Metabolism, Mitochondria and Epigenetics

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In Sickness and in Health

Disadvantage

- Diabetic
- Obese
- Sedentary
- Carnivorous
- Immuno-compromised
- SAD - highly processed food
- Exposed to pollutants, heavy metals

Advantage

- Pesco-vegetarian
- Mediterranean diet
- Low carbohydrate intake
- Whole foods
- Exercise habit
- Non-chaotic lifestyle
- Zest for life
- Clean environment
Insulin, IGF-1 and Diet

- **High sugar and carbohydrate intake** may ramp up insulin, a nutrition pump that some cancers use to drive rapid growth.

- Past a certain threshold of blood insulin, human livers make IGF-1, a potent growth factor and amplifier of hormone receptors. Linked to obesity and disease.

- IGF1 and IGF2 can promote cancer growth through paracrine and autocrine secretion.

- IGF-1 naturally occurs in the **meat and milk** of grass fed herd animals – eg. pigs and cows.

- **It is doubled if animals are corn-fed.**
Remember what happened to the last corn-based culture?

See “*Guns, Germs and Steel*”, by Jared Diamond, Pulitzer Prize winner 1998.
SAD – Standard American Diet

• Ancestral hunter-gatherer diets, for almost all of human history, provided a sodium to potassium ratio of 1:10.

• Pre-agriculture and early agriculture diets produced a NEAP net alkaline balance of 88 mEq daily.

• The modern western diet creates a Na to K ratio > 3:1 - a 30-fold change!

• And with it came a change to a net acid residue of 48 mEq daily - a 3 fold change in alkaline to acid!

• Acid forming foods: salt, sugar, sodas, and meat. Alkaline foods: plants.

• Acid reduces oxygen saturation, inducing hypoxia. Cancers are acid and hypoxic...

Acidosis, Hypoxia and Bone, Arnett, Arch. Biochem. Biophys. 2010; 503(1): 103-109

Cancer and Fetal Cells – Asymmetric Mitosis

• Humans start out as an egg and a sperm floating in a low oxygen fallopian tube.
• Undifferentiated biomass accumulates.
• In time the fetus implants and gets a strong blood supply by building a placenta. Oxidative metabolism increases.
• After the first trimester stem cells reproduce differentiated cells by asymmetric mitosis.
• Differentiated cells lost to apoptosis, autophagy, necrosis or trauma, are replaced by stem cells, which also give rise to a replacement stem cell.
Nuclear DNA Mutations and Cancer

• Somatic mutation theory postulates mutations in chromosomal DNA result in the cancer cell phenotype – exponential growth by symmetrical mitosis.

• Warren Schaeffer at University of Vermont showed that putting a highly mutated cancer cell nucleus into a normal enucleated cell did not convert that cell to a cancer phenotype.

• However, putting a normal, non-mutated nucleus into an enucleated cancer cell resulted in a fully malignant growth pattern.

Therefore cancer is driven by cytoplasmic factors: mitochondria!

Normal cell, normal nucleus
Normal growth

Cancer cell, mutated genome
Exponential growth

Normal cell, Cancer nucleus
Normal growth!

Cancer cell, Normal genome
Malignant growth!
Glycolysis Drives Cancer Growth and Spread

How fast a tumour grows and how aggressive the cancer is correlates with:

• a lower number of mitochondria - as low as 50% that of normal cells.

• remaining mitochondria in cancer cells are often damaged - distorted into dumbbell and cup shapes, missing internal membranes, and with abnormal fats and proteins.

• the increase in glycolytic fermentation of glucose.

Mitochondrial Carcinogenesis

Seyfried has shown damaged mitochondria unleash
→ activation of the p13/akt network
→ retrograde signalling
→ epigenetic changes
→ altered nuclear DNA
→ metabolic reprogramming
→ changes in many cellular processes
• Warburg showed cancer cells continue anaerobic glycolysis in the presence of oxygen.

• Pedersen circa 1978 showed increased fermentation as cancers grow faster and more aggressively, linked to lower number and structural abnormalities of mitochondria.

• Seyfried showed mitochondrial damage alters signals to transcription factor MYC controlling about 15% of the genome, triggering carcinogenesis – reversion to a primitive anaerobic metabolic state.

• Retrograde signalling - cytoplasm to nucleus - precedes nuclear mutations!


