Systemic Formulas: Solutions Here & Now • Research Report #8

Mitochondrial Biogenesis

A MORE EFFECTIVE METHOD TO INCREASE LIFE-ENERGY FOR HEALING & OPTIMAL HEALTH

A Clinician To Clinician Colloquy By Dr. Jack Tips (N.D., Ph.D., C.C.N., C.Hom.)

Cellular energy production is first based on healthy cell wall membranes and mitochondrial-membranes, and in this Report, we'll examine processes that occur within the mitochondrial mtDNA and the cell nucleus nDNA that presents a revolutionary approach to nutritional support of the body's innate processes that contribute to the increase in the number of healthy mitochondria[1].

Mitochondrial synthesis of ATP (Adenosine Triphosphate—the chemical energy of life) via the *Citric Acid Cycle*[2] [as well as *Beta Oxidation*[3] that converts fats to Acetyl CoA for the Citric Acid Cycle] can help solve the human energy crisis with nutritional funding (oxygen, fatty acids, vitamins, nutrients), but there is another way, an even better way—that has not been effectively introduced to health professionals until now. This new way is still dependent on functional mitochondrial ATP processes, and it is synonymous with youthfulness, disease prevention, increased athletic performance, and more optimal health. What is it? It's ***mitochondrial biogenesis*** whereby a cell can increase the number of its life energy producing engines—the mitochondria, and here we will examine five biogenic pathways that respond to supplementation to increase the number of mitochondria.

Energy is like money in your pocket. You can do so many wonderful things when your pockets are full of money, but you can only heave a wistful sigh if your pockets are empty. Here we'll discuss not only how to fill your cell's energy pockets for abundant health and longevity, but how to have more pockets to hold even more energy.

Modern science has a renewed interest in the biology of the mitochondrion and its role in the redox production of cellular energy (ATP), thermogenesis (heat), and apoptosis (self-initiated cell death), because the micochondrion is the new arena where the drama between health and disease is played. Of critical importance is the recognition that mitochondrial function contributes to several inherited and practically all acquired human diseases and the aging process. So let's get acquainted with the regulatory mechanisms involved in the biogenesis and energy-metabolic function of mitochondria because our cells are the wellspring of our quality of life, and nutrition is often the determining factor between health and disease.

In Research Report #7: *ATP—The Energy of Life*, we discussed the importance of ATP (Adenosine TriPhosphate—the chemical energy of life). We established that our patients today are deficient in adequate ATP energy, and this

1 **Mitochondrion** (singular), **Mitochondria** (pleural) – inside most cells are organelles known as 'mitochondria' that often referred to as "cellular power plants" because they generate most of the cell's **a**denosine **t**ri**p**hosphate (ATP) which is the source of the body's chemical energy. Mitochondria are also involved in cellular communication (signaling) where the cell's innate intelligence is able to perceive changes in its environment and direct responses such as tissue repair, immunological actions, and homeostasis.

2 **The Citric Acid Cycle** — aka tricarboxylic acid cycle (TCA cycle), Krebs cycle, or Szent-Györgyi-Krebs cycle — is a series of enzymecatalyzed chemical reactions, which is of central importance in all living cells, especially those that use oxygen as part of cellular respiration. In human cells, the Citric Acid Cycle occurs in the matrix of the mitochondrion.

3 **Beta oxidation** is the process by which fatty acids, in the form of Acyl-CoA molecules, are broken down in mitochondria and/or in peroxisomes to generate Acetyl-CoA, the entry molecule for the Citric Acid cycle.

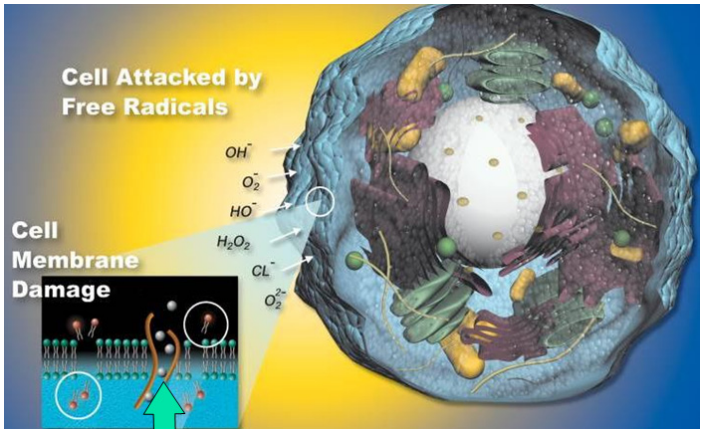
inadequacy prevents the effective healing results our patients need. Further, we discussed how today's environment of toxins (pesticides, chemicals, air pollution) and non-ionizing, electromagnetic radiations (microwave, wifi, cell phones, electrical appliances) damage mtDNA, resulting in lower ATP production as well as planting the seeds of destruction (apoptosis, cancer). These two onslaughts, coupled with errant food choices (processed foods), inadequate nutrient density (commercial agriculture), and deranged foods (genetically-modified commercial corn, soy, Hawaiian papaya, etc.) cause poor nutrition and becomes the "recipe for health disaster" that is contributing to the alarming rise in chronic, degenerative, and autoimmune diseases.

To summarize those key points, our toxic global environment

is not just putting unwanted poisons in our bodies that we have to detoxify; today, the chemical toxins cause cellular inflammation and free radical[4] damage to the mitochondrial ATP production processes, and thus inhibit the body's ability to perform healthy cellular functions. With reduced ATP, our bodies simply cannot recover and repair—they don't have the cellular energy to do the work of repairing DNA, increasing mitochondrial ATP, and rebuilding tissue function. Thus, we find that the tools we used in the 20th Century (herbs, vitamins, minerals, nutriments, natural therapies) do not work as well now as they did back then. This is the reason for Systemic Formulas' campaign to develop and market cellular healing formulas for increased clinical results.

