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SYNTHESIS PAPER

Mitochondrial Correction: A New Therapeutic Paradigm for Cancer and Degenerative Diseases

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Introduction

Cancer and other degenerative diseases are increasing to epidemic proportions in all industrialized countries. Many of these degenerative diseases show some familial association, thus a genetic basis has been assumed. Yet, the nature and frequency of genetic variants in the human population has not changed significantly in the past 50 years, even though the incidence of these diseases has climbed continuously (Wallace, 2005). Therefore, because the increased and increasing incidence of cancer cannot be attributed to population-wide genetic change during this short timeframe, the cause must be external to the genome, in the "environment", which with relation to diet and chemical exposures, has altered radically in the past few decades. Cancer has been widely considered a genetic disease involving nuclear mutations in oncogenes and tumor suppressor genes; this view persists despite the numerous inconsistencies associated with the somatic mutation theory. In contrast to the somatic mutation theory, emerging evidence suggests that cancer is a mitochondrial metabolic disease, according to the original theory of Otto Warburg (Warburg, 1956). Respiratory insufficiency is the origin of cancer according to Warburg's theory. We are proposing cancer as a mitochondrial disease where diseased or damaged mitochondria become more dependent on glucose and glutamine for fuel. A shift from oxidative phosphorylation to fermentation can cause cellular de-differentiation, an important characteristic of malignancy.

As described already in the 1920s by Otto Warburg, cancer cells often show a shift in energy production from mitochondrial oxidative phosphorylation (OXPHOS) to cytosolic glycolysis (Warburg, Posener, Negelein & Ueber den Stoffwechsel der Tumoren, 1924). This so-called aerobic glycolysis, in which glucose is converted to pyruvate and lactate in spite of the presence of oxygen, is a major characteristic of most tumor cells. Importantly, this increase in glycolytic activity was similar to that observed in early embryonic cells. Thus cancer cells seem to resume a more primitive metabolic pattern (Gonzalez et al., 2012). This brings us to Albert Szent Gyorgi's elucidation of malignancy as a reversion to the primordial state (Alpha State) from the oxidative or Beta State of normal cell functions. We can support these concepts by providing information about the nature, etiology and function of mitochondria in normal and cancer cells.

Aerobic glycolysis not only provides the cell with ATP from

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the readily available substrate glucose, but the rapid glycolytic flux can also provide the cells with the necessary substrates and metabolic intermediates for lipid, amino acid and DNA synthesis that are needed for growth. For example, NADPH, ribose, acetyl-CoA and glucose-derived non-essential amino acids can be provided by aerobic glycolysis. In addition to an altered use of glucose, cancer cells make energetically inefficient use of glutamine to supply the nitrogen for the synthesis of nucleotides and non-essential amino acids, and to facilitate import of essential amino acids and support NADPH production. Glycolytic metabolism and the associated metabolic re-programming not only support rapid growth, although at the expense of other cells, but they also make the cancer cell less dependent on oxygen availability while generating an acidic micro-environment that enhances malignancy. It has been long appreciated that under hypoxic conditions glycolytic rates are enhanced, with a resulting increase in lactate production.

Cancer cells produce far less ATP per molecule of glucose (i.e., reduced efficiency); nevertheless, they can produce ATP at a much faster rate due to rapid consumption of substrates. Cancer cells produce ATP almost a hundred times faster than normal cells (Demetrius, Coy & Tuszynski, 2010). Cancer cells actively produce more glucose transporters on their cell surface membranes, so that more glucose is brought inside the cell. This increase in glucose metabolism through glycolysis allows the generation of glycolytic intermediates that funnel into biosynthetic pathways that support the production of NADPH, lipids, proteins and nucleotides.

Respiration cannot operate smoothly unless all of the delicate interior structures inside mitochondria are intact and functional. Mitochondria have evolved with a process called retrograde response (RTG), which helps them deal with temporary stress or damage. The retrograde response was designed for temporary emergency use, not long-term use, and yet cancer cells appear to stay in this mode. Whereas the RTG response evolved to protect cells from sudden energy failure, a persistent RTG response with inadequate respiration can cause genomic instability, and eventually this can result in tumorigenesis (Butow & Avadhani, 2004). Genome instability is linked to mitochondrial dysfunctions through retrograde signaling. Thus, this emerging evidence supports an important role for metabolic aberrancies and mitochondrial dysfunction in cancer. In general, suggesting that cancer is primarily a mitochondrial metabolic disease (Gonzalez et al., 2012; Seyfried & Shelton, 2010).

Mitochondria and Cancer

The mitochondria are ancient bacterial symbionts with their own mitochondrial DNA (mtDNA), RNA, and protein synthesizing systems. Each human cell contains hundreds of mitochondria. Margulis theorized that mitochondria are probably descended from free-living bacteria that survived endocytosis by a eukaryotic host cell. Such symbiosis is a potent and largely unappreciated and unrecognized force in evolution.

Mitochondria play a greater physiological role than have been previously appreciated. Some important mitochondrial functions are: (a) energy conversion with production of adenosine triphosphate (ATP), (b) regulation of membrane potential, (c) signaling and messaging through reactive oxygen species, (d) calcium signaling, (e) apoptosis and autophagy, (f) cellular metabolism, (g) iron metabolism and heme synthesis, and (h) steroid synthesis (Seyfried & Shelton, 2010).

Mitochondria synthesize the universal energy molecule ATP. They accomplish this through glycolysis, oxidative phosphorylation (OXPHOS) and electron transport in conjunction with the oxidation of metabolites by the Kreb's cycle and the breakdown of fatty acids by Beta oxidation. Because of their capacity to generate ATP, mitochondria are known exclusively for their ability to produce ATP, the main fuel for the basic energy demands of the cell. We inherit our mitochondrial DNA from our mothers. Although mitochondria are present in sperm, they are not transferred to the ova during the process of fertilization since most of them are in the tail which is lost in the process.

Mitochondria are so efficient at producing energy that their arrival on the evolutionary scene is thought to be responsible for the increase in complexity of living things. Building and supporting elaborate new creatures with specialized organs and capabilities requires a superabundance of energy (for organization, compartmentalization, order, and communication). If large quantities of energy are not constantly produced to maintain form, function, order and organization; then complex organisms will gradually succumb to entropy or chaos. For cells, this will mean that they regress, and as their DNA becomes unstable; they can lose their cellular shape, they become more disorganized, inter-cell communication is impaired, and they start reproducing uncontrollably as a survival mechanism (Gonzalez et al., 2010).

Mitochondria are active, mobile intracellular organelles that undergo constant fission and fusion. They form an interconnected network with other cellular organelles; and their functions extend beyond the cell membranes to include influence on the organism's entire physiology by affecting communication between cells, tissues and organs. Unsurprisingly therefore, any small defect in any of these functions could elicit mitochondrial dysfunction and promote a combination of diseases including cancer, metabolic disorders, and neurodegenerative diseases (Elliott, Jiang & Head, 2015).

Mitochondria are continually confronted with factors that can jeopardize how well they function. These factors in-

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clude: chronic stress, sleep disturbances, hyperglycemia, xenobiotics such as drugs, antibiotics, organic pollutants and environmental toxins. These factors can cause mitochondrial dysfunction, which can be characterized by any of four ways; (a) insufficient number of mitochondria, (b) insufficient substrate or nutrient co-factors needed for oxidative phosphorylation, (e.g., nutrient deficiency due to poor diet or drug-induced nutrient depletion), (c) acquired dysfunction in the ATP synthesis machinery, or (d) damage to the mitochondrial membranes. Mitochondrial dysfunction results in a number of cellular consequences, including: (i) decreased ATP production; (ii) increased reliance on alternative anaerobic energy sources; and (iii) increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Of interest is that ROS/RNS can also have a variety of normal roles, which include regulation of gene expression (Turpaev, 2002; Dalton, Shertzer & Puga , 1999). At physiological concentrations, ROS/RNS function as "redox messengers" in intracellular signaling and regulation. ROS/RNS molecular recognition occurs at both the atomic and at the macromolecular level which expands the potential number of ROS/RNS-specific receptors and interaction sites. Nevertheless an unbalanced production of ROS/RNS can be detrimental to mitochondrial function and viability.

At the molecular level, a reduction in mitochondrial function occurs as a result of the following changes: (a) a loss of maintenance of the electrical and chemical transmembrane potential of the inner mitochondrial membrane, (b) alterations in the function of the electron transport chain, including those due to insufficiencies of nutrients and cofactors/coenzymes essential for mitochondrial function such as magnesium, thiamine, ubiquinone, lipoic acid or (c) a reduction in the transport of critical metabolites into mitochondria. In turn, these changes result in a reduced efficiency of oxidative phosphorylation and a reduction in the production of ATP (Nicolson, 2014a). Many of the organic cofactors/coenzymes and structural fatty acids and phospholipids essential for mitochondrial function are damaged or destroyed. Several components of this system require routine replacement, and this need may be facilitated with specific dietary/substrate supplements.