Kinases, Phosphatases and Hexokinase

• Kinases are signalling proteins. They attach a phosphate group to proteins to turn on a function.
• Phosphatases cleave off phosphate groups, often inactivating the protein or enzyme.
• Cancer cells produce hexokinase II to turn glucose to glucose-6-phosphate, but unlike normal hexokinase H2 is not slowed by build-up of its product. The fermentation throttle is stuck on.
• Hexokinase binds to voltage dependent anion channels VDAC that release cytochrome c to initiate apoptosis. Hexokinase II compensates for energy loss due to damaged and absent mitochondria, and immortalizes damaged cells.
Mighty Mitochondria from Mommy

• Up to 40% of a cell’s cytoplasm.
• 100,000 in an oocyte.
• 100 in a spermatozoa.
• 10 trillion in an adult.
• 10% of our body weight.
• Generate our body weight in ATP daily.
• 9 ounces of ATP in circulation at any moment.
Other Mighty Mito Functions

• Redox modulation.
• Generation of ROS for cellular signal transduction, regulation of nuclear transcription factors.
• Biosynthetic precursors – acetyl-co-A and pyrimidines.
• Biosynthesis of anabolic carbon skeletons and nucleic acid precursors.
• Regulation of cytosolic ionic calcium levels.
• Control of apoptosis – via permeability transition pore for caspases.
Mitochondrial DNA

• 24 genes in mitochondria.
• Bacteria-like circular DNA! A billion years of symbiosis with eukaryote cells.
• 3,000 mitochondrial related genes in nuclear chromosomal DNA.
• 13 critical OXPHOS genes in mtDNA, some in nuclear chromosomal DNA.
• Mitochondria have their own DNA repair systems. 17X higher mutation rate than nuclear DNA.
• High oxidative stress from leakage of oxygen and free electrons during oxidative phosphorylation. 10X higher ROS exposure than nuclear DNA. Mitochondrial NADPH protects from ROS.
• Darlington circa 1948 found mitochondrial DNA far more sensitive to known “carcinogens” than chromosomal DNA.
Mitochondrial Poisons

• arachidonic acid.
• alcohol, tobacco, cocaine, methamphetamines,
• AIDS drugs such as AZT; anti-viral nucleoside analogues such as ganciclovir.
• antifungals such as ketoconazole, griseofulvin, cyclosporine; cordyceps (?)..
• NSAIDs such as ibuprofen, indomethacin, acetaminophen, aspirin.
• antibiotics such as rifampin, isoniazid, tetracycline, gentamycin, fluoroquinolone, adriamycin.
• cyclophosphamide, amiodarone, valproate, phenytoin, chloroquine, quinidine, clofibrate, fenofibrate, fluoxetine, haloperidol, risperidone, chloroform, amytal, propofol, hydrazine, isoflurane, chlorpromazine, metformin, lidocaine, bupivacaine, capsaicin, cholic acid, L-DOPA.
• cyanide, heavy metals, and pesticides eg heptachlor, chlordane, rotenone, and dioxin.
Mitochondria Burn Out

• Mitochondrial DNA and it’s repair systems are distinct from and less robust than for parental, nuclear, chromosomal DNA.

• Electrons transport spills 1 to 2% of electrons and 6% of oxygen as ROS (free radicals of oxygen) eg superoxide radical.

• Over-feeding of sugars and carbohydrates are stoking these fires.
Mitochondria Damage and Lifespan

- 8-oxo-7,8-dihydro-2’-deoxyguanosine (8-oxodG), is a marker of oxidative stress.
- Inverse relationship between maximum lifespan and 8-oxodG mtDNA – not observed with nuclear DNA.
- 8-OHdG > 4 = high toxic load, eg mercury, tobacco, persistent organic pollutants (POPs).

Autophagy is mediated by membrane phospholipids, and mTOR.

Autophagy removes protein accumulations involved in neurodegenerative diseases, and purges and recycles damaged cell organelles.

Dysfunction of autophagy may result in abnormal mitophagy.

Loss of mitochondrial function and oxidative stress are hallmarks of aging.

Support autophagy with sulforaphane, resveratrol, co-enzyme Q-10, berberine, quercetin, green tea EGCG, vitamin E, curcumin.
Mitochondriopathies

- Metabolic syndrome
- Diabetes
- Cardiovascular disease
- Neuro-degenerative disease
- Neuro-behavioural disorders
- Psychiatric disease
- Fatigue syndromes
- Musculo-skeletal disease
- Aging

Mitochondriopathies (MCP) should be considered in any patient with unexplained progressive multisystem disorder. Finsterer 2004
Mitochondriopathies

- **Central nervous system**: schizophrenia, bipolar disease, migraine headaches, upper motor neuron signs, ataxia, extrapyramidal manifestations, calcifications, epilepsy, Alzheimer’s neurodegenerative dementia, atrophic dementia, Parkinson’s disease, amyotrophic lateral sclerosis, transmissible spongiform encephalopathies, transient ischemic attack, stroke, MELAS syndrome - mitochondrial encephalopathy, lactic acidosis, and stroke-like-episodes, myoclonic epilepsy with ragged red fibers (MERRF) syndrome, Kearns-Sayre syndrome (KSS), maternally inherited Leigh syndrome (MILS), and the neuropathy, ataxia, and retinitis pigmentosa (NARP)

