The Role of Mitochondria in Cancer and Other Chronic Diseases

Dorothy D Zeviar,[1] Michael J Gonzalez?,[*2] Jorge R Miranda Massari,[2] Jorge Duconge,[2] Nina Mikirova[3]

[1] University of Western States, Portland, OR
[2] University of Puerto Rico, Medical Sciences Campus, San Juan, PR
[3]Riordan Clinic, Wichita, KS * Correspondence should be addressed: Dr. Michael J Gonzalez, University of Puerto Rico, Medical Sciences Campus School of Public Health, Department of Human Development, Nutrition Program. GPO Box 365067 San Juan PR 00936-5067; email: michael.gonzalez5@upr.edu

Abstract *Nutrition is the foundation and basis of good health; therefore, it stands to reason that a proper diet would assist in the prevention of common 21st century chronic diseases such as heart disease, diabetes, neurodegenerative diseases, and cancer. In this article we explain the roles of mitochondria in health, and the biochemistry of mitochondria in degenerative disease. We examine the role of oxygen in both (aerobic) oxidative phosphorylation (OxPhos) and (anaerobic) glycolysis, and how the latter may contribute to chronic disease states. We discuss the biochemical mechanisms behind adenosine triphosphate production and the simultaneous production of Reactive Oxygen Species (ROS) (free radicals), and the chronic effects of cellular ROS damage. Lastly, we discuss the cellular health-enhancing effects of reductive molecules (antioxidants) and an alkaline environment, and how this contrasts with an acidic environment/ diet, which contributes to chronic disease and the pathological state.*

Mitochondrial Basics

Mitochondria serve several important cellular roles, but first, we shall discuss some background history, structure and the roles mitochondria play in cellular health. It is generally recognized and agreed that mitochondria originated from an aerobic bacteria approximately 1-3 billion years ago, which merged with a pre-existing unicellular organism. Both organisms developed a symbiotic relationship which provided a way to create aerobic cellular respiration and produce much more energy. This in turn, supports the development of complex multi-cellular aerobic organisms. Mitochondria are the only subcellular organelle/organism with their own mtDNA.[1]

Because mtDNA is maternally transmitted by the ovum at conception (inherited from one's mother), its genetic defects or variants, deficiencies (if any) are limited to the mitochondria; the cellular-nuclear DNA (nDNA) is governed by Mendelian inheritance principles. In contrast to nDNA which is made up of 3.3 billion base pairs (bp) of genes, mtDNA is circular and composed of 16,569 bp. These bp include 37 genes, of which 24 encode for mitochondrial translation and 13 encode for the cellular respiratory chain.[2] nDNA is protected by histones which shield nDNA from free radical damage, however, mtDNA is not protected by histones, so they are more susceptible to oxidative damage.[3] mtDNA may generate up to 10 times the number of

nDNA mutations for two reasons – mtDNA resides close to the electronic transport system (ETS) inside the inner mitochondrial membrane and mtDNA lacks repair mechanisms, so once damaged, the mitochondria may be slated for apoptosis.[4]

Mitochondria Structure and Roles

The number of mitochondria per cell is energy/function dependent; i.e., those cells that require and expend the most energy contain the highest number of mitochondria. Most cells have between a few hundred to over 20,000 mitochondria; they are concentrated most heavily in cells of the heart, brain, liver, muscles, gastrointestinal tract, and kidneys.[5]

Mitochondria are composed of two membranes. The more porous outer membrane contains porin and allows molecules up to approximately 10 kDa to freely diffuse across the membrane. The inner, more tightly constructed (less permeable) membrane contains cardiolipin, a phospholipid which has both a higher affinity for inner membrane proteins, and, having two unsaturated bonds, is more susceptible to oxidative damage. Components of the electron transport system (ETS) are found along the inner membrane. The space between the two membranes is the intermembrane space where Cytochrome c is found. Inside the inner membrane is the mitochondrial matrix which contains many of the enzymes necessary for adenosine triphosphate (ATP) production (enzymes associated with the Kreb's Cycle), as well as the mitochondrial genome.[6]

Mitochondria play many important roles in human biology, including synthesis of heme, lipids, amino acids and nucleotides. As mentioned above, they are involved in initiating cellular apoptosis. Their most important role, however, is the production of ATP. Mitochondria generate 95% of the ATP in the cell, and rely on ATP for its own functions.[7,8]

Due to the location of the ETS adjacent to the inner mitochondrial membrane, the generation of free radicals as a normal part of oxidative phosphorylation (production of ATP), as well as the lack of histone protection for mtDNA, much oxidative damage can occur to mitochondria, and indeed does occur in normal physiological reactions as well as in chronic disease. Later, we will discuss the role that an alkaline diet can play in preventing much of this oxidative damage.

