Reasonably good
  - Readily available
- Both elevated lactate and pyruvate
  - Helpful, but not great
  - Readily available
- Succinate in the middle of major chronic diseases

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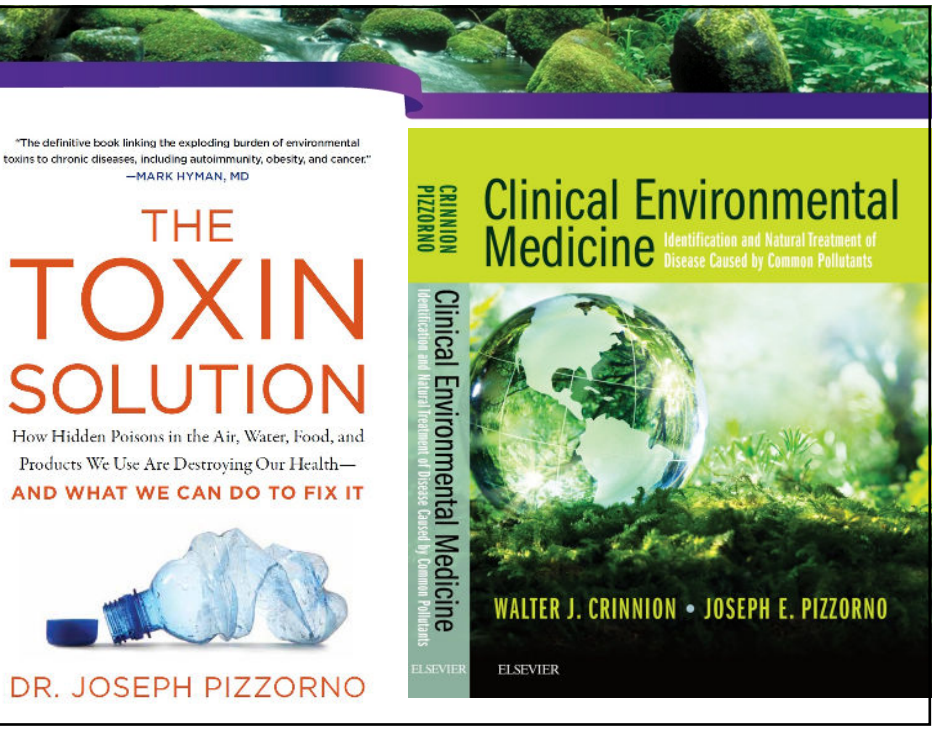

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