- **Peripheral nervous system**: neuropathic pain, myopathy, polyneuropathy.
Mitochondriopathies, continued

- **Cardiovascular system**: cardiomyopathy, coronary artery disease, impulse generation or conduction defects, left ventricular non-compaction heart failure, heart ischemia.
- **Metabolic**: diabetes, lactacidosis, short stature, hyperhidrosis, hyperlipidaemia, hypogonadism, amenorrhoea, delayed puberty
- **Sensory**: retinitis pigmentosa, cataract, glaucoma, optic atrophy; deafness, tinnitus, peripheral vertigo.
- **Gastrointestinal**: hepatitis C, primary biliary cirrhosis, dysphagia, vomiting, diarrhea, pancreatitis, pancreas insufficiency, pseudo-obstruction.
- **Other**: chronic fatigue syndrome, fibromyalgia, renal failure, renal cysts, sideroblastic anaemia, premature aging.
Mitochondrial Phospholipids

- Mitochondrial inner membranes see oxidative damage to phospholipids like cardiolipin and other molecules, resulting in loss of transmembrane potential, electron transport function, and generation of high-energy molecules.

- Lipids are central in restoring mitochondrial function and reducing fatigue in aged subjects and patients with a variety of clinical diagnoses that are characterized by loss of mitochondrial function and include fatigue as a major symptom, eg CFS.

- Oral supplements for membrane repair and replacement utilize mixtures of glycerophospholipids, n-3 and n-6 unsaturated FA and other lipid components derived from legumes, milk, liver, fish, krill, and seal oil.
Mitogenesis

- Mitogenesis is mediated by peroxisome proliferator–activated receptor gamma γ coactivator 1α (PGC-1α); PPAR is inhibited by FWGE and red wine.
- PGC is relevant to mitochondrial dynamics since it is a transcriptional coactivator of the fusion mediator mitofusin-2.
- Mitochondrial fusion with endoplasmic reticulum networks the oxygen and nutrient-sensing pathways.
- Mitochondrial-ER calcium channels regulate PDH activity and apoptosis.
- The mitochondria and endoplasmic reticulum also interact to create micro-environments that direct fission.

Mitochondrial Biogenesis

- Exercise.
- Cellular nitric oxide levels; increased by grapeseed extract.
- Activation and/or increased content of the protein AMPK - AMP-activated protein kinase, a metabolic master switch. AMPK is activated by berberine.
- Activation and/or increased content of the “fountain of youth” sirtuin protein SIRT1, a NAD-dependent histone deacetylase; SIRT1 is increased by caloric restriction, resveratrol, quercetin and exercise.
- PGC-1α transcriptional coactivator is also key to mitogenesis, and is also increased by resveratrol.
Rx, or take a walk....... 

• **Metformin** activates the enzyme AMPK (5’AMP-activated protein kinase) which directly stimulates mitogenesis.

• So does **curcumin, quercetin, (-)-epigallocatechin-3-gallate (EGCG in green tea) extract, and resveratrol**

• So does **exercise**.
Mitochondrial Biogenesis

• Activation and/or increased content of the “fountain of youth” sirtuin protein SIRT1, a NAD-dependent histone deacetylase; SIRT1 is increased by caloric restriction, resveratrol, quercetin and exercise.

• PGC-1α transcriptional coactivator is also key to mitogenesis, and is also increased by resveratrol.

• PQQ – pyrroloquinoline quinone stimulates biogenesis.

• Fuelled by high energy substrates such as ketones and lactate which can be scavenged from stromal fibroblasts.
Mitochondrial Rescue

- R+ ALA 300 mg bid – tid
- D-ALA by IV 150 mg biweekly
- Thiamine or benfotiamine - vit. B1 - 100-160 mg bid.
- Acetyl-L-carnitine 1,000 mg bid
- Co-enzyme Q-10 300+ mg
- Glumetza (ER metformin) Rx 500 mg qd-bid.
- Low-dose Naltrexone Rx 4.5 mg hs.
- IV-DCA, LAMC, thiamine, grapeseed extract, quercetin, berberine, HBO2T, riboflavin-5-phosphate, niacinamide, Ca, Mg, Zn, Cu, Cr, Fe, proline.
- Acup: CV-4, PC-6, ST-36.

Mitochondrial Resuscitation

• PQQ- pyrroloquinoline quinone – potent continuous cycling antioxidant. Activates AMPk an enzymatic master regulator of energy metabolism.

• Synergistic with Co-Q10 in managing electron transport, protecting mitochondrial membranes and DNA from oxidative damage. Rx 10 – 20 mg.

• Melatonin, vitamin A, magnesium, B-complex vitamins, selenium, SOD, glutathione, resveratrol, coriolus, berberine and iodine.

• Aerobic exercise can help, and foods such as olive oil, lemongrass, berries, grapes, pomegranate, apples, chili peppers, onions, garlic, Brassicas and whole grains.