Proof of the importance of metabolic and mitochondrial dysfunction in the cellular etiology of cancer is evidenced by the observations that damaged mitochondria can turn healthy cells into transformed cells, and that healthy mitochondria can reverse cancerous behavior in tumor cells. These observations provide an insight that cancer is not simply or exclusively a genetic disease, but more so a mitochondrial disease (Gonzalez et al., 2012; Seyfried & Shelton, 2010). Mitochondrial dysfunction plays a central role in a wide range of diseases in addition to cancer. These diseases include: neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, and Friedreich's ataxia; cardiovascular diseases, such as atherosclerosis and other heart and vascular conditions; diabetes and metabolic syndrome; autoimmune diseases, such as multiple sclerosis, systemic lupus erythematosus, and type 1 diabetes; neurobehavioral and psychiatric diseases, such as autism spectrum disorders, schizophrenia, and bipolar and mood disorders; gastrointestinal disorders; fatiguing illnesses, such as chronic fatigue syndrome and Gulf War illnesses; musculoskeletal diseases, such as fibromyalgia and skeletal muscle atrophy; and chronic infections (Pagano et al., 2014).

Many pharmaceuticals have been identified as mitochodrial toxicants (Meyer et al.,2013; Goodson et al., 2015; Narayanan et al., 2015). The high lipid content of mitochondrial membranes facilitates accumulation of lipophilic compounds and also of organic chemicals, particularly amphiphilic xenobiotics such as pharmacologic agents, including anti-bacterials, anti-psychotics, anti-depressants, anti-arrhythmics, anorexic agents, cholesterol-lowering agents, and others. Cationic metal ions, such as lead, cadmium, mercury, and manganese, have also been shown to accumulate in mitochondria. Another factor contributing to mitochondrial susceptibility is the presence of cytochrome P450s in mitochondria, which can activate chemicals that are relatively non-reactive prior to metabolism. At the same time, mitochondria can also be protected in several ways, including greater redundancy of their contents, ability to replace defective components; via mitophagy, biogenesis, complementation and apoptosis.

An important property in mitochondria is their controlled leak of matrix protons. Leaky mitochondria cause uncoordinated electron transport that causes energy to be wasted as heat instead of being converted into ATP. This mitochondrial uncoupling has been shown in faster-growing tumors that are actually warmer because of this effect. Increased proton leak will increase oxygen consumption (uncoupled respiration, UCR) and the energy will be dissipated as heat instead of being trapped as useful energy.

Metabolic normalization of cancer cells and concomitant inhibition of carcinogenesis may potentially also be attained by induction of mitochondrial biogenesis and mitochondrial correction. Moreover, studying the role of mitochondria in cancer cell de-differentiation/differentiation processes may allow further insight into the pathophysiology of transformation, and could lead to the development of new cancer therapies. Increases in mitochondrial respiration, restoration of mitochondrial membrane potential, increases the population doubling times, and reduction of cell proliferation may be important steps in overcoming the cancer state. By restoring failing mitochondrial energetics cancer morphogenesis may be reversed.

An example of the process of cancer re-differentiation via mitochondrial correction is the repair of aconitase dysfunc-

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tion using frataxin that reverses cell transformation (Schulz et al., 2006; Ristow et al., 2002). Aconitase is an enzyme that catalyses the stereo-specific isomerization of citrate to isocitrate via cis-aconitate in the tricarboxylic acid cycle within the mitochondria. Frataxin, a highly conserved protein found in prokaryotes and eukaryotes, is required for efficient regulation of cellular iron homeostasis and functions to activates mitochondrial energy conversion and oxidative phosphorylation. Frataxin functions as an activator of oxidative phosphorylation, leading to an increased mitochondrial membrane potential and an elevated cellular ATP content.

Additional evidence exist showing that normalizing mitochondrial function is capable of suppressing tumorigenesis. The strongest evidence that cancer may be a mitochondrial disease has been demonstrated by nuclear-cytoplasm transfer studies. Many of these studies, even those done in cell cybrids, have shown that a nucleus from a malignant cell when placed in a cell with normal cytoplasm will not produce malignant daughter cells; (i.e., mutations in nuclear DNA are insufficient to cause cancer when placed within a normally functioning cellular context with normal mitochondria). It was also shown that normal cell nuclei could not suppress tumorigenecity when placed in tumor cell cytoplasm, (i.e., in the context of dysfunctional metabolism and mitochondria, cancer can be induced despite normal nuclear DNA). Therefore, in these studies, normal nuclear gene expression was unable to suppress malignancy. These studies showed that it was the cytoplasm and not the nucleus that dictated the malignant state of the cell (McKinnell, Deggins & Labat, 1969; Mintz & Illmensee, 1975; Li, Connelly, Wetmore, Curran & Morgan, 2003; Minocherhomji, Tollefsbol & Singh, 2012; Elliott, Jiang & Head, 2015; Parikh et al., 2009). If this is the case, and tumor cells are defective as Warburg suggested, then malignant suppression should result from the introduction of normal mitochondria from normal cells to a malignant cell. Indeed these nuclear-cytoplasmic transfer studies in various cell types confirm that the integrity of mitochondrial respiration prevents carcinogenesis. In other words, cancer arises from respiratory insufficiency just as Warburg postulated many decades ago (John, 2001). In summary, the origin of tumorigenesis requires damaged or ineffective mitochondria in the cytoplasm. Normal isolated mitochondria co-cultured with cancer cells could be taken into the cancer cells, where they can then reverse aerobic glycolysis and inhibit cell growth (Anand et al., 2008; Shanmugam, Reddy, Guha & Natarajan, 2003; Wen et al., 2006; Dandona, Chaudhuri, Ghanim & Mohanty, 2007; Klement & Kämmerer, 2011; Pollak, 2008).

Mitochondrial Correction

The first step in correcting damaged mitochondria involves addressing lifestyle factors. Studies show that increasing physical activity improves mitochondrial function, so encouraging regular moderate exercise is essential (Anand et al., 2008; Klement & Kämmerer, 2011; Seyfried, 2015). Combining exercise with a diet rich in organic vegetables and moderated in organic, grass-fed meats, free range poultry and wild caught fish and very low in refined carbs and sugar may be essential. In addition, implementing reduced stress practices, such as meditation or yoga, as well as ensuring good sleeping habits are also important. Finally, detoxifying the body by removing fat-stored xenobiotics that inhibit mitochondrial function while replacing essential components should substantially help improve mitochondrial function.

When the mitochondria become unable to adequately perform their functions, cells will either die, become dormant, or undergo malignant transformation. The possibility exists to cause such cells to revert to normal aerobic cells, capable of normal function via metabolic and mitochondrial correction, which can be accomplished in a number of ways. The current genocentric pharmacologic approach has been to kill such cells with toxic therapies chemotherapy and radiation rather than attempt to reconvert them back to normal function. This cytotoxic approach has been largely unsuccessful, therefore, considering other paradigms that yield alternative approaches may prove to be useful and less damaging.

Diet

Nutrition is an important part of cancer treatment because the components of the diet are determinants of cell functionality. For cancer patients, eating the right kinds of foods can help them feel better, stay stronger and most importantly, survive the disease. All tumors depend heavily on glucose for survival. Research shows a strong connection between high blood sugar (hyperglycemia), diabetes, and cancer. High blood glucose raises insulin levels. High blood glucose also raises levels of Insulin-like Growth Factor 1 (IGF-1). Cancer cells with receptors on their surfaces for IGF-1 grow more rapidly because IGF-1 activates metabolic pathways that drive tumor cell growth (Shanmugam, Reddy, Guha,& Natarajan, 2003; Wen, 2006; Dandona, Chaudhuri, Ghanim & Mohanty, 2007).

Studies have consistently estimated that 30% or more of all cancers may be due to dietary factors (Anand et al., 2008). Bioactive food components that affect various aspects of metabolism may be important tools to reverse glycolytic to oxidative metabolism and enhance sensitivity to apoptosis. The success of such a strategy may depend on several factors, acting in concert. Glycolytic metabolism and the associated metabolic reprogramming not only support rapid growth of cancer cells, but they also make the cancer cells less dependent of oxygen availability and generate a favorable (acidic) micro-environment. Inhibition of glycolysis may have therapeutic implications in cancer treatment as a strategy to suppress or even eliminate cancer cells. Such a

strategy may also make use of bioactive food components.