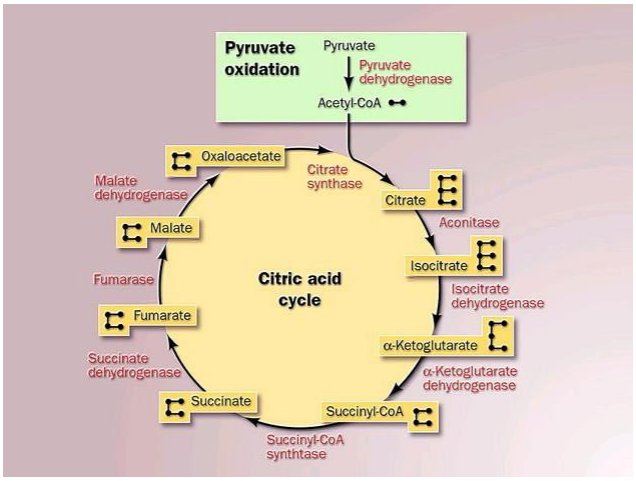
The "game of health maintenance" has changed. No longer can we simply provide nutrients to the body and expect the body to "fix" itself, because the foods and nutrients are not able to get past the inflamed cell membranes (cell wall, mitochondrial membrane, nucleus membrane) with the molecules necessary for self-healing to correct errant functions. You've heard the phrase, "It takes money to make money." In cellular biology, "It takes ATP to make ATP." It takes ATP for nutrients to be absorbed and assimilated. It takes ATP to process and humanize nutrients. It takes ATP to get nutrients inside the cells. Once there, the nutrients need to create more ATP than they took to get there. And it takes ATP to detoxify the environmental and metabolic wastes. This is why you've heard the phrase, "Energy is everything." Our health and our lives are based upon energy and the circulation of energy. Doc Wheelwright's nutritional insights presented in the book: *The Pro-Vita! Plan For Optimal Nutrition* specifically addresses the need for nutrition to deliver more energy than it takes to manage the nutritional processes.

For many years, nutritional companies have marketed



formulas that support ATP with ingredients such as magnesium, Co-enzyme Q10, alpha ketogluterate, B-vitamins, and so forth. While being cutting edge to address the ATP topic, such formulas fail to address the underlying cause of mitochondrial distress and most often the results are less than what was desired. Simply providing the body with the various nutrients known to support the mitochondrial processes of making ATP – *Citric Acid Cycle, Beta Oxidation* – is no more effective than giving a check to a hungry person

4 **Free Radical** – An atom or group of atoms that has at least one unpaired electron and is therefore unstable and highly reactive. In animal tissues, free radicals can damage cells and are believed to accelerate the progression of cancer, cardiovascular disease, and age-related diseases.



on Sunday when the banks are closed.

The focus of such formulas has been on the *Citric Acid Cycle* processes that are necessary for ATP energy production. Here's a quick refresher:

- **Oxidative Phosphorylation** – A metabolic pathway that uses energy released by nutrient oxidation to produce ATP. Highly efficient way of releasing energy, compared to alternative fermentation anaerobic glycolysis.
- **Electron Transport System** – Redox is carried out by protein complexes within mitochondria. These linked sets of proteins are called *electron transport chains*.
- **Chemiosmotic Gradient** – (Respiratory Control) Electron Transport cannot take place without pumping protons out of the mitochondrial membrane gradient, plus (+) to minus (–). Proton pumping produces, restricts, and protects the rate of Electron Transport, thus the rate of ATP production. The gradient is responsible for ATP synthesis.
- **ATP Synthase** – Energy is tapped by protons flowing back across the membrane, down the chemiosmotic gradient, through an enzyme-machine called *ATP Synthase*.
- **Beta Oxidation** is the process by which fatty acids, in the form of Acetyl-CoA molecules, are broken down in mitochondria and/or in peroxisomes[5] to generate Acetyl-CoA, the entry molecule for the *Citric Acid Cycle*. The *beta oxidation* of fatty acids involves three stages: 1) activation of fatty acids in the cytosol, 2) transport of fatty acids into mitochondria (carnitine shuttle), 3) *Beta oxidation* proper in the mitochondrial matrix. Fatty acids are oxidized by most of the tissues in the body; however, the brain can barely utilize fatty acids for energy requirements (a safeguard against loss of fatty brain tissue), while red blood cells and the adrenal medulla cannot use them at all. With other cells, beta oxidation is a method to tap into the huge energy reserves inherent in their membranes.

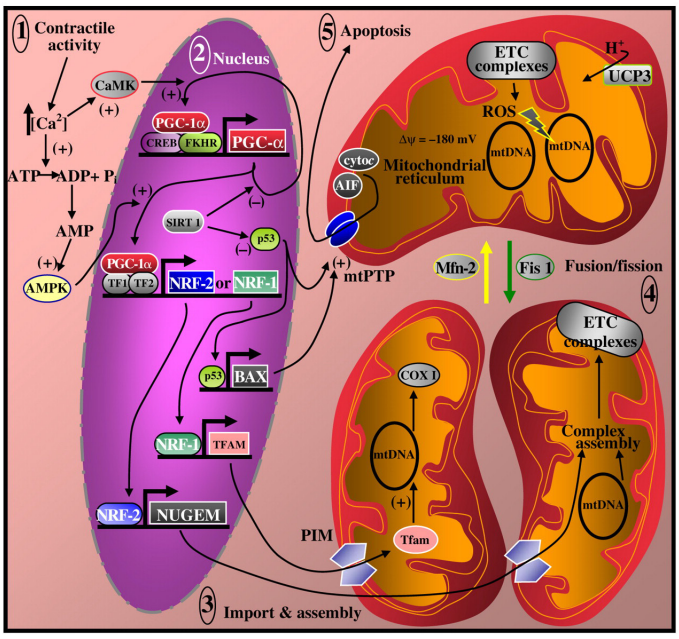
The feeding of the *Citric Acid Cycle* is a basic, nutritional approach to ensuring that the components of energy production are available. The Citric Acid Cycle is dependent upon :

- Vitamins: B-1, B-2, B-3, B-5, C, D3, E
- Proteins: Carnitine, Cysteine, Tryptophan, Glutamine, Histadine, Glutamic Acid, Valine, Isoleucine, Methionine, Proline, Tyrosine, Phenylalanine, etc.
- Minerals: Iron, Magnesium, Zinc, Phosphorus, Manganese, Sulphur, Potassium, Sodium, Selenium
- Nutrients: Lipoic Acid, CoEnzyme Q-10, Alpha Ketogluterate, etc.