• *Centella asiatica* reduces mitochondrial ROS and prevents dysfunction of lipids, proteins and DNA.


• Heavy metals increase mito ROS increasing DNA mutations. Cadmium is a potent mitochondrial poison. Walter Crinnion, ND - liver enzymes that detoxify organics function better after toxic metals are removed.
DCA - Dichloroacetate

• DCA selectively promotes mitochondria-regulated apoptosis and inhibits tumour growth in preclinical models by shifting the glucose metabolism in cancer cells from anaerobic to aerobic glycolysis.

• DCA selectively induces phosphatidylserine externalisation but suppresses caspase 3/7 activation, interfering with efficacy of cisplatin and doxorubicin.

• DCA does not influence the cytotoxicity of temozolomide, use freely.

• Accumulates in nervous tissue. Neuropathy limits its oral use. Published results with human brain tumours at 6.25mg/kg bid - about 750 mg daily.

• Oral doses of 12.5 mg/kg X 1 month, about 500 mg bid, then tid - or double dose, until AEs occur – numbness, tingling, psychosis, paralysis, ataxia.
DCA activates pyruvate dehydrogenase kinase, triggering an influx of acetyl-CoA into mitochondria. This drives more NADH into complex I.

Superoxides that form are converted into hydrogen peroxide by manganese-super oxide dismutase. The H2O2 inhibits proton (H+) efflux, reducing mitochondrial membrane potential Δψm, the proton-driving force → ATP.

This opens the mitochondrial transition pore (MTP), inhibiting calcium ion entry via voltage-dependent channels. Reduced intra-mitochondrial calcium (Ca++) suppresses a tonic activation of nuclear factor of activated T-lymphocytes (NFAT).

NFAT1 is a nuclear transcription activator, similar in action to activator protein 1 (AP-1) and nuclear factor kappa B (NFκB).

This reduces Kv1.5 expression, increasing potassium ion K+ efflux, reducing inhibition of caspases, and finally triggering cancer cell apoptosis.

Managing DCA Neuropathy

- **Thiamine** or B1 as fat soluble **benfotiamine** 100-200 mg bid prevents peripheral neuropathy

- **R+ alpha lipoic acid** 300 mg bid – tid prevents sedation, confusion, hallucinations, memory problems, hand tremor. Can be given IV or nebulized.

- Proton pump inhibitors such as **Pantoprazole** (Pantoloc) 40 mg qd prevents heartburn, nausea, vomiting and indigestion.

- **Methylcobalamin** (B-12) 1000-2000 mcg, acetyl-L-carnitine 1,000 mg tid.

IV-DCA

• Lemmo protocol: DCA – 1,000→2,000→3,000 mg (ramp up in 3 increments: 4, 8 and 12 mL of 250 mg/mL DCA).
• Saline 100 ml.
• Vitamin C – 2,500mg.
• B-complex – 1 cc.
• B12 – 1 mg.
• B6 – 100 mg.
• B5 – 250 mg.
• B1 – 100 mg.
• Infused over 30-60 min.
• Twice weekly for two weeks, then a week break, repeat.
• Evaluate progress at 10 – 12 infusions.

DCA Synergies

• Give piggy-back with D-ALA 150 mg infusions.

• Caffeine can improve responses to DCA, in doses of about 480 mg daily or about 12 cups daily of black tea.

• Metformin is highly synergistic. Other synergists are grapeseed extract, curcumin, quercitin, resveratrol, selenium, IV-vitamin C, Temozolamide.

• An interesting new concept is weekly alternating with artemesinin, or IV artesunate, as DCA helps cancer cells recharge with iron.
Alpha Lipoic Acid

• Antioxidant, hypoglycemic, mitochondrial and epigenetic effects.
• Potent natural PDK activator (cf thiamine – B1), inhibits PDK1 and reprograms cancer cell metabolism, like DCA.
• Modulates cancer stem cells, chelates heavy metals, increases glutathione & immunoglobulins. Inhibits TGFβ-1, angiogenesis, NFκB.
• Prevents and treats neuropathy.
• May provoke hypoglycemia. May mildly inhibit thyroid function.
• Avoid curcumin and artemesinin while on ALA therapy.


IV-D-ALA

- Biweekly D-ALA 150 mg IV drips.
- 10 mL of 15 mg/mL D-ALA in 250 mL saline.
- nothing else in the bag.
- protect from light, with foil.
- run in ≤ 1 gtt/sec.
- takes about 1.5 hours.
- continue oral dosing of R+ALA 300 mg bid.