One class of bioactive food components that affect energy metabolism and may have anti-cancer effects are polyphenols. Quercetin, a polyphenol present in apples, onions, tea and wine, affects energy metabolism. Another polyphenol with anti-cancer potential is resveratrol. Resveratrol is well known as a compound that is present in red wine. Bioactive food molecules, that affect energy metabolism, may also function as anti-cancer agents using mechanisms distinct from their effect on energy metabolism. Despite being categorized as antioxidants, most dietary anti-oxidant compounds exhibit their functional effects through specific cellular mechanisms, rather than though general, direct anti-oxidants effects. Mechanisms such as cancer cell growth limitation, anti-angiogenesis and normalization of the glycolytic metabolism are possible.

Carbohydrates provide rapidly usable cellular energy but, unlike proteins and fat, also stimulate potent insulin signals that can be powerful mitogens. A carbohydrate-restricted diet will slow cancer growth in patients by decreasing the secretion and circulating levels of insulin. Tumor glucose uptake can be stabilized and decreased with a carbohydrate restricted diet. Hyperglycemia activates monocytes and macrophages to produce inflammatory cytokines that play an important role in the progression of cancer (Shanmugam, Reddy, Guha & Natarajan, 2003, Wen et al., 2006; Dandona, Chaudhuri, Ghanim & Mohanty, 2007; Klement & Kämmerer, 2011; Pollak, 2008; Seyfried, 2015; Tisdale & Brennan, 1983). High plasma glucose concentrations elevate the levels of circulating insulin and free IGF1, two potent anti-apoptotic and growth factors for most cancer cells (Pollak, 2008).

Paleolithic-type diets that by definition exclude grain products, have been shown to improve glycemic control therefore are expected to help against cancer. A low carbohydrate, high fat diet to increase the blood levels of ketones, along with supplements or foods rich in citric acid, can impair glycolysis and may prove a beneficial adjunct in the treatment of many cancers (Klement & Kämmerer, 2011).

A ketogenic diet characterized by minimal carbohydrate intake, a moderate amount of protein, and higher amounts of fat seems to limit cancer cell growth. This shift in macronutrients causes the body to switch to utilizing ketones (produced by burning fats) instead of glucose as its primary source of fuel. Ketones (e.g., acetoacetate, ß-hydroxybutyric acid and acetone) are produced in the liver when lipids are burned instead of glucose. Low-carbohydrate diets reduce the extreme glucose peaks and help patients avoid both hyperglycemia and rebound hypoglycemia, providing more sustained energy throughout the day. Ketones are efficiently used for the generation of ATP (energy) in mitochondria. Cancer cells cannot use ketones as an energy source (Zhou et al., 2007). The ketogenic diet mimics the metabolic state of starvation, forcing the body to utilize fat as its primary source of energy.

The Ketogenic diet may be beneficial in optimizing mitochondrial function. The transition from glucose metabolism to ketone metabolism is also a powerful anti-inflammatory strategy. The goal of this diet is to shift the body from burning mostly glucose (sugar) to burning mostly ketones (fat). The quickest way to get into the therapeutic zone is to start by fasting (water only) for 3-5 days. During the induction phase, carbohydrate withdrawal symptoms may occur, which typically include lightheadedness, nausea, and headaches (Keto Flu). An alternative to this fasting is to limit carbohydrates to less than 12 grams per day and limit protein to 0.8 to 1.2 grams per kg body weight per day (0.4 to 0.6 grams per pound body weight). With this less extreme plan, patients may need up to several weeks to reach the recommended therapeutic zone values. Ketogenic diets may also facilitate easier surgical reduction in tumor burden, as ketosis can reduce blood vessel mass, inflammation, and tumor size; thereby facilitating surgical removal of the tumor mass. The increase of ketones in the blood can also inhibit the activity of phosphofructokinase, an enzyme that plays a key role in the regulation of glycolysis. Citric acid, an intermediary product of the Krebs cycle metabolism, has also been reported to block the actions of phosphofructokinase.

To support mitochondrial function, our patients are advised to eat 8–12 servings daily of a variety of whole, colorful vegetables and fruits; among different plants, color variation indicates phytochemical variety, thereby allowing the diet to provide a wide range of anticancer and metabolism-enhancing phytochemicals. Vegetables should be the primary focus, especially the bitter foods in the cruciferous family (such as broccoli, watercress and arugula), as these foods provide numerous anticancer benefits. Coconut oil, a brain-healthy saturated fat that contains medium-chain triglycerides (MCTs), also supports mitochondrial function via production of ketones.

Calorie and carbohydrate restriction, along with eating lean, clean (pesticide and toxin-free) proteins, high-quality fats and oils, and more plant foods may help to prevent or slow down all degenerative diseases. All grains are minimized or avoided on a Mitochondria restoration diet in order to achieve the desired goals of mild ketosis and low glycemic impact. Most malignant cells lack key mitochondrial enzymes necessary for conversion of ketone bodies and fatty acids to ATP (Pollak, 2008; Seyfried, 2015; Tisdale & Brennan, 1983).

Maintaining a lower and consistent insulin level is key to optimal mitochondrial health. A heavily processed, high-glycemic load diet of too many grains and added sugars can lead to increased insulin and inflammation with associated

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and accelerated mitochondrial dysfunction. Minimizing grains, especially highly processed ones, and using low-glycemic vegetables and fruits as the main source of carbohydrates helps to stabilize blood sugar and protect mitochondria.

High quality proteins are the best choice, including grass-fed, organic, non-genetically modified organism (GMO) sources. For fish, patients should choose wild-caught salmon as farmed salmon may contain hormones and toxic chemicals. We encourage the consumption of minimally refined, cold-pressed, organic, non GMO fats and liquid oils whenever possible. When possible, we advise phytonutrient-dense, unfiltered, extra-virgin olive oil, Avocado oil or Coconut oil, add to dress salads and vegetables. Medium Chain Triglycerides (MCT) oil is another option that can also be used for cooking and for dressings.

Cancer patients should aim for a minimum of 4–6 servings of organic vegetables every day (ideally, 10–12 servings per day). A serving is only ½ cup of cooked vegetable or 1 cup of raw leafy greens. Patients get four servings of vegetables in one meal, by filling your plate with vegetables or eating a hearty salad. All greens (including collard, dandelion, kale, mustard, and turnip greens), along with chard/Swiss chard, spinach, sea vegetables, and the many green vegetables in the cruciferous family have been found to support the mitochondria via effects such as antioxidant protection, anti-inflammatory benefits and enhancement of xenobiotic clearance.

Patients are instructed to eat a rainbow of colors: red peppers, tomatoes, and radishes; orange carrots, peppers, and pumpkin; yellow summer squash and peppers; green asparagus, avocado, and green beans; blue/purple eggplant and cabbage; and white/tan mushrooms, jicama, and onions. Patients are also counsel to purchase organic vegetables (and fruits) when possible. Foods should be “organic” grown without chemical pesticides; given that many pesticides are neurotoxins, mitochondrial toxins, carcinogens and endocrine disruptors.

Fruits with a low to moderate glycemic response can be consumed when patients are feeling the need for something sweet. All berries along with pomegranate seeds and grapes with the skin have shown to increase levels of glutathione in the body. Fruit juices are not encouraged as they are dense sources of sugar and can increase blood sugar levels, thereby promoting oxidative stress, immunosuppression and hyperinsulinemia.

Patients should to drink plenty of pure, filtered water daily. It is generally recommended to drink at least six to eight glasses. (One glass = 1 cup = 8 ounces). For variety and additional antioxidant and anticancer benefits, patients consider adding at least 2 cups of green tea daily with the general recommendation being Include herbal teas, especially those prepared from adaptogenic herbs like cordyceps, schizandra, ginseng, astragalus, and licorice can be used as desired and tolerated. The importance of pesticide and toxin-free food from local, free-range, grass-fed, and organic sources cannot be stressed enough.

Dietary Supplementation: Descriptions and Adult Doses

Several supplements are important in any regimen designed to boost mitochondrial health (Zhou, 2007). Dietary supplements can reduce the oxidative burden of ATP generation, provide additional substrate for oxidative phosphorylation, and repair leaky membranes which interrupt the electron transport system. In addition, mitochondrial biogenesis, or the generation of new mitochondria, can also be encouraged (Tarnopolsky, 2008).