However, a warped violin can never produce a pleasing note, and giving nutrients to damaged mitochondria simply won't get the job done. This is but one reason that nutritional therapeutics has to change in the 21st Century and address even deeper facets of life and energy.

So, let's turn our attention to the body's innate process called *mitochondrial biogenesis*. This is how the cells make new mitochondrial engines. If the cells can generate new,

5 **Peroxisomes** – organelles found in virtually all eukaryotic cells involved in the catabolism of very long chain fatty acids, branched chain fatty acids, D-amino acids, polyamines, and biosynthesis of plasmalogens, etherphospholipids critical for the normal function of mammalian brains and lungs. They also contain approximately 10% of the total activity of two enzymes in the pentose phosphate pathway, which is important for ATP energy metabolism.



healthy mitochondria and discard the old damaged ones, the body can reclaim its health and experience the symptom-free vitality called *optimal health*.

This means that a winning strategy for health restoration must first "Remove the Source" and this is why many practitioners utilize the information in Research Report #4: *A New Model For Detoxification* as a necessary prerequisite to all healing endeavors.

Then, provide the mitochondria the nutrients for foundational function. This includes nutritional intake of fuel (polysaccharides[6]), as well as functional nutrients (vitamins, minerals, enzymes, nutriments, phyto-anti-oxidants), and most importantly our strategy must advance our nutritional work into the 21st Century by providing nutrients that support mitochondrial biogenesis.

In The Midst of Greatness. Look at how our focus on cellular healing is the nutritional key to protecting human life in the 21st Century. We address six processes essential to cellular healing:

- **Remove The Source** with the Systemic Detoxification Program—and do it right!
- **Reduce Inflammation** and promote youthful genetic expressions with ROX (Super Antioxidant with Resveratrol), and break the inner cellular free radical cascade called the "NO/ONOO cycle" with EPIC (Metabolic NO/ONOO),
- **Reestablish Methylation** with the necessary methyl groups that switch off disease processes and switch on proper cellular function with MoRS (Methyl Donors),
- **Regenerate Cell Membranes** for proper cell respiration and function with the VISTA membrane formulae,
- **Restore** ATP and increase mitochondrial biogenesis with eNRG (Quantum ATP) – our topic here,
- **Repair** DNA and strengthen tissue integrity for optimal performance with the tissue-specific BioFunction Formulas.

The Problem: Mitochondrial Damage. Several key factors are conspiring to destroy mitochondrial function. This was not the problem in the past that it is today. In the past, the mitochondria dwelt in sacrosanct safety inside the cells protected by two membranes (the cell wall and the mitochondrial membrane) like kings and queens in their fortresses of city walls and castle walls. But the conspirators have found ways to breach the defenses and kill the king and queen or poison them into madness and irrational behaviors.

6 **Polysaccharide** – refers to carbohydrate structures ($C_6H_{10}O_5$ -- comprised of carbon, hydrogen and oxygen),that are linked together as repeating units. Poly means "many" and saccharide means "carbohydrate". Polysaccharides play an important role as part of the optimal fuel for the cell to create energy. They also play a major role in the workings of the immune system, reproductive system, elimination of pathogens, blood clotting, and body-development.

Here is a brief list of conspirators. See how many are affecting you personally.

- Lack of antioxidant nutrients (How's your Meta-Oxy score?)
- Refined Sugar ("Okay, just this once. That dessert looks sooooo good.)
- Lack of phytonutrients (How's your raw vegetable and fruit intake?)
- Pesticides (Do you only eat organic? That commercially-produced spinach salad last night contained over 48 neurotoxic chemicals[7].)
- Genetically modified (GMO) foods. (Do you eat commercial corn or soy? Corn is in practically every processed food.) Foods with altered molecules (GMO and microwave-cooked food) do not support cellular health and cause confusion in the body's life processes.
- Environmental toxins (Do you breathe, eat, drink, have plastics, use commercial cosmetics, use canned foods, use cleaning products, etc.)
- Non-ionizing radiation (do you fly on airplanes, use a cell phone, have a wifi, use Bluetooth® devices, sleep in hotels, drive a car?) [And of course there's ionizing nuclear radiation getting into the food supply (milk, meat, etc.) due to nuclear reactor leakage and other sources.]

The issue with today's environment is not just that it's toxic, it's that the toxins breech the city and castle walls and damage the mtDNA and nDNA. Thus the conspirators have found a way to damage the cell's life code—the instructional manual for all life processes. Damaged life code results in diseases such as cancer, and kills millions of people every year and drains nations' financial coffers with expensive, ineffective treatments.

Our patients used to come to us with nutritional depletion, massive toxins, and weakened tissues. Natural therapies: increase nutrition, eliminate toxins, and strengthen tissues! This was the basis for the amazing success and growth of the natural health movement from 1960 to 1990 where it became a multi-billion dollar industry. Note: the self-perpetuating, localized free radical cascade (NO/ONOO) had not been identified by Dr. Martin Pall yet. No one suspected that the ubiquitous methyl groups could be depleted and methylation impaired, and science had not figured out that ATP was being depleted faster than a cell phone battery downloading a video.

By 1990, nutritional therapies became less effective as the old methods could not address the new, insidious cellular damages occurring within: 1) the cell membranes; 2) mitochondrial energy production processes, and 3) the cell nucleus and the chromosomes.

Twenty years later, cancer, iatrogenic disease, heart disease, chronic degenerative disease and autoimmune diseases have skyrocketed destroying millions of lives while the medical cartel uses governmental laws to monopolize the industry and big pharma ensures that treatments only palliate and don't cure. Out of this sad state of affairs comes a new hope for people via nutritional therapeutics.