Review of ATP Biosynthesis

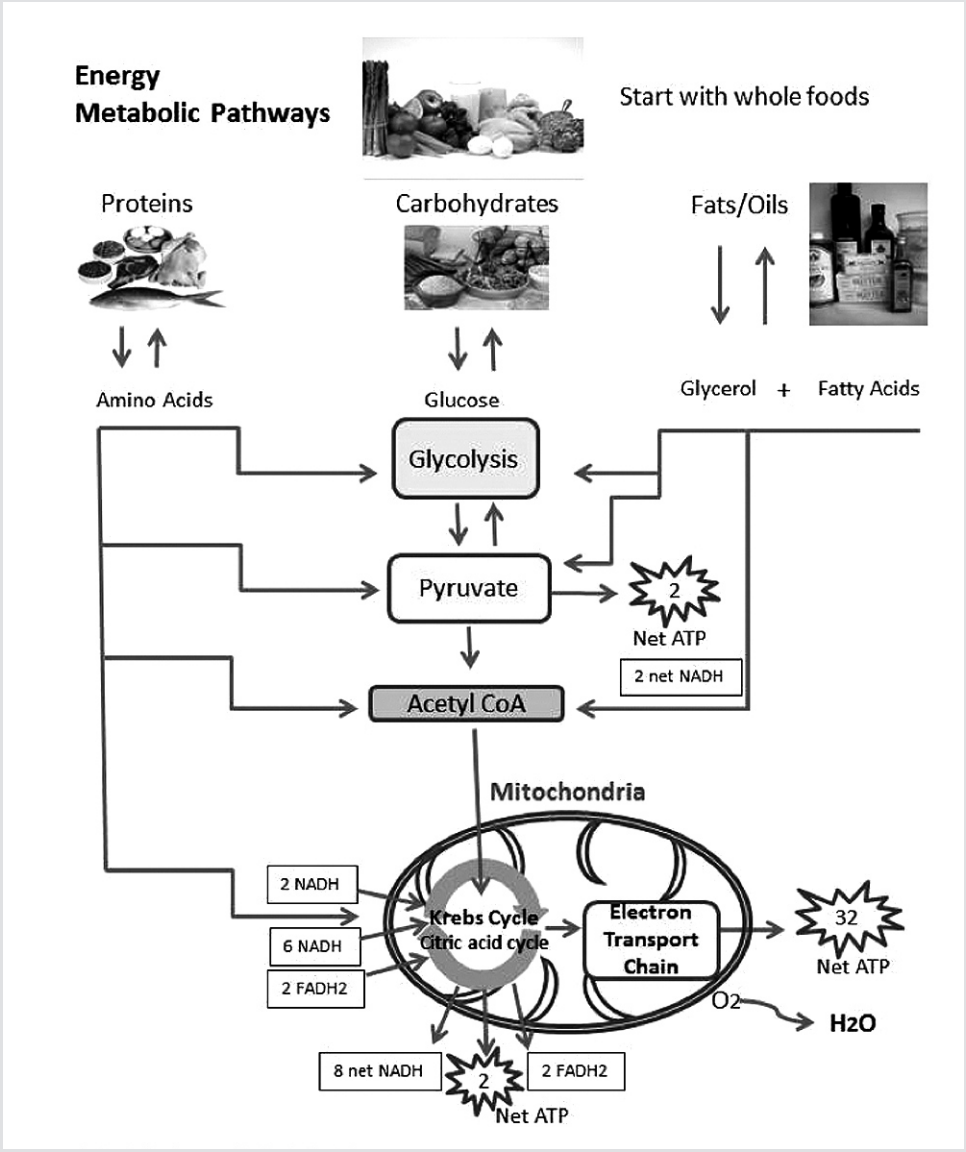
As stated above, the primary role of mitochondria is to synthesize ATP (cellular energy). This process is also known as cellular respiration. As humans, we derive all our energy from the food we eat, which the mitochondria metabolize into glucose, amino acids and fatty acids. Because we derive all our cellular energy from the food we eat, this fact emphasizes the point that eating whole food is necessary for proper ATP production and general cellular functions. Recent research has linked all chronic disease, including cancer, to deficiencies in mitochondrial structure and function.[1]