Nebulizing D-ALA

• Injectable grade 15 mg/mL D-ALA. NOT racemic DL-ALA!
• Always keep out of the light as much as possible.
• Rent or purchase a nebulizer from a pharmacy.
• Use a 3 cc syringe to pull out the medicine from a rubber-top multi-dose vial.
• Always wipe the top of the vial with alcohol before putting away in the fridge.
• Put 1 mL medicine in the medicine cup of the nebulizer, which is protected from light by wrapping it with tinfoil. Dilute in 4 mL clean water.
• Over time you can try increasing the dose to 2 to 3 mL of medicine, diluted in 2 to 3 mL clean filtered water qs to make 5 mL total.
Nebulizing D-ALA and DCA

- Turn on the pump and through a face mask or breathing tube breath in the medicine as a mist. Breathe normally. After about 10 minutes the medicine well will go dry and you’ll hear it sputtering. Turn off the nebulizer pump, and rinse everything off for next time.

- You can do this twice a day at home, it is about as effective as an intravenous drip, and a lot cheaper.

- It is synergistic to add DCA (dichloroacetate) 250 mg/mL with the D-ALA. We start with 1 mL of each medicine, plus 3 mL of water. Later we can go up to 2 mL of each plus 1 mL water. Do not let stand long, as a precipitate can form.
Lipoic Acid Mineral Complex

• Poly-MVA is a palladium-lipoic acid complex.
• Redox agent, facilitates energy charge transfer, co-factor for oxidation of pyruvate to acetyl co-A.
• Reduces lipid peroxidation and increases GSH.
• Oral doses: 10 - 20 mL bid – tid.
• IV – 5 to 40 mL 2X weekly in 100 - 250 mL D5W/NS.
• In stage 4: up to 5 days/week X 4 weeks, then 3X/week X 8 weeks, then 1X/week for 12 weeks.
• Synergistic with thiamine, dichloroacetate.
Polygonatum spp.

**Solomon’s seal herb** or *Polygonatum* can:
- induce autophagy in cancer cells.
- Induce apoptosis in cancer cells.
- Both involve mitochondria-mediated ROS-p38-p53 pathways.
- Also blocks Ras-Raf and P13K-Akt pathways.
- Blocks epidermal growth factor receptor EGFR.
- **Inhibits expression of hexokinase II which** drives glycolysis or fermentation, and locks the mitochondrial voltage dependent anion channels (VDAC) through which ATP, caspases and cytochrome c, blocking apoptosis and immortalizing the cancer cell.


Quercitin

- Abundant in apples and onions. The most consumed bioflavonoid in the human diet.
- Plants use it to extract nitrogen – less if artificially fertilized, so eat organic.
- Is quercitin mutagenic and \textit{carcinogenic}? Not to human DNA.
- Inhibits mitochondrial membrane-bound hexokinase. Hexokinase supports OXPHOS while hexokinase II supports glycolysis.
- Blocks lactate export, supports mitochondria.
- Supports clearance of cancer cells by apoptosis, via mitochondrial cytochrome-C release.
- Inhibits Heat Shock Protein 90 which suppresses apoptosis.


Quercitin

• Quercitin can increase or decrease mitochondrial membrane potential Delta Psim (ΔΨm) depending on concentration, inducing apoptosis (Kellner 2004, Kothan 2004, Yang 2006, Zhang 2005).

• This versatile anti-cancer agent interferes with glycolysis via reduced generation of glycolytic substrates adenosine diphosphate and inorganic phosphate.


The Effect of Flavonoids on Aerobic Glycolysis and Growth of Tumor Cells, Suolina, Buchsbaum & Racker, Cancer Res. 1975; 35 (7): 1865-1872.
Metformin

- Biguanide is found in goat rue herb *Galega officinalis*
- ↓ liver gluconeogenesis, ↓ glycogenolysis.
- Hypoglycemic, ↓ insulin, ↓ IGF-1, ↑IGFBP-1.
- Activates AMPK, which inhibits lipogenic enzymes, and inhibits fatty acid release from adipose cells.
- Reduced lipid biosynthesis inhibits cell membrane generation, slowing tumour growth.
- Reduces protein synthesis.
Metformin Hurts Cancer

• Inhibits mTOR signalling
• Inhibits MAPK involved in glutaminolysis.
• Inhibits NFkB
• inhibits VEGF
• Inhibits cyclin D1
• Inhibits ovarian cancer cell growth, proliferation, metastasis and increases survival time.
• **Turns off cancer stem cells** in breast, ovarian and endometrial cancers.
Berberine

• Berberine significantly increase mRNA expressions of AMPK, PGC1α, UCP2, CPT1α, and Hadhb related to mitochondrial energy metabolism.

• This may be driven by increased expression of Fiaf - fasting-induced adipose factor, a key protein negatively regulated by intestinal biome.

• Berberine increases insulin sensitivity and protein kinase C-dependent up-regulation of insulin receptor expression.

• Reduces insulin resistance without provoking hypoglycemia.

• Davis Lamson, ND cautions that berberine is not completely interchangeable with metformin.