Dr. Shayne Morris, grandson of A.S. "Doc" Wheelwright whose herbal research changed the course of herbal therapeutics in the 20th Century, started investigating the role of nutritional therapeutics to solve the plight of the cells in the 21st Century. From his metabolomic[8] research, Dr. Morris has developed effective, cutting edge formulas that restore clinical effectiveness to the nutritional

7 Pesticide Residues on Fresh and Processed Fruit and Vegetables, Grains, Meats, Milk, and Drinking Water, Outlooks on Pesticide Management, June, 2005.Punzi, JS, Lamont, M, Haynes, D, Epstein, RL, USDA Pesticide Data Program

8 **Metabolomics** – the scientific study of chemical processes involving metabolites and the unique chemical fingerprints (metabolic profiles) that specific cellular processes leave behind.

based therapies. Pursuant to this Report is the eNRG (Quantum Cellular ATP) formula which not only focuses on comprehensively supporting the *Citric Acid Cycle* and *Beta Oxidation* processes that allow the cellular machinery to manufacture more ATP, but it directly supports *mitochondrial biogenesis*—and this is a major breakthrough in nutritional therapeutics.

Mitochondrial Biogenesis is the natural cellular process by which additional mitochondria are created. The process is activated by several different signals that most often occur during times of cellular stress or in response to various environmental stimuli that occur when the Innate Cellular Intelligence recognizes that there is an increasing demand for energy to survive lean times, weather a brutal winter, migrate to a better climate, or conduct more muscular work; the cells can generate more mitochondria to make more energy for survival. The mitochondria are the cells key metabolic regulators, and is also an important organelle in both production and degradation of free radicals necessary to produce ATP.

The universal call for mitochondrial biogenesis comes from exercise. Figure that in the history of humankind, threats to life usually involved exercise as a solution – the exercise of generating a fever, the exercise of fleeing from enemies, the exercise of migration, the instant flight or fight response to attackers, moving to keep warm, the exercise of building shelter, and acquiring clothing and food. The more the body exercises, the more the cells acknowledge and respond to the need for more energy production by cloning mitochondria and creating more ATP-producing engines.

Mitochondria are produced from the transcription and implementation of genetic information both in the nuclear genome and in the mitochondrial genome. The majority of mitochondrial protein comes from the nuclear genome, while the mitochondrial genome encodes most parts of the electron transport chain along with mitochondrial rRNA and tRNA.

The cells "read" their state of energy via numerous sensors (various stressors, cold, caloric requirements, nutrients, exercise level, inner cellular processes) that tell the cells to increase mitochondrial production of ATP through mitochondrial biogenesis. The master regulators of mitochondrial biogenesis are the peroxisome proliferator-activated receptor gamma (PGC) family of transcriptional coactivators. PGC-1α, in particular, is known as the "master regulator" directly responsible for transcribing nuclear-encoded mitochondrial proteins[9]. All the genes involved with mitochondrial biogenesis have receptors for PCG.

The Master Regulator: PGC-1α – Peroxisome Proliferator-Activated Receptor Gamma Co-activator 1-alpha.

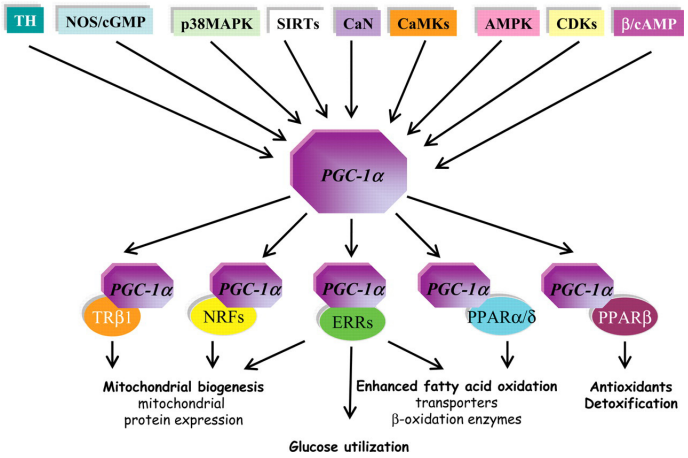
This master regulator transcriptional protein is the chief pathway for mitochondrial biogenesis[10]. Among its various roles in cellular biology, it increases lipid and glucose oxidation for ATP energy[11]. In the muscles, it helps reduce inflammation. Further, while PGC-1α increases the redox processes of creating ATP, it also helps support the processes that protect the cells from free-radical damage[12].

9 *Bioenergetic Analysis of Peroxisome Proliferator-activated Receptor γ Coactivators 1aand 1b (PGC-1α and PGC-1b) in Muscle Cells*, J. Biological Chemistry, Vol. 278, No. 29, Issue of July 18, pp. 26597–26603, 2003

10 *Mechanisms Controlling Mitochondrial Biogenesis and Respiration through the Thermogenic Coactivator PGC-1*. Wu, Puigserver, Andersson, Zhang, Adelmant, Mootha, Troy, Cinti, Bradford Lowell, Scarpulla, Spiegelman. Dana-Farber Cancer Institute, Department of Cell Biology Harvard Medical School Boston, Department of Cell and Molecular Biology Northwestern University Medical, Division of Endocrinology and Metabolism Department of Medicine Beth Israel Deaconess Medical Center Boston, Istituto di Morfologia Umana Normale-Anatomia Facolta di Medicina e Chirurgia Universita di Ancona

11 *AdvPhysiolEdu 30:145-151, 2006 PGC-1α*: a key regulator of energy metabolism Liangand Ward Department of Cellular and Structural Biology, Audie Murphy Veterans Administration Medical Center and University of Texas Health Science Center, San Antonio, Texas, Barshop Institute for Longevity and Aging Studies, Audie Murphy Veterans Administration Medical Center and University of Texas Health Science Center Department of Physiology, Audie Murphy Veterans Administration Medical Center and University of Texas Health Science Center, San Antonio, Texas

12 PGC-1a regulates the mitochondrial antioxidant defense system in vascular endothelial cells, Cardiovascular Research 66 (2005) 562–573



PGC-1α Suppresses Inflammation

Physical Activity. We all know that inadequate physical activity is linked with many diseases such as diabetes and heart disease. Exercise somehow improves cellular function, reduces insulin resistance, increases bone density, improves blood pressure and arterial health, and promotes detoxification. We also know that too much exercise increases free radical damage and creates a need for more antioxidant foods (fruit and vegetables) and today, increases the need for anti-oxidant supplementation. What is unknown, at this point, is how muscle metabolism imparts systemic benefits to cells throughout the body.