The Role of Oxygen in Both (Aerobic) Oxidative Phosphorylation and (Anaerobic) Glycolysis

As presented in **Figure 1,** (p.159) the "normal" process of oxidative phosphorylation (OxPhos) creates approximately 38 ATPs per glucose molecule and approximately 90% of the cell's energy requirements. Under normal aerobic conditions, pyruvate is oxidized by NAD+ and a dehydrogenase enzyme that converts pyruvate to Acetyl-CoA and CO2. This reaction requires oxygen to oxidize NADH back to NAD+ to continue the metabolic process.[9]

This section will provide a simplified explanation of the ETS and OxPhos in the inner membrane of the mitochondria. Research has identified five protein complexes on the inner mitochondrial membrane related to the ETS and OxPhos processes; Complexes I, II, III, IV are part of the ETC, and Complex V is where OxPhos or the conversion of ADP to ATP actually takes place. This process requires co-factors that actually carry the electrons "down" the ETS such as cytochrome C and Co-Q, as illustrated in **Figure 2.** (p.160) The entire process is actually one of oxidation

Figure 1. The oxidative phosphorylation process.



of NADH and FADH2, by-products of the Kreb's Cycle, to H_2O. [10]

Complexes I, III, and IV "pump" protons from the inner membrane across the membrane into the intermembrane space, creating a "proton gradient" that is necessary for ATPase conversion of ADP to ATP (phosphorylation). The potential of hepatocytes, for example, has been measured at 170mV, but the normal cell potential is 50-70 mV. A proton gradient is necessary for efficient ETS function. The combination of movement of protons "down" the ETS and the phosphorylation of ADP in Complex V is called the coupling of cellular respiration with the synthesis of ATP. It is said that the efficiency with

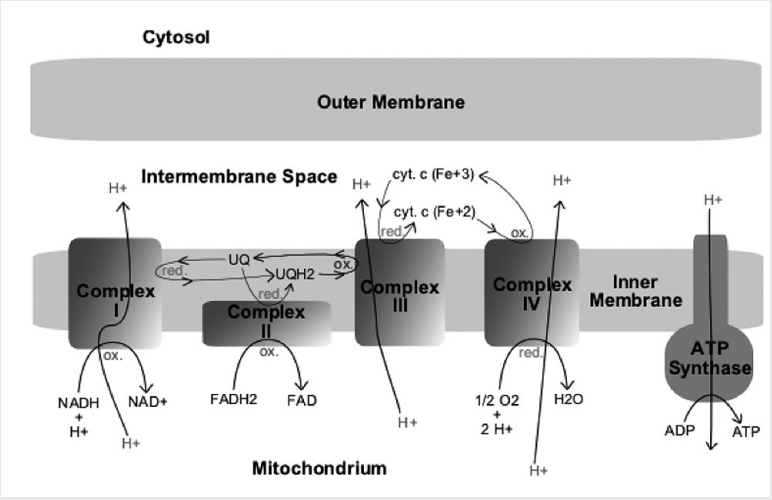
which foods are metabolized and converted to energy is determined by the efficiency of this "coupling" process. It is estimated that each complex pumps four protons across the membrane.[10,11] The "pumping" of protons into the intermembrane space helps maintain an alkaline pH inside the mitochondria, which then creates a negative potential with respect to the cytosol.[11] Acidic substances, xenobiotics, and drugs can also "uncouple" the ETS from OxPhos. As previously stated, the entire ETS and OxPhos process produces approximately 38 ATP.