• It is a cold herb, and may be mildly immuno-suppressive.
Acetyl-L-Carnitine

- Fat soluble conditional energy source for mitochondria and brain.
- Acetyl-L-carnitine restores beta-oxidation of fatty acids to acetyl-co-A.
- Outstanding for chemo brain – also stroke and head injury.
- Synergistic with R+ Alpha Lipoic Acid for neuropathies and mitochondrial rescue.
- May have role in neuropathy prevention with Taxanes.
- L-carnitine overcomes resistance to EPO blood builders.
- Protects the heart from Herceptin.
- Contraindicated in seizure disorder, or if there is a history of epileptic seizures.
Co-enzyme Q-10

• Electron transport molecule in oxidative respiration, essential to ATP production.

• Free radical scavenger. Protects mitochondria from oxidative stress.

• Co-Q10 strongly protects the heart from damage from anthracyclines. Doxorubicin is an antibiotic lethal to healthy cells as well as cancer cells, linked to injury to mitochondria, which have bacteria-like properties.

• Supports recovery from organ failure including heart, liver and kidneys.

• Rx daily 300+ mg of ubiquinone or 100+ mg of ubiquinol.
• Pyrroloquinoline quinone is a very potent antioxidant found in parsley, green tea, green peppers, spinach, carrots, kiwi, papaya, and tofu.
• Supplemented at 10-40 mg it is highly effective for memory.
• Protects mitochondria from oxidative stress.
• Stimulates mitochondrial biogenesis.
• Chemo-protective, neuro-protective, stimulates nerve growth factors, blocks intrinsic nitric oxide synthase, protects cells from beta amyloid.
Niacinamide – Vitamin B3

• Niacinamide becomes nicotinamide adenine dinucleotide (NAD+), a critical regulator of redox and mitochondrial function.
• NAD+ determines function of sirtuin metabolic sensors and regulators.
• Mammalian longevity protein sirtuin SIRT1-7 utilizes NAD+ to deacetylate proteins in different functional subcellular compartments with a strong convergence on optimizing mitochondrial function.
• NAD+ is needed by PARP [poly(ADP-ribose) poly-merase] family, protectors against genotoxic stress.

Miscellany for Mitochondria

• Cysteine
• N-Acetyl-Cysteine
• Methionine
• Hesperidin
• Diosmin
• DHEA
• Vit. B2 - Riboflavin
• D-ribose
• Carnosine
• Melatonin

• Resveratrol
• Ellagic acid
• Curcumin,
• Cinnamic acid
• Lutein & Zeaxanthin
• Lycopene
• Indole-3-carbinol
• Selenium
• Ginkgo biloba
• Vit. E - mixed tocopherols
Epigenetics

• Epigenetic switches determine the expression and function of genes without changing the inherited nucleotide sequences. Cells can adapt and reprogram the gene set to optimize survival.

• Environmental signals “select, modify, and regulate gene activity.....Our genes are constantly being remodeled in response to life experiences....Our perceptions of life shape our biology.”

Bruce Lipton The Biology of Belief 2015 Hay House
Simple gene set – but complex controls

• The human genome is remarkably simple, but the complexity of the epigenetic modulators is also remarkable.

• Epigenetic controls act through changes in DNA:
  o methylation and hydroxyl-methylation
  o methylation, acetylation, and phosphorylation of histone tails
  o non-coding microRNA
  o chromatin structure

*Epigenetics: A Primer for Clinicians, Paluch, Naqash, Brumberger, et al., Blood Rev. 2016*
Genes ↔ Metabolism

• Nutrition, behaviour, stress and toxins → adaptive patterns of methylation and hydroxyl-methylation; methylation, acetylation, and phosphorylation of histone tails, non-coding microRNA, chromatin structure, and non-coding RNA → Epimutations.

• These epigenetic changes are reversible or modifiable by dietary polyphenols such as soy genistein, resveratrol, curcumin, sulforaphane and catechins.

• Nutrients and metabolites such as NAD+, iron, acetyl-coA, ketoglutarate, and S-adenosylmethionine are necessary for DNA repair enzymes, methylation, histone modifications, microRNA and chromatin rearrangements. These depend on mitochondrial function and the balance of glycolysis and aerobic metabolism.

• “Gene regulation is thus linked to the metabolic status of cells.”


Chromatin Remodeling

• Chromatin states determine activity in many tumour-promoting genes.
• Chromatin remodeling factor Bmi-1 is suppressed and its phosphorylation decreased by green tea polyphenol EGCG.
• Bmi-1 is a member of the polycomb repressive complex 1 which protects DNA integrity.
• Inhibiting Bmi-1 reduces survival of transformed cells such as squamous cell cancers.