One likely candidate to explain the profound benefits of exercise is PGC-1a[13], as it controls several aspects of muscle metabolism including muscle plasticity and suppression of numerous inflammation pathways. A simple correlation between work-saving devices—cars, escalators, elevators, washing machines, etc.—and the increase of a broad spectrum of diseases such as obesity, diabetes, heart and cardiovascular concerns, musculoskeletal, neurodegenerative disorders and hypertension; has caused researchers to investigate the molecular role of physical exertion and its role in good heath.

From that correlation science can unequivocally state that a sedentary lifestyle is a strong predictor of mortality and disease[14]. Thus, the shift in childhood activities from sports and work to video/computer games and television watching is directly correlated to childhood obesity and disease; and the same holds true for elderly people who retire from physical activity.[15]

In contrast to the dismal statistics of sedentary lifestyles is research that extols the virtues of physical activity as curative for diseases such as Osteoporosis, Diabetes Type 2, Alzheimers, Multiple Sclerolosis, Sarcopenia, and Obesity, in and of itself, and rivals or exceeds the benefits of prescription drugs.[16]

Most, if not all, chronic degenerative diseases are associated with chronic cellular inflammation. Insulin resistance, for example, is closely linked with immune cell infiltration (inflammation) in the white adipose tissue[17]. The biogenesis and progression of tumors is stimulated by pro-inflammatory cytokines.[18] Atherosclerosis and arterial disease is directly caused by the inflammation processes (the oxidation of cholesterol that the body uses to protect itself).[19]

The anti-inflammatory benefits of activated processes are governed by gene-expressions that control Reactive Oxygen Species (ROS). One of PGC-1α's roles is the suppression

13 Nature. 2008 July 24; 454(7203): 463–469.The role of exercise and PGC1α in inflammation and chronic disease.Handschin, Spiegelman.Institute of Physiology and Zurich Center for Integrative Human Physiology, University of Zurich; Dana-Farber Cancer Institute and Department of Cell Biology, Harvard Medical School.

14 Eriksson G, et al. Changes in physical fitness and changes in mortality. Lancet. 1998;352(9130):759–762.

15 Booth FW, Lees SJ. Fundamental questions about genes, inactivity, and chronic diseases. Physiol Genomics. 2007;28(2):146–157.

16 Knowler WC, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393–403.

17 Hotamisligil GS. Inflammation and metabolic disorders.Nature. 2006;444(7121):860–867.

18 Lin WW, Karin M. A cytokine-mediated link between innate immunity, inflammation, and cancer.J Clin Invest. 2007;117(5):1175–1183.

19 Haffner SM. The metabolic syndrome: inflammation, diabetes mellitus, and cardiovascular disease. Am J Cardiol.2006;97(2A):3A–11A.

of inflammation through the utilization of ATP and the detoxification of ROS through uncoupling proteins that prevent chronic cellular free radical mediated inflammation.[20] Particularly noteworthy is the fact that PGC-1α regulates the mitochondrial free radical defense system that protects the mitochondrial DNA from damage and the mitochondrial membrane from inflammation.[21]

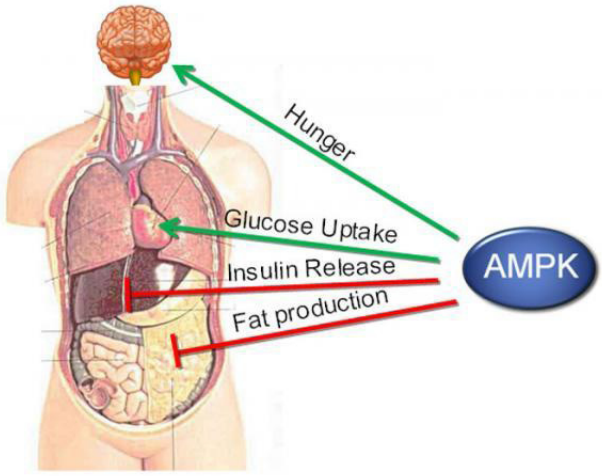
Further, PGC-1α plays vital roles in many body processes including generating heat from brown fat tissue, brain function, heart performance, skeletal muscle operations, liver function, metabolic disease prevention, and cellular insulin sensitivity[22]. The gene that controls the transcription (expression) of PGC-1α is SIRT1, the longevity gene.

Most of the other molecules that trigger mitochondrial biogenesis are activators of PGC-1α.

The Cell's Fuel Gage: AMPK (5' adenosine monophosphate-activated protein kinase)

From its name, we can quickly gather that AMPK is a protein-enzyme. It is activated when the cell runs short of ATP. So when the cell perceives that its energy is low, it takes survival measures and activates AMPK to do certain things to conserve energy and increase energy production. Thus AMPK maintains the energy balance in the cell.

AMPK's purpose is to "uncouple," thus it's known as an "uncoupler[23]." Externally derived uncouplers are considered toxins because they interfere with the Electron Transport Chain (ETC) and anything that interferes with the ETC messes with the proton gradient that allows ATP synthesis. But the cell's innate intelligence knows where and when to internally uncouple for their benefit.



Pesticides are uncouplers. Some antibiotics are uncouplers. Carbon monoxide from the burning of fossil fuels is an uncoupler. But AMPK is the body's own uncoupler, and responds to uncoupling needs by reducing ATP utilization. This serves a specific and beneficial purpose for the cells—the same way that reducing spending helps keep your bank account from overdrawing. Thus, uncoupling is a natural process of the cell's innate processes. Nutritional support of AMPK via quercetin, lipoic acid, and Resveratrol means that the cells can utilize AMPK for better health and energy.