CoQ10 (Ubiquinone)

Coenzyme Q10 (CoQ) is a small lipophilic molecule critical for the transport of electrons from complexes I and II to complex III in the mitochondrial respiratory chain. Furthermore, CoQ is essential for the stability of complex III in the mitochondrial respiratory chain, functions as an antioxidant in cell membranes, and is involved in multiple aspects of cellular metabolism. CoQ10 also reduces lactic acid levels, improves muscle strength, and decreases muscle fatigability. CoQ10 protects against beta-amyloid-induced mitochondrial malfunction. Statin drugs are thought to cause mitochondrial damage in part by lowering levels of CoQ10, and supplementation with CoQ10 has been shown to counteract some of the negative effects of statins and is an important supplement to counteract the adverse effects of cancer therapy (Conklin & Nicolson, 2008). CoQ10 is probably the most widely used cofactor for treating mitochondrial-related diseases. CoQ10 is also a strong antioxidant in its reduced form, and it can affect the expression of certain genes involved in cell signaling, metabolism, and transport. However, the main role of CoQ10 is its involvement in the transfer of electrons along the multiple complexes of the mitochondrial electron transport chain. In combination with lipoic acid, CoQ10 may have had the ability to increase ATP production, resulting in decreased utilization of alternative energy sources and a decrease in resting plasma lactate concentrations (Zhou et al., 2007; Rodriguez et al., 2007).

Ubiquinone: 100 mg tid.

L-Carnitine (3-hydroxy-4-N-trimethylaminobutyrate)

L-carnitine is a naturally occurring fatty acid transporter. It is directly involved in the transport of fatty acids into the mitochondrial matrix for subsequent β-oxidation, but it also functions in removal of excess acyl groups from the body

and in the modulation of intracellular coenzyme A (CoA) homeostasis. L-carnitine helps fatty acids cross the inner mitochondrial membrane to be used as energy. It also scavenges reactive oxygen and binds iron. L-carnitine also has been shown to prevent the damaging effects of statins on the mitochondria. L-carnitine protects against mitochondrial dysfunction associated with oxidative stress caused by a series of conditions such as aging, ischemia reperfusion, inflammation, degenerative diseases, cancer and drug toxicity (Nicolson, 2014a; Rodriguez et al., 2007; Nicolson, 2013). L-carnitine has been used to increase the rate of mitochondrial oxidative phosphorylation. L-carnitine also is essential for the detoxification of environmental pollutants, meaning it can protect the mitochondria on a number of levels.

L-Carnitine: 500 mg bid.

Acetyl-L-Carnitine

Acetyl-L-Carnitine (ALCar) is an ester of the trimethylated amino acid L- carnitine, and it is better absorbed and more efficiently crosses the blood-brain barrier ~~as~~ compared to L-carnitine. Dietary supplementation with Acetyl-L-Carnitine might reverse age-related mitochondrial changes. ALCar helps to restore mitochondrial membrane potential and Cardiolipin levels. Cardiolipin is an important component of the inner mitochondrial membrane, and it constitutes about 20% of the total lipid composition. ALCar facilitates fatty acid transport into mitochondria, and it increases overall cellular respiration. ALCar enhances cognitive performance, increased production of neurotransmitters, and helps restores levels of certain hormone receptors to more youthful levels. ALCar reverses many aspects of age-related cellular dysfunction, principally through maintenance of mitochondrial function (Ames & Liu, 2004).

Acetyl-L-Carnitine: 250 mg bid.

Idebenone (2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone)

Idebenone is a CoQ10 analog that, while sharing some of CoQ10s properties, offers unique mitochondrial-protective benefits on its own. Idebenone is a powerful mitochondrial free radical quencher that reduces the ever-increasing damage to mitochondrial membrane and DNA that occurs with age. Idebenone has also been shown to be more effective than CoQ10 in protecting the electron transport chain. When cellular oxygen levels are low, idebenone is actually superior to CoQ10 for preventing free radical damage while helping cells maintain relatively normal ATP levels (Giorgio et al., 2012).

Idebenone: 150 mg qd.

N-Acetyl Cysteine

N-Acetyl Cysteine (NAC) is the acetylated precursor of both the amino acid L-cysteine and reduced glutathione (GSH). A major cause of mitochondrial dysfunction is due to changes that take place in the respiratory chain where oxidative phosphorylation occurs. NAC has a positive effect on key elements of the respiratory chain. It increases the activities of mitochondrial Complexes I, IV and V. NAC also helps maintain levels of glutathione, an important antioxidant capable of preventing damage to important cellular components caused by reactive oxygen species. NAC protects cells by promoting oxidative phosphorylation, improving mitochondrial membrane integrity, and enhancing mitochondrial homeostasis (Banaclocha, 2001).

N-Acetyl-Cysteine: 600 mg qd.

(R) Alpha Lipoic Acid (1,2-dithiolane-3-pentanoic acid)

Alpha-lipoic acid (ALA) is a potent antioxidant, transition metal ion chelator, redox transcription regulator, and anti-inflammatory agent. It acts as a critical cofactor in mitochondrial α-keto acid dehydrogenases, and thus it is important in mitochondrial oxidative-decarboxylation reactions. ALA is an amphipathic molecule with both hydrophilic and hydrophobic properties. This makes ALA a perfect molecule to establish communication between the cytoplasm and mitochondria. ALA acid may also have mitochondrial resuscitating properties. By providing ALA for two weeks mitochondrial oxygen consumption was completely restored. It was also found that ALA, like ALCar, increased mitochondrial membrane potential of by up to 50 percent. ALA supplementation also increased mitochondrial glutathione and vitamin C concentrations, indicating ALA may have the ability to reverse the age-associated decline in low molecular weight antioxidants, therefore reducing the risk for oxidative damage that occurs with aging. ALA supplementation improves mitochondrial function, alleviates some of the age-related loss of metabolic activity, increases ATP synthesis and aortic blood flow, and increases glucose uptake. Furthermore ALA supplementation may be a safe and effective means to improve general metabolic function (Hagen et al., 1999).

(R) Alpha Lipoic Acid: 300 mg bid.

Omega 3 Fatty Acids (Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA))

Omega-3 fatty acids from fish oils are cardio-protective. They minimize ~~d~~ the increase in mitochondrial calcium content, increase ~~d~~ levels of phosphatidylcholine, and prevent ~~s~~ the decrease in cardiolipin content. Omega-3's may also be important in mitochondrial membrane restoration. An ome-

ga-3 rich diet directly increases mitochondrial membrane cardiolipin concentrations, increases the ratio of mitochondrial membrane omega-3 to omega-6, and increases tolerance of the heart to ischemia and reperfusion (Hansford, Naotaka & Pepe, 1999). The propensity for ROS/RNS emissions increases with omega-3 supplementation, although there are no changes in markers of lipid or protein oxidative damage. These results demonstrate that omega-3 supplementation improves mitochondrial ADP kinetics, suggesting post-translational modification of existing proteins (Herbst et al., 2014).

Omega 3 Fatty Acids: 1g tid. (molecularly distilled)

Vitamin C (Ascorbic Acid)

Vitamin C may improve mitochondrial function by providing needed H from the conversion of ascorbic acid to dehydroascorbic acid (Herbst et al., 2014). Also related to Vitamin C's electron moving ability it may be considered an ergogenic aid (Gonzalez, Miranda & Riordan, 2005). Vitamin C is taken up by the mitochondria and is able to preserve mitochondrial membrane potential (Gonzalez et al., 2010; Ohta, 2012; Heaney et al., 2008). Even modest blood glucose elevations as they typically occur after a Western diet meal competitively impair the transport of ascorbic acid into immune cells (Ohta, 2012; Heaney et al., 2008). Vitamin C is structurally similar to glucose so it competes for the Glut receptors (Krone & Ely, 2005; Ely & Krone, 2002; KC, Cárcamo & Golde, 2005; Gonzalez et al., 2005).

Vitamin C: 500 mg tid. Consider bowel tolerance dosing or intravenous administration

B-Complex Vitamins

The B vitamins are water-soluble vitamins required as cofactors for enzymes essential in cell function and energy production (Depeint, Bruce, Shangari, Mehta & O'brien, 2006).

Thiamine (Vitamin B1)

Thiamin is active in the form of thiamin pyrophosphate (TPP). As a cofactor, TPP is essential to the activity of cytosolic transketolase and pyruvate dehydrogenase, as well as mitochondrial dehydrogenases -ketoglutarate dehydrogenase and branched chain keto acid dehydrogenase. Large doses of thiamine (vitamin B1) have been used to stimulate NADH, which then augments oxidative phosphorylation at Complex I (Depeint, Bruce, Shangari, Mehta & O'brien, 2006; Lou, 1981).

Thiamine: 100 mg qd.