Because ATP production occurs in the cristae of the inner membrane, close to the ETS where protons are "pumped" and occasionally "lost," the mitochondria are subject to great oxidative damage themselves by their own processes. Although aerobic OxPhos is the optimal process for producing ATP, it is not without inherent danger to the mitochondria themselves, as it also produces ROS such as the superoxide radical O_2.-, hydrogen peroxide H_2O_2, the hydroxyl radical HO. ,the perhydroxyl radical HO_2. , and peroxynitrite ONOO- . During normal OxPhos, 0.4 – 4% of all oxygen consumed is converted in mitochondria to superoxide O_2.-.[1] These ROS contribute to enzymatic damage, membrane damage and subsequent apoptosis. Not only do ROS accumulate with age, but they negatively affect mtDNA replication and repair processes. Organelles that have sustained damage to their DNA, membranes, or respiratory chain (ATP synthesis) proteins will suffer from a chronic energy shortage and diminished or nonexistent proton gradient.[12] Defective mitochondria accumulate most in ATP-active organs such as the brain, heart and muscle, which may partly explain the increasing incidence of chronic diseases involving these organs. These ROS can be "paired" and neutralized in the cell with a diet high in antioxidants, found in a typical alkaline diet rich of fresh fruits and vegetables.

Anaerobic Glycolysis

This discussion about ROS damage to mitochondria relates to anaerobic glycolysis. From the point in the metabolic pathway where pyruvate metabolizes to Acetyl-CoA, pyruvate can also take another form as lactate ($C_3H_5O_3$-) under conditions of low oxygen. The attention should be directed to the one-way arrow emerging from pyruvate ($C_3H_4O_3$) to Acetyl-CoA ($C_{21}H_{36}N_7O_{16}P_3S$) to indicate that, at this point in the metabolic process, pyruvate can only metabolize to

Figure 2. Oxidation of NADH and $FADH_2$.



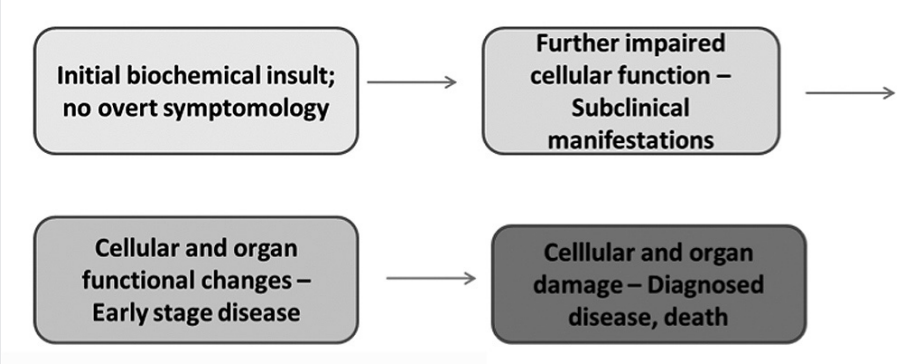
Acetyl-CoA in the presence of oxygen. When muscles have over-exercised and "used up" the available oxygen, pyruvate cannot convert to Acetyl-CoA and instead turns to lactic acid ($C_3H_6O_3$). This phenomenon occurs during heavy exercise or stress, for example, but can also occur in the initial stages of cancer and other degenerative and chronic diseases which affect cellular integrity. Lactic acid creates an acidic cellular environment that, if not immediately corrected, contributes to a chronic acidic cellular environment which is conducive to cellular breakdown, loss of function and predisposition to cancer. The usual disease progression may follow the pattern depicted in Figure 3. (below)[13]

Recall that mtDNA lacks protective histones and repair mechanisms; therefore, they are more susceptible to oxidative damage. And although each cell contains numerous mitochondria (from hundreds to over 20,000), one would think that occasional mitochondrial damage would not significantly impact a cell or an organ. And occasional mitochondrial damage does not affect cellular or organ function. However, years of cumulative oxidative damage to both mtDNA and subsequently nDNA does indeed adversely affect cellular and organ function which leads to disease states, cancer and aging.

ROS Damage

As stated above, a two-edged sword regarding ATP production is the simultaneous production of necessary ROS that may have a role in gene regulation and excessive damaging ROS leading to the disease state, under both aerobic and anaerobic conditions. One explanation for how ROS damage contributes to chronic disease conditions is that excess calories (or poor quality calories), and the lack or excess of exercise generate more electrons than the ETS can handle, leaving more electrons in the inner membrane space (because they can't be pumped back out into the intermembrane space). This adversely affects the proton gradient necessary for ADP coupling with P to create ATP, stalling the ETS process. Additionally, with less oxygen available to pair with the protons created in the ETS process, the cells cannot make H_2O as a by-product of OxPhos, so more ROS accumulate in the cells, contributing further to mtDNA damage and subsequent nDNA damage.[14] ROS contributes to mtDNA damage/deletions/mutations, and as less ATP is produced and cellular functions diminish, subsequent replicated mitochondria become less and less robust and unable to successfully carry out cellular and organ functions, thus contributing to chronic degenerative disease.