Other benefits of activated AMPK include better insulin sensitivity (thus is involved with reducing and correcting insulin resistance), and reduced appetite. When AMPK is activated in the brain, the appetite decreases and the body becomes more lean. In the liver, AMPK helps prevent tumors. Also, AMPK slows cholesterol production, and assists with proper fatty acid oxidation in the liver. It stimulates the PGC-1α pathway that results in mitochondrial biogenesis. Here at the cellular level, there is an enzyme, AMPK, that plays numerous beneficial roles in the body and two things support its benefits—nutrition and exercise, thus, activating AMPK stimulates mitochondrial biogenesis[24].

20 St-Pierre J, et al. Suppression of Reactive Oxygen Species and Neurodegeneration by the PGC-1 Transcriptional Coactivators.Cell. 2006;127(2):397–408.

21 Valle I, et al. PGC-1alpha regulates the mitochondrial antioxidant defense system in vascular endothelial cells. Cardiovascular research. 2005;66(3):562–573.

22 **PPARγ Coactivator-1 (PGC-1) Family** – themedicalbiochemistrypage.org

23 **Uncoupler**–the separation of the energy stored in the ion gradients inside mitochondria from the synthesis of ATP. Since this energy is not used to do work, it is dissipated as heat. This strategy is used by hibernating animals and infants to keep warm because their heat energy needs are higher than their ATP needs. Artificial decoupling has been used as a diet aid, often with disastrous results.

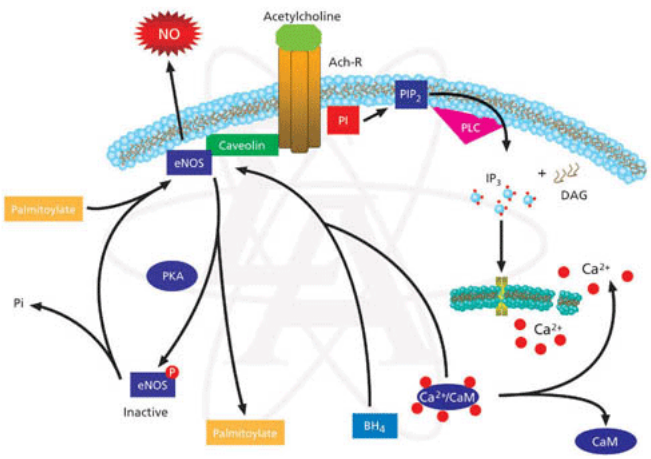
24 AMP kinase is required for mitochondrial biogenesis in skeletal muscle in response to chronic energy deprivation. Zong, Ren, Young, Pypaert, Mu, Birnbaum, Shulman. Howard Hughes Medical Institute and the Departments of Internal Medicine, Cell Biology, and Cellular and Molecular Physiology, Yale University School of Medicine, Bristol-Myers Squibb, Princeton, NJ and University of Pennsylvania Medical School

AMPK is activated when cellular levels of ATP drop and levels of AMP (adenosine monophosphate) increase. Because the production of ATP as a triphosphate involves access and utilization of ADP, a diphosphate, and AMP, a monophosphate; the cells can quickly read when ATP is being consumed faster than it's being replenished

When the AMPK fuel gage reads that ATP is low, it slows down the use of ATP, increases the ATP-generating processes such as fat-burning and stimulates the uptake of glucose from the blood into the cells to fuel the ATP production process. Looking at the glucose uptake and fat burning aspects of AMPK, we can quickly discern that AMPK plays a role in cells avoiding or reversing the diabetic diasthesis.

Nitric Oxide

In Research Report #2: *Mitochondrial Dysfunction & The NO/ONOO Cycle*, we learned about how the beneficial molecule Nitric Oxide (NO) can get caught up in a destructive, free-radical, inflammatory cascade when the mitochondria lack the ability to donate electrons from an antioxidant such as glutathione (GSH), superoxide dismutase (SOD), and catalase. In Research Report #3: *Acute Coronary Syndrome*, we learned how NO helps support the heart and arteries by dilating the vessels and helping control blood pressure. And in the webinar, *"The Secret Life of the Mitochondria"* posted at www.systemicformulasmedia.com, we discussed that NO controls the oxygen supply to the cells by regulating the binding and release of oxygen from hemoglobin making NO an important factor in ATP production. [The HQ (Heart Energy) formula addresses cardiac ATP, and EVENTA (Super Amino) addresses NO production.]



Another beneficial function of NO is mitochondrial biogenesis. Through the vehicles of the amino acid, Arginine, plus oxygen, plus the enzyme Nitric Oxide Synthase (NOS), NO can stimulate PGC-1α to initiate more ATP energy production via mitochondrial biogenesis.

"If NO indeed regulates the mitochondrial number in human skeletal muscle, it might be possible to stimulate production of mitochondria in muscles … in order to increase sports performance, reduce obesity, or even reverse aging. We now know that low levels of NO produced by eNOS [endothelial Nitric Oxide Synthase] can stimulate aerobic metabolism by increasing blood perfusion, unloading oxygen from hemoglobin, inducing growth of new blood vessels, and stimulating the biogenesis of mitochondria", said Brown in the article, "*NO Says Yes To Mitochondria*".

In addition to NO inducing PGC-1α, it impacts the SIRT1 gene to express as if in a calorie-restricted mode, thus contributing to reduced aging processes and increased longevity processes. In our culture it's difficult to live in a calorie restricted mode because it means that you must now live on 35% fewer calories. Nutritional support of SIRT1 processes for mitochondrial biogenesis is how the body can maintain longer youthfulness while living a lifestyle of abundant (but not excessive) food.