Riboflavin (Vitamin B2)

Riboflavin is a precursor to flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). As prosthetic groups they are essential for the activity of flavoenzymes including oxidases, reductase and dehydrogenases. Riboflavin is a water-soluble B vitamin (B2). It is a key building block in complex I and II and a cofactor in several other key enzymatic reactions involving fatty acid oxidation and the Krebs cycle. Riboflavin improved exercise capacity in a patient with a mitochondrial myopathy due to a Complex I dysfunction (Arts, Scholte, Bogaard, Kerrebijn & Luyt-Houwen, 1983; Driver & Georgiou, 2002).

Riboflavin: 100 mg qd.

Niacin (Vitamin B3)

Niacin is a precursor to reducing groups nicotinamide adenine dinucleotide (NAD+) and nicotinamide adenine dinucleotide phosphate (NADP+). These molecules are involved in more than 500 enzymatic reactions. For the focus of this review, it is important to note that NAD/NADP are involved in reactions pertaining to mitochondrial respiration, glycolysis or even lipid Beta-oxidation. Niacin ameliorated age-related changes in bioenergy (Driver & Georgiou, 2002; Huskisson, Maggini & Ruf, 2007).

Niacin: 50 mg qd.

Pantothenic Acid (Vitamin B5)

Pantothenic acid is the precursor of coenzyme A (CoA), a molecule essential for 4% of known enzymatic reactions. In the interest of this review it is important to note the role of CoA in heme synthesis, lipid metabolism or as a prosthetic group in the TCA cycle (Bratman & Kroll, 2000).

Pantothenic Acid: 50 mg qd.

Magnesium

Magnesium ion plays an important role in a wide variety of biochemical processes including optimizing mitochondrial function and the creation of ATP, regulation of blood sugar, and the activation of muscles and nerves. Magnesium ions are critical for the optimization of the mitochondria, which have enormous potential to influence cancer. In fact, optimizing mitochondrial metabolism may be at the core of effective cancer treatment (Gröber, Schmidt & Kisters, 2015).

Magnesium (Citrate) 500 mg tid. Dose may be reduced

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as needed per osmotic laxative effect.

Phospholipids

Phospholipids are an important class of lipids found in all cellular membranes. Glycerolphospholipids, the type of phospholipid found in cellular and intracellular membranes, are made up of two fatty acids (long chains of hydrogen and carbon molecules), which are attached to a glycerol 'head.' The glycerol molecule is also attached to a phosphate group, and this is the hydrophilic part of the molecule. The glycerolphospholipids help cellular membranes and act not only as diffusion barriers but also as dynamic cell organelles, contributing to the synthesis of intracellular mediators, such as arachidonic acid and inositol phosphates. Glycerolphospholipids interact and work with integral membrane proteins to modulate various cellular activities. As membrane phospholipids are known to be essential to cellular membrane function and cell viability, their modification and restoration by exogenous dietary phospholipids remains a useful approach for maintaining and restoring cellular membrane function.

Cell membranes control a variety of cellular processes, as well as the maintenance of ~~a~~ structural and ionic barriers and intercellular communication networks (as mentioned above). They are also involved in cell transport, secretion, recognition, adhesion and other important cell functions. Membrane lipids provide at least four major requirements for cellular health. They are used as: (1) an important energy storage reservoir; (2) the matrix for all cellular membranes, enabling separation of enzymatic and chemical reactions into discrete cellular compartments; (3) bioactive molecules in certain signal transduction and molecular recognition pathways; and (4) important functional molecules that undergo interactions with other cellular constituents, such as proteins and glycoproteins. This latter characteristic is an absolute requirement for the formation, structure and activities of biological membranes (Nicolson, 2013; Nicolson & Ash,2014; Nicolson et al., 2016; Nicolson, 2014b). Phospholipids contribute to the physicochemical properties of the membrane and thus influence the conformation and function of membrane-bound proteins, such as receptors, ion channels, enzymes, and transporters, and they also influence cell function by serving as precursors for prostaglandins and other signaling molecules. Finally, they can modulating gene expression through the activation of transcription.

One of the fundamental biochemical differences between tumor cells and normal cells is the composition of the membrane lipid matrix, including glycophospholipids and other lipids and their oxidation state. Membrane peroxidation can modify phospholipid structure, affecting lipid fluidity, permeability and membrane function (Nicolson & Ash, 2014; Nicolson et al., 2016; Nicolson, 2014b). In addition, the intracellular trafficking of phospholipids, which plays a crucial role in phospholipid homeostasis, can also be modified by peroxidation events. In the mitochondria the activities of the enzymes involved in cellular respiration are markedly influenced by the composition and oxidation state of the phospholipids of the inner mitochondrial membrane. Oxidation of inner mitochondrial membrane phospholipids can result in increased leakiness of the inner mitochondrial membrane. Leaky mitochondrial membranes cause mitochondrial impairment and loss in the production of ATP. When there is progressive functional loss of mitochondrial function, such as in the excessive oxidative modification of the mitochondrial membrane phospholipids, can cause changes in health that could progress to disease.

The outer mitochondrial membrane encloses the entire organelle and has a protein-to-phospholipid ratio similar to that of eukaryotic plasma membranes. The outer mitochondrial membrane contains transport proteins called porins (Kühlbrandt, 2015). The inner mitochondrial membrane is rich in the phospholipid cardiolipin, which is characteristic of the bacterial plasma membrane and is important in electron transport function and provides yet more evidence suggesting the mitochondrion's bacterial origin.

Maintenance of the appropriate phospholipid composition in the mitochondrial membranes is essential for mitochondrial structure and function. Thus, mitochondria depend on phospholipid metabolism, the transport of phospholipids into mitochondria, and supply of appropriate lipids from the diet. Regulation of the synthesis, trafficking, and degradation of phospholipids is essential to maintain phospholipid homeostasis in the mitochondria. An important element of phospholipid homeostasis is that the phospholipids in the mitochondria can be modified by dietary glycerolphospholipids and fatty acids.

Membrane Lipid Replacement (MLR), the use of functional oral supplements containing cell membrane glycerolphospholipids and antioxidants, can safely replace damaged membrane phospholipids. Most if not all clinical conditions are characterized by membrane phospholipid oxidative damage, resulting in loss of membrane and cellular function (Nicolson & Ash, 2014; Nicolson et al., 2016; Nicolson, 2014b). Orally ingested phospholipids can be degraded into their constituent parts and absorbed; they can be taken in as intact molecules without degradation, or they can be absorbed as small phospholipid droplets and micelles (Nicolson & Ash, 2014; Nicolson et al., 2016; Nicolson, 2014b). Eventually they are delivered to tissues and cells where they are transferred by membrane contact and carrier or transport proteins to various cellular and organelle membranes.

MLR plus antioxidants has been used to reverse ROS/RNS damage and increase mitochondrial function in certain

clinical disorders, such as chronic fatigue, CFS and Fibromyalgia (Nicolson & Ash, 2014; Nicolson et al., 2016; Nicolson, 2014b). In these disorders MLR has been found to be effective in preventing ROS/RNS-associated changes and reversing mitochondrial damage and loss of function (Nicolson & Ash, 2014). MLR is possible because cellular lipids are in dynamic equilibrium in the body. Thus functional oral MLR supplements containing cell membrane glycerolphospholipids and antioxidants, has been used to replace damaged, usually oxidized, membrane glycerophospholipids that accumulate during aging and in various clinical conditions. Once delivered to membrane sites, they naturally replace and stimulate removal of damaged membrane lipids. Various chronic clinical conditions are characterized by membrane damage, mainly oxidative but also enzymatic, resulting in loss of cellular function. This is readily apparent in mitochondrial inner membranes where oxidative damage to phospholipids like cardiolipin and other molecules results in loss of transmembrane potential, electron transport function and generation of high-energy molecules.

Phospholipids (mixed): 1g tid for anti-aging and 2g tid for chronic illnesses.

Ginkgo Biloba (Salisburia Adiantifolia)

Ginkgo biloba is one of the oldest living tree species. It is also one of the best-selling herbal supplements in the United States and Europe. Ginkgo leaves contain flavonoids and terpenoids. A growing volume of data confirms that Ginkgo biloba extract (GBE) reduces oxidative stress and improves mitochondrial respiration (Eckert, 2012). Ginkgo biloba extract has been found to protect mitochondrial DNA (MtDNA) against oxidative damage and oxidation of mitochondrial glutathione (Eckert et al., 2003).

Ginko Biloba: 40 mg bid.

Succinate (Succinic acid)

Succinate is a tricarboxylic acid (Krebs) cycle intermediate that donates electrons directly to Complex II. Succinates have been widely used for their alleged ability to enhance athletic performance (Sastre, Pallardo, De la Asuncion & Vina, 2000; Nowak, Clifton & Bakajsova, 2008). Succinate Ameliorates Energy Deficits (Nowak, Clifton & Bakajsova, 2008). It seems that the use of succinates is even more effective when a balance of several salts is used, especially combinations of magnesium and potassium.