Methyl Cycle

Methyl cycle influences:
- Ornithine/arginine cycling.
- Catecholamine reduction.
- Histamine reduction.
- Sulfite reduction.
- Phase 2 primary detox: ammonia, urea.
- Rapidly growing tissues: GI lining, bone marrow, muscle, cancer.
- Low methylation = low AMP!
Agouti Mice  (from NWNPC 2012)

• Short lifespan due to cancer, diabetes, obesity – if fed basic Purina Rat Chow.
• Hypo-methylation leads to loss of imprinting of the IGF-1 gene.
• Feeding extra zinc, methionine, folate, choline and B12 alters their genes, and as long as a good diet is given, the offspring are normal for generations!
Methylation in Cancer

• Methylation is a critical epigenetic modulator of oncogenes.
• Methylation resources are used up in detoxification of carcinogens, excess hormones, catecholamines, hormone disruptors, and toxic pollutants ie POPs. Glutathione depletion correlates with methylation arrest.
• Methylation deficit triggers inactivation of phosphatases. The damaged phosphatases localize to the nucleus, triggering dysregulation of cell cycle proteins, and inactivation of controllers of mitosis.
• Reactivation of the fetal growth gene cassette → symmetrical mitosis → undifferentiated and exponential cancer cell growth.
PP2A Methylation

- An epigenetic brake on excess mitosis is methylated phosphatase PP2A.
- Cellular distribution of methylated PPA2 is altered by accumulation of triglycerides, creating dysmethylation.
- Poor methylation of PP2A allows the insulin receptor to operate unopposed, triggering mitosis.
- Unmethylated PP2A fails to dephosphorylate M2 pyruvate kinase (PK) and pyruvate dehydrogenase (PDH). They remain inactive, creating a biochemical bottleneck, which creates a new metabolic economy.
Methylation of microRNA and Carcinogenesis

- Methylation of specific microRNAs (MIR1, MIR9, MIR124, MIR137, MIR34B/C) often occurs in an age-dependent manner, as a field defect in some instances, and may be an early event in colitis-associated carcinogenesis.
- Specific mRNA signature patterns could be used to identify patients with ulcerative colitis (UC) patients who are at increased risk for colorectal neoplasia.
- Methylation of all miRNAs was significantly higher in samples from patients with dysplasia or CRC compared to samples from patients without neoplasia.
- Methylation levels of miRNAs in rectal mucosa accurately differentiated patients with CRC from those without.

Betaine

- Betaine is found in food such as whole grains, marine invertebrates/seafood, and spinach: eg Pesco-vegetarian Mediterranean diet.
- Betaine is a methyl donor. Methylation is vital to lipid metabolism and epigenetic controls.
- Key in metabolism of B6, B12, folate, methionine, homocysteine.
- Betaine protects proteins, enzymes and cells from stress.
- Prevents and treats fatty liver disease (steatosis) due to excess intake of sucrose, fructose and fat.
- Betaine and methylation resources are used up in detoxification of carcinogens, excess hormones, hormone disruptors, and toxic pollutants. So...organic pesco-vegetarian Mediterranean.

Leaving a Legacy

• DNA methylation is alterable and durable through generations.
• Non-coding RNA and chromatin proteins in gametes transmit phenotypes to offspring.
• Environmental memories passed on for 14 generations in roundworms.

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• Nematodes briefly exposed to high temperatures alter the methylation of histones in transgenes for fluorescence.
• These genes remain activated in 14+ generations of progeny kept at lower temperatures than would activate the gene.
• Short-lived worms leave a very long legacy of their environmental challenges.


Sins of the Father

• Paternal gene methylation is remodeled during spermatogenesis.
• Lifelong exposure to folate excess or deficiency caused variance in gene methylation.
• Sperm methylation changes can also be seen 10 years after chemo for osteosarcoma.
• Offspring inherited unstable methylation patterns and increased risk of mortality.

Epigenetic Miasms – Taints that Last a Lifetime, or More.

- Epigenetic changes have been found in the lungs of smokers and cord blood of infants prenatally exposed to smoke.
- Studies show an association between famine in Sweden, Germany and China and shortened lifespans and schizophrenia in subsequent generations.
- In mice and humans studies of nutritional deficiencies that lead to disease, there is an indication that epigenetic changes may occur early in life and can be heritable.
- The modern revolution in gene sequencing has revealed many mutations in cancers that control epigenetic factors.

The Gamete Game

• Pre-diabetic fathers have changes in their sperm cytosine methylation.
• Differentially methylated loci can be transmitted to pancreatic islet cells in progeny. These increase risk of diabetes for at least 2 generations!
• Other epigenetic alterations in gametes, including chromatin changes and non-coding RNA, can transmit phenotypes to offspring.
• Gamete epimutations are seen in fruit flies, roundworms, rats, mice and humans.

Perinatal and Childhood Imprints

A critical set of 9 inflammation regulating genes is influenced by neo-natal, peri-natal and childhood circumstances, including:

- Socioeconomic status
- Birth in a stressful period, such as the dry season in the tropics
- Extended parental absences in childhood
- Nutritional stress
- Microbial stress
- Psychosocial exposures

Impacts occurrences in adult life of inflammatory diseases such as cardiovascular events.