Here we once again encounter the importance of Resveratrol, and can see why this nutrient is so important to human health. It invokes longevity, serves as an anti-inflammatory nutrient, and coupled with Arginine (e.g. the EVENTA formula), it provides a double "longevity" impact on the SIRT1 gene expression. Thus ROX + eNRG + EVENTA is an excellent recipe for longevity via nutrition.

PQQ. Pyrroloquinolinequinone

PQQ is a cell-signaling[25] cofactor with antioxidant and B vitamin-like activity. When discovered, researchers Kasahara and Kato proposed in their Nature Magazine article[26], *Nutritional biochemistry: A new redox-cofactor vitamin for mammals*, that PQQ should join niacin and riboflavin under the umbrella of B vitamins. Further research established that rather than a vitamin, PQQ is better classified as one of a few compounds that act as cell signaling molecules.

Further, PQQ supports mitochondrial, cognitive, and cardiovascular health so it is labeled a"neuroprotectant" and "cardioprotectant." PQQ is naturally present in vegetables and in the human body, including breast milk.

PQQ promotes cardiovascular health by supporting heart muscle function, cellular oxygen utilization and protecting cell membranes from oxidative stress. PQQ maintains neural health by supporting nerve growth factor (NGF), neuronal receptor activity and molecular signals that promote mitochondrial function. Recent studies show that PQQ supports mental processing and plays a role in thought analysis and memory.

The benefits of Pyrroloquinoline Quinone supplementation include:

- An overall improvement in energy levels[27]
- Improved cognitive function and memory[28]
- Reduction in mitochondrial degradation[29]
- Increased skin elasticity[30]
- Neuro-protectant[31]
- Cardio-protectant[32]
- Enhanced nerve growth[33]
- Supports mitochondrial biogenesis through the PCG-1a transcription[34]

PQQ is a nutritional requirement in the human diet and is prevalent in many healthy foods. Without it, our biochemical functions stop and cannot operate properly. PQQ is prevalent in many foods associated with a healthy diet, so people that eat well-rounded meals should get enough to sustain their biological need. However, modern dietary patterns do not provide optimal amounts due to food processing and cultural avoidance of whole foods. Key foods include: parsley, celery, spinach, cabbage, papaya, raw milk, and legumes.

Currently, PQQ is marketed to people concerned with "graceful aging" as well as for athletic performance based on PQQ's ability to optimize mitochondrial function. From the name, one can see that PQQ is cooperative with Co Enzyme Q-10.

The Fountain Of Youth Gene – SIRT-1: (Sirtuin-1)

SIRT1 is a survival gene that protects cells during times when

25 **Cell Signaling** – Human cells have a complex communication system that coordinates activities between various cells. Cells have innate intelligence and the ability to perceive and respond to their environment. Cell signaling is the basis of proper immune response, tissue repair, detoxification, homeostatic function. Faulty cell signaling can result in auto-immune diseases, cancer, and diabetes.

26 Nature422, 832 (24 April 2003) Nutritional biochemistry: *A new redox-cofactor vitamin for mammals.* Kasahara & Kato

27 Altering Pyrroloquinoline Quinone Nutritional Status Modulates Mitochondrial, Lipid, and Energy Metabolism in Rats, Bauerly, Harris, Chowanadisai, Graham, Havel, Tchaparian, Satre, Karliner, Rucker

28 Neuroprotection by pyrrolo quinoline quinone (PQQ) in reversible middle cerebral artery occlusion in the adult rat. Zhang, Feustel&Kimelberg,Brain Research Volume 1094, Issue 1, 13 June 2006, Pages 200-206

29 Biochemical Pharmacology, Vol 65, Issue 1, 1/2003, Pgs 67-74 Antioxidant and pro-oxidant properties of pyrroloquinolinequinone (PQQ): implications for its function in biological systems

30 Enzymatic and nonenzymatic cross-linking of collagen and elastin. Reiser, McCormick, Rucker Dept of Internal Medicine, University of California, Davis.

31 *Vitamin-Like PQQ Offers Antioxidant, Neuroprotective, and Mitochondrial Health Benefits*, eMedia Health, 11/2010.

32 Altering Pyrroloquinoline Quinone Nutritional Status Modulates Mitochondrial, Lipid, and Energy Metabolism in Rats. Bauerly, Harris, Chowanadisai, Graham, Havel, Tchaparian, Satre, Karliner, Rucker

33 Principles and applications of quinoproteins By Victor L. Davidson

34 Pyrroloquinoline Quinone Stimulates Mitochondrial Biogenesis through cAMP Response Element-binding Protein Phosphorylation and Increased PGC-1a Expression Chowanadisai, Bauerly, Tchaparian, Wong, Cortopassio, Rucker

CO-Q10

The natural Ubiquinol form of CoQ10 is 2,3-dimethoxy-5-methyl-6-poly prenyl-1,4-benzoquinol. CoQ10 exists in three redox states:

- Completely oxidized –Ubiquinone
- Partially reduced –Semiquinone or Ubisemiquinone
- Fully reduced – Ubiquinol).

Usability in the body is based on accompanying fatty acids, water solubility, and ability of the body to convert and use it for specific processes such as the citric acid cycle, membrane support, and an antioxidant. While various marketing companies often cite that the fully reduced Ubiquinol is superior, there isn't really much research that demonstrates that one form is better than the other in a well functioning body, and it would depend on if the CoQ-10 were being rated for its impact on 1) citric acid cycle output of ATP or 2) membrane support, or 3) antioxidant activity.

food (and therefore energy) are scarce. Therefore it is known to activate under caloric restriction and promote cellular longevity.

I saw few die of hunger; of eating, a hundred thousand.

– Benjamin Franklin

SIRT1 acts as a "rescue gene" because it initiates damage repair from free radicals, and extends cell life. It also causes mitochondria to produce energy at the higher levels that are typically associated with younger cells. As a result, SIRT1 is believed to be a principal regulator of lifespan and is called the "longevity gene".