Succinate: 125 mg qd.

Pyrroloquinoline Quinone (PQQ)

PQQ is a small molecule that has act as a Redox agent in cells, it can modify cell signaling and support mitochondrial function. PQQ is reported to participate in a range of biological functions. PQQ protects mitochondria from oxidative stress. It also promotes the spontaneous generation of new mitochondria, a process known as mitochondrial biogenesis or mitochondriogenesis (Rucker, Chowanadisai & Nakano, 2009; Stites, Mitchell & Rucker, 2000; Chowanadisai, Bauerly, Tchaparian & Rucker, 2007). This effect is an improvement in mitochondrial function.

Pyrroloquinoline Quinone: 20 mg qd.

Sodium Bicarbonate

Sodium bicarbonate (NaHCO3) is a salt composed of sodium ions and bicarbonate ions. The glycolytic nature of malignant tumors contributes to high levels of extracellular acidity in the tumor microenvironment. The extracellular pH of malignant tumors is acidic (pH 6.5-6.9) compared to normal tissue (pH 7.2-7.4). Tumor acidity is a driving force for cellular division, invasion and metastases (Griffiths, 1991; Vaupel, Kallinowski & Okunieff, 1989; Wike-Hooley, Haveman & Reinhold, 1984; Robey & Martin, 2011). Recently, it has been shown that buffering of extracellular acidity through systemic administration of oral bicarbonate may inhibit the spread of metastases.

Sodium Bicarbonate: No suggested dose.

Nicotinamide Adenine Dinucleotide (NADH)

NADH functions as a cellular redox cofactor in over 200 cellular redox reactions and as substrate for certain enzymes. NADH delivers electrons from metabolite hydrolysis to the electron transport chain, but in its reduced form, it can also act as a strong antioxidant. Pyruvate is converted to lactate, which requires all the glycolytic NADH output to be converted to NAD+, and this lactate is then excreted from the cell. Thus, aerobic glycolysis does not produce any net output of NADH. NADH can be successfully administered orally or by intravenous/intraperitoneal infusion (Rex, Hentschke & Fink, 2002).

NADH: 20 mg qd.

D-Ribose

Ribose is a naturally occurring 5-carbon sugar produced in the body from glucose. In addition to serving as the carbohydrate backbone for ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), ribose is also an essential ingredient in the manufacture of ATP. Thus ribose provides the key building block of ATP. The mitochondria of high-energy output organs such as the heart, liver, adrenals, GI tract, brain, muscles and endocrine glands utilize two methods

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for building or conserving cyclic nucleotides like ATP, ADP and AMP. The first process by which these nucleotides are synthesized is the de novo pathway, in which nucleotides are made using ribose. This is the slower of the two pathways. The second or faster pathway is the salvage pathway, in which the mitochondria pick up ATP metabolites to form new ATP. In this manner ribose enables the cells to more quickly and efficiently recycle (i.e., salvage) the end products formed by the breakdown of ATP to form new ATP molecules. Thus, the ribose salvage pathway is known as the salvage pathway of ATP formation. Ribose is essential for both the salvage and de novo reactions to work, and it is formed in the body from glucose, through the pentose phosphate pathway. Aside from this relatively time-consuming pathway, there are no foods that are able to provide enough ribose to rapidly restore ribose levels, should the need arise, as when exercising or working, and especially during a heart attack or stroke.

D-ribose is another excellent addition to the mitochondrial resuscitation regimen. D-ribose reduces markers of oxidative stress that can form after high-intensity exercise (Seifert et al., 2009). It also boosts post-exercise ATP levels (Dhanoa & Housner, 2007) and has shown to have beneficial effects in heart disease patients (MacCarter et al., 2009). D-ribose replenishes low myocardial energy levels, improving cardiac dysfunction following ischemia. Studies also have shown it can improve ventilation efficiency in patients with heart failure (Seifert et al., 2009). The presence of ribose in the cell stimulates the metabolic pathway to actually produce ATP. If the cell does not have enough ribose, it cannot make ATP.

Oral or intravenous ribose has been found to rapidly restore ribose levels in nerves and muscles. Ribose supplementation can dramatically improve recovery of failing ATP levels during and following acute or chronic anoxia or ischemia. Research has shown that taking ribose has a positive effect on ATP production in all muscle fiber types, especially the heart. Ribose supplementation increases the de novo production of ATP through oxidative phosphorylation by more than 300 percent. Ribose also activates the salvage pathway, causing nucleotides to be revitalized into the manufacture of ATP by over 500 percent (Berg, Tymoczko & Stryer, 2002).

Ribose has also been shown to increase athletic performance. Supplementation (ten grams per day) in young male recreational bodybuilders resulted in significant increases in muscular strength and total work performance after four weeks, compared with pre-treatment levels. No changes were noted in those using a placebo (Van Gammeren, Falk & Antonio, 2002).

D-Ribose: 5g qd.

Citrate

A citrate is a derivative of citric acid. Citric acid is a weak organic tricarboxylic acid. It occurs naturally in citrus fruits. It is an intermediate in the citric acid cycle, which occurs in the metabolism of all aerobic organisms. Citrate inhibits the phosphofructokinase enzyme blocking glycolysis at the start; citrate also inhibits the pyruvate dehydrogenase enzyme complex. Citrate also inhibits the succinate dehydrogenase enzyme. These citrate or citric acid properties have the capacity to inhibit glycolysis and a step in Krebs cycle; the citrate inhibits three base enzymes in the mitochondrial metabolism of Krebs cycle (Tornheim & Lowenstein, 1976; Taylor & Halperin, 1973; Hillar, Lott & Lennox, 1975; Velichko, Trebukhina & Ostrovskii, 1981; Bucay, 2007).

Citrate: No suggested dose.

Creatine

Creatine is an essential, natural substance that is synthesized in the body from three amino acids: glycine, arginine, and methionine. Creatine plays a very powerful role in energy metabolism as a muscle fuel in its role in regenerating ATP. Creatine combines with phosphate in the mitochondria to form phosphocreatine. It serves as a source of high-energy phosphate, released during anaerobic metabolism. It also acts as an intracellular buffer for ATP and as an energy shuttle for the movement of high-energy phosphates from mitochondrial sites of production to cytoplasmic sites of utilization (Keys, 1943; Kreider et al., 1998; Vandenberghe et al., 1997; Stone et al., 1999; Urbanski, Vincent & Yuaspelkis, 1999; Volek et al., 1997; Cooke et al., 2014; Ferraro et al., 1996; Tarnopolsky, 2000; Hespel, 2000; Cooper, Naclerio, Allgrove & Jimenez, 2012). Operating through the ATP/ADP cycle, creatine phosphate maintains ATP levels by serving as a reservoir of high-energy phosphate bonds in muscle and nerve tissues. The energy required to rephosphorylate ADP into ATP depends on the amount of phosphocreatine (PCr) stored in muscle tissues. As phosphocreatine is depleted during exercise, energy availability declines due to a loss of ability to resynthesize ATP at the rate required.

In 1943, it was shown that creatine supplementation extended the cycling times of athletes (Keys, 1943). Creatine enhances both strength and endurance in athletes (Keys, 1943; Kreider et al., 1998; Vandenberghe et al., 1997; Stone et al., 1999; Urbanski, Vincent & Yuaspelkis, 1999; Volek et al., 1997; Cooke et al., 2014; Ferraro et al., 1996; Tarnopolsky, 2000; Hespel, 2000; Cooper, Naclerio, Allgrove & Jimenez, 2012). Some researchers have shown strength gains with as little as five to seven days of supplementation (Cooper, Naclerio, Allgrove & Jimenez, 2012). In a double blind study that examined the effects of creatine in a

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weight training program in men over 70 It was shown that creatine had a significant advantage over placebo in terms of increased lean body mass, reduction in body fat, and increased muscular strength, and endurance (Cooke et al., 2014; Tarnopolsky, 2000). In Italy, physicians administered six grams of creatine each day to 13 patients hospitalized with congestive heart failure. After four days, they noted a reduction in heart size, reduced vascular resistance, and increased ejection fraction, all indicators of improved heart function (Ferraro et al., 1996).

In a review article, Tarnopolsky concluded that creatine monohydrate supplementation results in an increase in skeletal muscle total and phosphocreatine concentrations, increased fat-free mass, and enhanced high-intensity exercise performance in young healthy men and women (Tarnopolsky, 2000). He also noted neuroprotective effects, which have been proposed to be of benefit in Parkinson's disease, Alzheimer's disease, ALS, and after ischemia. He concluded that creatine appeared to have potential to attenuate age-related muscle atrophy and strength loss, as well as to protect against neurodegenerative disorders. The U.S. FDA has granted orphan drug status to creatine as a treatment for patients with amyotrophic lateral sclerosis (Lou Gehrig's disease), based on creatine's demonstrated ability to enhance cellular energy production. In addition, a European patent has also recently been issued for the use of creatine compounds to prevent aging effects and to treat muscle atrophy (Hespel, 2000).