Epigenetic Taints are Reversible

• Mice exposed to trauma pass along to progeny increased glucocorticoid receptor expression in the hippocampus, altering behavioural responses to stressors relative to controls.
• The GR gene is relatively demethylated in the germline cells of stressed mice. The “sperm methylome” passes to the progeny.
• The adaptive and coping responses to trauma are enhanced, including increased avoidance of stressors.
• This GR alteration can be corrected by providing a very calm and supportive environment for the impacted progeny. Enhanced sensory, motor and cognitive stimulation and socialization reverse the inherited changes.

Hug ‘em up!

- Holding and attending to infants improves their resistance to epigenetic aging.
- High contact children had altered methylation in 5 genes, involving functions such as immunity and metabolism.
- They exhibit less stress and fussing. They thrive.
- Four years later the benefit persists.
- Perinatal physical contact and comfort improves their life, lifelong.

Demethylation by Botanicals

- O6-methylguanine-DNA methyltransferase (MGMT) eliminates mutagenic, carcinogenic and cytotoxic lesions from O6-alkylguanines induced by exogenous alkylating agents.
- **Neem, ashwagandha, holy basil** and **oregano** increase MGMT microRNA and its demethylation activity, increasing DNA repair, protecting the genome.
- Less potent MGMT effects are seen with **gooseberry, spearmint** and **common basil**.

Histone Regulation

Modulating histone protein de/acylation prevents silencing of good tumor suppressor genes, turns off oncogenes, and supports DNA regulation:

• vitamin C.
• cruciferae isothiocyanates – eg sulforaphane downregulates deacetylation enzymes.
• curcumin, green tea EGCG, grape cyanidins.
• garcinol, milk thistle silymarin, parsley apigenin, baicalein, rosemary, niacinamide.
Citrate Replaces Pyruvate

• Cancer cells must find another way to obtain acetyl-Co-A, since pyruvate is no longer generated. Instead, tumours rely on lipolysis and fatty acid β-oxidation from body fat stores.
• This acetyl-Co-A is condensed into citrate.
• Less ketone bodies and butyrate are produced, de-inhibiting histone protein deacetylation.
Loss of Oncogene Silencing Histones

Shifts in histone deacetylation trigger up-regulation of oncogene kinases. Tyrosine kinases are necessary to reprogram mitosis.

Insulin-tyrosine kinase signaling increases, triggering an influx of glucose, an increase in mitosis, and an inhibition of apoptosis, i.e. increased cancer cell survival.

Switching off of pyruvate kinase and pyruvate dehydrognase kinases favors tumor production of cellular components: lipids for cell membranes, RNA, DNA, ribosomes, etc. This mixed aerobic and anaerobic economy supports rapid cell reproduction.

Epigenetics and Extravirgin Olive Oil

• Olive oil acts through the endocannabinoid receptor CB1 to up-regulate CNR1 gene.
• 10 days intake resulted in a 4-fold increase in CB1 activity.
• This stimulation was inversely correlated with DNA methylation at the CNR1 CpG promotor miR23a and miR-301a.
• This may be used prevent or treat colon cancer.

Foods that Protect and Repair Genes

- Red bell peppers
- Tomato
- Paprika
- Cinnamon
- Epazote spice
- Endive
- Spinach
- Asparagus
- Tea polyphenols
- Berries
- Cruciferous vegetables
- Broccoli sprouts
- Mustard greens
- Turnip greens
- Basil
- Ginger
- Garlic
- Persimmons
- Grapes
- Eggs
- Duck liver
Vitamins and Epigenetics

• Vitamin C potentiates TET’s catalytic activity.
• Vit. A stimulates expression of ten-eleven translocation demethylases (TET).
• Synergistically they enhance reprogramming of differentiated cells.
• Vitamin C enhancement of DNA histone demethylases regulates epigenetic signatures of stem cells, improving somatic cell reprogramming.
• Vitamin C also acts as a cofactor for Fe+2/αKG-dioxygenases which regulate stem cell epigenetics.

Keys to Healthy Metabolism, Mitochondria, & Epigenetics

• Mediterranean diet – vegetables, seafood, whole grains, olive oil, legumes, seeds, berries.
• Reduce sugar, salt, meat.
• Vitamin C, quercetin, alpha lipoic acid, thiamine, resveratrol, curcumin, sulforaphane, catechins, proanthocyanidins, omega 3 oils, Co-Q10, PQQ.
• Berberine, *Centella asiatica*.
• Exercise.
• A peaceful, secure, supportive environment.
• Cognitive and social stimulation. Hugs. Love.
• Detox from heavy metals, avoid drugs, and dechemicalize.