Because of its ability to regulate insulin and increase fat metabolism, SIRT1 is also called the "skinny gene," and it assists with weight loss by inhibiting fat storage and utilizing fat stores to make energy. By causing the body to store less energy in fat cells, SIRT1 can also slow the aging process by reducing the risk of age-related diseases and health threats, including strokes, heart attacks, diabetes, arthritis, amyloid diseases (Alzheimer's—actually a free radical/inflammatory disease), and osteoporosis.

Additionally, SIRT1 reduces inflammation and oxidative stress, the two primary causes of aging. Studies show that centenarians have lower levels of oxidative stress, meaning less free radical damage to cells, than those who only live to be 70. Oxidative stress is a more accurate indicator of heart disease than cholesterol levels or other factors. This is why the Meta-Oxy test, and improving lipid peroxidation, is so important.

SIRT1 is activated by calorie restriction as well as by the compound in grapes and red wine known as *Resveratrol*. The concept of "fasting one day a week" is a practice that activates the SIRT1 gene and promotes longevity because of the rest and repair that can occur when the body is not occupied with processing food.

"Those who fast one day a week live more in accord with the body's natural cycles. There are always blessings in store for those who live in accord with Nature. People who fast one day a week usually notice a balancing trend in their health—weight normalizes, allergies clear up, constipation is relieved, and the immune system strengthened."

– The Pro-Vita! Plan For Optimal Nutrition[35]

"Resveratrol has been shown in studies to activate the SIRT1 enzyme which in turn helps tell a cell it should try to survive and repair itself. Resveratrol in turn also helps to increase the function of the mitochondria within a cell. This can help a cell, and in turn our bodies, to burn more fat, recover faster, increase endurance, mimic the effects of calorie restriction diets, and improve insulin sensitivity, among many other things.

Resveratrol and SIRT1 have become so important in research that it is said to have the potential to cure or treat numerous issues such as prostate cancer, diabetes, mitochondrial encephalopathy syndrome, poor aging, and numerous other possibilities.

The body's response to calorie restriction is an example of

35 *The Pro-Vita! Plan For Optimal Nutrition* by Dr. Jack Tips presents Doc Wheelwright's dietary research. Available at www.apple-a-day-press.com

"hormesis[36]," in which a normally dangerous stressor can actually be beneficial in small amounts. Although an animal will die if it starves, moderate calorie restriction can actually increase its chances of survival by raising levels of SIRT1.

But starving your way to better health is not necessarily the right approach. Certainly there are many people who make a living of overeating, or perhaps we should say, "make a dying of overeating," and certainly reducing food intake is a beneficial health practice – we want quality, not quantity. But there are other ways to induce SIRT1, and eating red grapes (nature's source of Resveratrol) plays an important role with the quercetin and other molecules found in Resveratrol.

Exercise

All the mitochondrial biogenesis benefits discussed in this Report are activated by exercise. Unfortunately, the world has changed and now includes elevators and automobiles and for most people, exercise is something that is grossly neglected.

Here's how to get the most out of a little exercise! eNRG's nutrients sensitize the body to respond to exercise and activate mitochondrial biogenesis. So to get the most from your exercise, and have optimal cellular energy and function, we now know of nutritional components that help the body gain the benefit of lengthy exercise regimes in a much shorter time by priming the beneficial cellular pathways to respond quickly and generously, even with short intervals of exercise.

For Health Professionals Only. Webinar: *The Secret Life of the Mitochondria* delves into the Citric Acid Cycle and Mitochondrial Biogenesis at www.sysemicformulasmedia.com

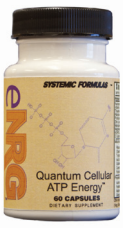
Disclaimer: This Research Report does not propose a method for diagnosing or treating any disease whatsoever—a process exclusive to the practice of medicine by licensed individuals. This information refers only to whole body nutrition to support the body in caring for itself. It features insights from one individual's clinical perspective and does not constitute labeling for any product.

Mitochondrial Biogenesis with two meals a day take:
- 2 eNRG (Quantum ATP)
- 2 EVENTA (Super Amino)
- 2 ROX (Super Anti-ox)

Ultimate Heart Mitochondrial Support
with two meals a day take:
- 2 eNRG (Quantum ATP)
- 1 EVENTA (Super Amino)
- 2 ROX (Super Anti-ox)
- 2 HQ (Heart Energy)

Super Brain Build with two meals a day take:
- 2 eNRG (Quantum ATP)
- 2 MoRS (Methyl Donor)
- 2 droppers VISTA 2 (Membrane)
- 1 ea. caps VISTA 1 (Membrane)
- 1 B (Brain)
- 1 I (Eye)
- 1 Gb (Pituitary)

36 **Hormesis** – a term for generally favorable biological responses to low exposures to toxins and other stressors. A pollutant or toxin showing hormesis thus has the opposite effect in small doses as in large doses.



Key Ingredients:

Niacinamide; Vitamin A; Thiamine Nitrate; Riboflavin 5 Phosphate; Pyridoxine Alpha Keto Glutarate; Zinc Lipoic Acid; Manganese Chelate; Magnesium Citrate; K2HPO4; D Calcium Pantothenate; Ribose; Mannose; Ca Pyruvate; Kudzu Extract (Diadzin); Red Clover Extract (Biochanin); Tryptophan; Resveratrol; Alpha Keto Glutaric Acid; Sodium Gluconate; Malic Acid; Glutamine; N Acetyl Carnitine; Succinic Acid; Coenzyme Q10; Medium Chain Triglycerides; Fumarate; Quercetin; Carnosine; Valine Alanine; Aspartic Acid; Nucleosides RNA/DNA; Pantethine; ATP; Luteolin; Irish Moss; Pimento; Mulberry Root; Cleavers Herb; Ginger Root; Ginseng Root; Pyrroloquinoline quinone.

eNRG Keynotes:

- Boost ATP production
- Encourage mitochondrial biogenesis
- Improve cognitive function
- Improve DNA repair
- Cardio-protectant
- Protect from reactive oxygen species
- Neuro-protectant
- Support Citric Acid Cycle
- Support SIRT-1 (longevity gene)
- Supports PGC-1a activation
- Supports AMPK pathways
- Boosts cellular function