Creatine: 5g qd.

Shilajit

Shilajit is a thick, sticky tar-like substance with a color ranging from white to dark brown (the latter is more common) found predominately in Himalaya and Tibet mountains. It is an ancient Indian adaptogen. Shilajit enhances CoQ10's mitochondrial benefits and supports levels of the active ubiquinol form. Components of shilajit can serve as electron reservoirs, replenishing electrons lost by CoQ10 and allowing this vital coenzyme to remain active longer (Surapaneni, 2012).

Shalajit: 200 mg qd.

Mushrooms

Coriolus versicolor (Turkey tail), is a mushroom of the Basidiomycetes class from which the extracts Polysaccharide-K and Polysaccharide-Peptide (PSK, PSP, respectively) have demonstrated to inhibit various carcinomas in animals and humans. This is achieved by inducing apoptosis and activating a cascade of pathways involving the activation of p38 MAPK signaling cascades and over-expression of pro-apoptotic protein Bax (Kobayashi, Matsunaga & Oguchi, 1995). PSK was approved for clinical use in various cancers in Japan in the 1980s. Other mushrooms that seem to have analogous effects on mitochondria are Reishi (Ganoderma lucidum; Ko & Leung, 2007; Cherian, Sudheesh, Janardhanan & Patani, 2009; Sudheesh, Ajith, Mathew, Nima & Janardhanan, 2012) Maitake (Grifola frondosa; Soares et al., 2011; Zhang et al., 2017) Shiitake (Lentinula edodes; Fang et al., 2006), Cordyceps (Ophiocordyceps sinensis; Lee et al., 2015), Chaga (Inonotus obliquus, Sun et al., 2011), Lion's Mane (Hericium erinaceus; Kim, Nam & Friedman, 2013).

Mushrooms: No suggested dose.

Herbs

Certain herbs such as Rhodiola rosea (Abidov, Crendal, Grachev, Seifulla & Ziegenfuss, 2003), Leuzea carthamoides (Azizov, Seifulla & Chubarova, 1997), Eleutherococus senticosis (Eschbach, Webster, Boyd, McArthur & Evetovich, 2000) and Schisandra chinensis (Panossian & Wikman, 2008) have shown certain capacity to activate synthesis and resynthesis of ATP.

Rhodiola has been taken 200 mg qd of an extract standardized to contain rosavins and salidrosides in a 3:1 ratio: For the rest of the herbs there is no suggested dose.

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is a methoxyindole, which is synthesized in the pineal gland of vertebrates through a multistep process starting from hydroxylation of tryptophan and culminating with transformation of serotonin to N-acetyl serotonin followed by methylation to the final substance melatonin. Melatonin is a ubiquitous molecule with a variety of functions including potent reductive properties. Due to its lipophilic character, it easily crosses cellular and intracellular membranes and reaches all subcellular organelles. Melatonin has been shown to protect the bio-energetic function of mitochondria (Acuña-Castroviejo et al., 2001; León et al., 2005; Petrosillo et al., 2006; Kleszczyński, Zillikens & Fischer, 2016).

Melatonin: 10 mg qd before sleep.

Arginine

Arginine is a basic amino acid and is classified as a conditionally essential amino acid. One of the main functions of arginine is its participation in protein synthesis. Arginine is utilized by a number of metabolic pathways that produce a variety of biologically active compounds such as nitric oxide, creatine, agmatine, glutamate, polyamines, ornithine, and citrulline. Also, arginine is involved in a number of roles in the body such as the detoxification of ammonia formed during the nitrogen catabolism of amino acids via the formation

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of urea; its potential to be converted to glucose (hence its classification as a glycogenic amino acid); and its ability to be catabolized to produce energy (Nagaya et al., 2001; Xu et al., 2016). Many of the benefits of arginine stem from its ability to generate nitric oxide, aided by an enzyme called nitric oxide synthase. Nitric oxide (NO) acts as a signaling molecule that induces smooth muscle cells to relax, expanding the blood vessels (vasodilation), blood pressure drops and blood flow is improved. More blood is delivered to the tissues, which are then better nourished with oxygen.

Arginine: 700 mg tid.

Resveratrol

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a plant-derived polyphenol that exerts diverse physiological activities, mimicking some of the molecular and functional effects of dietary restriction. Resveratrol has been shown to increase cellular mitochondrial content and induce apoptosis (Lagouge et al., 2006; De Oliveira, Nabavi, Manayi, et al., 2016; Ungvari, Sonntag, de Cabo, Baur & Csiszar, 2011).

Resveratrol: 20 mg qd.

Quercetin

Quercetin is a naturally occurring flavonoid which has a broad spectrum of bioactive effects. Among these, quercetin can impact mitochondrial biogenesis by modulating enzymes and transcription factors. Quercetin is now recognized as a phytochemical that can modulate pathways associated with mitochondrial biogenesis, mitochondrial membrane potential, oxidative respiration and ATP anabolism, intra-mitochondrial redox status, and subsequently, mitochondria-induced apoptosis (De Oliveira, Nabavi, Braidy, et al., 2016).

Quercetin: 500 mg bid.

Glutathione

Glutathione (GSH) is the major intracellular thiol compound, is an ubiquitous tripeptide produced by most mammalian cells and it is the main mechanism of antioxidant defense against reactive oxygen species (ROS) and electrophiles. GSH versatility permits it to counteract hydrogen peroxide, lipid hydroperoxides, or xenobiotics, mainly as a cofactor of enzymes such as glutathione peroxidase or glutathione-S-transferase (GST). GSH (γ-glutamyl-cysteinyl-glycine) serves as a cofactor for a number of antioxidant and detoxifying enzymes. GSH in the mitochondrial matrix plays a key role in defense against respiration-induced ROS and in the detoxification of lipid hydroperoxides and electrophiles. Moreover, as mitochondria play a central strategic role in the activation and mode of cell death, mitochondrial GSH has been shown to critically regulate the level of sensitization to secondary hits that induce mitochondrial membrane permeabilization and release of proteins confined in the intermembrane space necessary to induce cell death (apoptosis; Ribas, García-Ruiz & Fernández-Checa, 2014).

Oral glutathione supplementation does not efficiently increase intracellular glutathione levels, it can be absorbed intact into the blood stream. Since increased glutathione levels in the blood have been shown to slow the breakdown of nitric oxide, glutathione supplementation may be useful to augment nitric oxide boosters such as L-Citrulline or L-Arginine. N-Acetylcysteine (NAC) is a prodrug for L-cysteine, which is used for the intention of allowing more glutathione to be produced when it would normally be depleted. Through glutathione buffering, NAC provides antioxidative effects and other benefits, so is both more efficient and cheaper than glutathione. Liposome-encapsulated glutathione (Lypo-GSH) seems to be a more effective way to supplement this nutrient.

Glutathione: 250 mg qd.

Dichloroacetate (DCA)

DCA is a potent lactate-lowering drug. It activates the pyruvate dehydrogenase complex by inhibiting the activity of pyruvate dehydrogenase kinase, which normally phosphorylates and inhibits the enzyme. The ability of DCA to keep the pyruvate dehydrogenase complex in an active state reduces the accumulation of lactate in body tissues (Parikh et al., 2009; Khan, Govindaraj, Meena & Thangaraj, 2015; Avula, Parikh, Demarest, Kurz & Gropman, 2014). DCA can switch a cell from aerobic glycolysis to oxidative respiration. This drug induced apoptosis of cancer cells (Bonnet et al., 2007) by reducing mitochondrial membrane potential, blocking aerobic glycolysis (Warburg effect), and activating mitochondrial potassium-ion channels (Khan, Marier, Marsden, Andrews & Eliaz, 2014). Other mechanisms of DCA action against cancer cells have also been proposed. These include: (a) inhibition of angiogenesis; (b) alteration of expression of hypoxia-inducible factor 1-α (HIF1-α),21; and (c) alteration of pH regulators vacuolar-type H+-ATPase (V-ATPase) and monocarboxylate transporter 1 (MCT1) and other regulators of cell survival, such as p53-upregulated modulator of apoptosis (PUMA), glucose transporter 1 (GLUT1), B-cell lymphoma 2 (BCL2) protein, and cellular tumor antigen p53 (127).

An oral DCA regimen that included the natural neuroprotective medications acetyl-L-carnitine, R-α-lipoic acid, and benfotiamine (DD) has been used clinically. IV DCA up to 100 mg/kg/dose that have confirmed its safety. Shifts in ATP production from glycolysis to oxidative phosphorylation by inhibition of PDK1 with dichloroacetate (DCA) was shown to

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shift metabolism from glycolysis to glucose oxidation. Treatment with DCA increased mitochondrial production of ROS/RNS in all tested cancer cells, but not in normal cells (Michelakis, Webster & Mackey, 2008).

It is important to mention that DCA in high doses can damage mitochondria and produce peripheral neuropathy. Peripheral neuropathy is not uncommon with prolonged DCA treatment.

Dichloroacetate: No suggested dose.

3-Bromopyruvate

Bromopyruvic acid and its alkaline form, bromopyruvate, are synthetic brominated derivatives of pyruvic acid. They are lactic acid and pyruvate analogs. 3-Bromopyruvate (BP) has been shown by others to inhibit hexokinase (Ihrlund, Hernlund, Khan & Shoshan, 2008). Being a lactate analogue, it is likely taken up by cells via lactate transporters which are overexpressed in tumor cells (Ihrlund, Hernlund, Khan & Shoshan, 2008). This drug may have significant side effects.

3-Bromopyruvate: No suggested dose.

2-Deoxyglucose

2-deoxyglucose (DG) is a non-metabolizable glucose analogue. DG is a glucose analogue which is easily taken up by tumor cells via glucose transporters and is then phosphorylated by hexokinase, but it is not further metabolized in the glycolytic process (Pedersen, 2007). DG will thus titrate endogenous glucose and thereby block glycolysis (Zhao, Wieman, Jacobs & Rathmell, 2008; Cantor & Sabatini, 2012).

2-Deoxyglucose: No suggested dose.

EPI-743

EPI-743 is a new drug that is based on vitamin E. EPI-743 is a para-benzoquinone analog. Tests have shown that it can help improve the function of cells with mitochondrial problems. It works by improving the regulation of cellular energy metabolism by targeting an enzyme NADPH quinone oxidoreductase (Enns & Cohen, 2017).

EPI-743: No suggested dose.

Lifestyle and mitochondria

Exercise

Dietary interventions are just one part of the overall picture of optimizing mitochondrial function. Other lifestyle considerations like exercise, movement, stress and sleep also play a role in mitochondrial health. Exercise and movement has been shown to improve cellular energy production (Sahlin, 2014). Both aerobic and anaerobic exercise should be performed on a regular basis. Exercise also has an important role in mitochondrial disease therapy, as it has been shown to reduce the burden of unhealthy mitochondria; increase the percentage of healthy, non-mutated mitochondrial DNA (mtDNA); and improve endurance and muscle function.

Suggested exercise, combine aerobic exercises (such as cycling, walking, running, hiking, and playing tennis, basketball that focus on increasing cardiovascular endurance) and anaerobic exercises (such as weight training to increase muscle strength) for 45 min 3x a week.

Hyperbaric (high pressure, 100%) Oxygen Therapy (HBOT)

Hyperbaric oxygen treatment (HBOT) involves inhaling up to 100% oxygen at a pressure greater than one atmosphere (ATM) in a pressurized chamber. Excess oxygen reduces the activity of an enzyme called hexokinase II, which grabs onto glucose after it enters cells and traps it inside so it can be burned for energy. Also HBOT significantly ameliorates mitochondrial dysfunction (Dave et al., 2003; Rossignol et al., 2012; Palzur, Zaaroor, Vlodavsky, Milman & Soustiel, 2008; Moen & Stuhr, 2012; Poff, Ari, Seyfried & D'Agostino, 2013; Poff, Ward, Seyfried, Arnold & D'Agostino, 2015). When cells are proliferating and DNA is unwound, unprotected and being replicated: if high ROS levels are sensed at this time, the process is aborted and the cell can be driven into apoptosis.

Intravenous Laser Therapy (IVLT)

Laser Therapy works on the principle of inducing a biological response through energy transfer, in that the photonic energy delivered into the tissue by the laser modulate the biological processes within the tissue. Light energy transmitted through space as waves that contain tiny "energy packets" called photons (Duality). Each photon contains a definite amount of energy depending on its wavelength (color).

Intravenous or intravascular laser blood irradiation involves the in-vivo illumination of the blood by feeding low level laser light. It is a minimally invasive laser procedure in which a small needle is placed into the vein in the forearm, under the assumption that any therapeutic effect will be circulated through the circulatory system.

It works similar to photosynthesis; the correct wavelengths and power of light at certain intensities for an appropriate period of time can increase ATP production and cell membrane alterations could lead to permeability changes and second

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messenger activity resulting in functional changes (Ferraresi et al., 2015; Xu, Zhao, Liu & Pan, 2008; Momenzadeh et al., 2015; Huang et al., 2012).

Acupuncture treatment (needles in cardinal points), increases the patient's energy but only by mobilizing reserve energy (meridians), in contrast Laser therapy introduces additional energy into the system.

Mitochondria are the key to photobiomodulation. The cytochrome c oxidase can absorb red light converting the photonic energy into biological energy ATP. Cytochrome c oxidase is commonly accepted as a photo acceptor that catalyzes cellular level activity when exposed to red to near-infrared red light.

The absorption of different colors within the mitochondrial respiratory chain:

Complex 1 (NADH dehydrogenase) absorbs blue and ultraviolet light.

Complex 3 (cytochrome c reductase) absorbs green and yellow light.

Complex 4 (cytochrome c oxidase) absorbs red and infrared light.

Mitochondria changed to "giant mitochondria" after laser-irradiation with activation of various metabolic pathways and increased production of ATP due to activation of the respiratory chain and increased ATP-synthesis. ATP is also used as a signaling molecule in communications between nerve cells and other tissues.

There is a normalization of the tissue metabolism due to increased O2. There is also an increase of enzymes. An increase of ATP-synthesis occurs with a normalization of cell membrane potential. Irradiation in the red range is effective to increase the absorption spectrum of cytochrome-C-oxidase in the respiratory chain with a concomitant stimulation of the ATP-synthesis.

There is an increased change of the redox potential in mitochondria and cytoplasm by oxidation at the NADH. Thereby the proton motor force is increased which drives the backflow of the protons into the matrix and by doing so increases the ATP turnover. In addition the electron transfer is accelerated, both effects cause an increase of ATP synthesis.

IVLT has Pleiotropic action that produces a cascade of events due to increased Energy.

Treatment: IVLT 10 min of each color twice a week. This therapy be accompanied by mitochondria-supporting supplements.

Conclusions

Mitochondrial dysfunction has been identified as one of the principal causes of bioenergetic decline. Although there is no single silver bullet or an exact combination of substances or supplements that will unfailingly resuscitate all aspects of failing mitochondria, it has been reported that a number of nutrients, supplements and prescription substances may alleviate or restore many aspects of mitochondrial failure. Combinations of these, acting on multiple targets, may normalize and/or improve mitochondrial function, increase cellular and systemic energy production, alleviate mitochondrial-related disease, and delay age-related decline in many organs and systems of the body.

The rise in the incidence of cancer and deaths from cancer not only parallels the rise in the development and use of toxic chemicals and materials in the environment, but also toxins in our food and water supplies and pharmaceuticals. The rise in cancer incidence and deaths is thought to be directly caused by such toxic ingestion and the body's increasing inability to cope with the toxic overload of xenobiotics that profoundly affects the mitochondria. It is conceivable that combinations of various mitochondrial enhancers/resuscitators, acting on various portions of the mitochondrial energy production pathway will have complementary/additive effects and decrease the cancer incidence and death rates.

Here we have proposed a combination of diet, exercise and supplements containing a mixture of nutrients mentioned herein to significantly enhance mitochondrial function to help restore oxidative respiration to a level of favoring malignant cell re-differentiation or to at least restore apoptotic mechanisms since the intrinsic apoptotic pathway in cells is regulated largely by functional mitochondria. When restoring mitochondrial function, we may reverse aerobic glycolysis, inhibit cancer cell growth and possibly, reverse malignancy.

Scientific support for the use of vitamin-based and cofactor-based mitochondrial therapies is accumulating. This Mitochondrial Correction (Mitochondrial Rescue, Mitochondrial repair) approach is intended to promote critical enzymatic reactions, reduce putative sequelae of excess free radicals, and scavenge toxic metabolic molecules, which tend to accumulate in mitochondrial diseases. Some supplements also may act as alternative energy fuels or may bypass biochemical blocks within the respiratory chain. We believe this concept can have an important repercussion in the treatment of degenerative diseases.

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