Figure 3. Anaerobic glycolysis and disease progression.



Apoptosis

Recall that another important role of mitochondria is that of regulating cellular apoptosis. Because ROS damage negatively impacts ATP production, necessary for ALL cellular functions, regulation of apoptosis is also affected. Apoptosis is the process of programmed cell death, necessary for the renewal of all body cells, and for the continuity of life. Approximately 30-50 billion cells are replaced daily in the average human. [15] However, too much apoptosis can cause muscle and organ failure, and too little may contribute to tumorigenesis.

Recall that the mitochondrial inner membrane is composed primarily of cardiolipin, an easily oxidized phospholipid. When the mitochondrial membrane is damaged (due to any of the stressors mentioned above), apoptotic signals are released which cleave to nDNA and initiate cell death. The more membrane damage, the more rapid cellular degradation occurs. Several proteins and other substances in the mitochondria initiate apoptosis. During this process, cytochrome C is released from the intermembrane space into the cytosol which causes cell death (after other substances are triggered and released). So although 30-50 billion cells are replaced daily, if apoptosis in one body system is greater than the number of cells replaced, systemic disease and/or organ failure ensues. As cells continue to die off through apoptosis, tissue function decreases, which eventually lead to symptoms and chronic degenerative disease (refer to boxes 2 and 3 in Figure 3).[13]

Chronic Disease, Cancer and Mitochondria

As discussed earlier, lacking histones and with lowered ATP production, mitochondria have limited ways of self-repair once damage from ROS has been inflicted. In this situation, cells cannot even make the RNA and DNA they require to function without mitochondria. When mtDNA becomes damaged, it is more difficult to copy accurately, resulting in errors of transcription, deletions and mutations. Oxidation from ROS results in a series of cellular insults: cell membranes lose their integrity, the proton gradient is diminished causing less ATP to be produced, cellular proteins necessary for all other cellular functions unfold and lose their affinity for their enzymes, and cytochrome C is released into the cytosol stimulating apoptosis, all in a continuous feed-forward cycle of cellular, tissue and organ dysfunction (chronic degenerative disease). Production of ATP is the key differentiator and chief purpose of mitochondria in the cell; they are the keystone to proper tissue and organ function and even gene regulation in humans. This point cannot be over-stated or over-emphasized; without fully functioning mitochondria, we cease to exist. Research is finding that cancer cells also exhibit increased mitochondrial damage by ROS.[9] As discussed above, ROS impedes the ETS, resulting in not only reduced production of ATP, but an excess of unoxidized NADH and pyruvate, which in turn get reduced to lactate. Additionally, high ROS concentrations permit histone acetylation to predominate, which accelerates (faulty) nuclear transcription and thus replication, and initiates the release of NFkB into the nucleus (a significant pro-inflammatory cytokine which also damages nDNA). At the same time, however, cell differentiation and apoptosis signals are silenced with histone acetylation, eventually resulting in over-replication favoring tumorigenesis. [16]

Gonzalez et al further explained the connection between dysfunction in the ETS and apoptosis: more CO is produced as a by-product of inefficient cellular respiration, which also blocks apoptosis. Cancer cells have a lower proton gradient: only -15 mV compared to a normal cell of 50-70 mV. A reduced gradient simultaneously reduces ATP output. Complicating this metabolic scenario is the fact that without sufficient ATP, cells lose their ability for cell-to-cell communication, so as "individualized" unicellular cells, must form colonies to survive, forming what we know as the tumor. Thus, cancer is a cell survival mechanism in a hostile (acidic) environment, since cancer cells have a hard time surviving in an alkaline environment.[16] ROS contributes both to chronic disease manifestation through the mechanisms of mitochondrial dysfunction and subsequent tissue/ or-

gan loss of function; as well as tumorigenesis progression through the mechanisms of uncontrolled nDNA replication without differentiation. Cancer cells appear to thrive under anaerobic conditions; this phenomenon was first observed by Warburg in the 1930s.

Early History of Cancer Research – Warburg, Szent-Gyorgyi, and Pauling

According to the CDC, cancer (all forms) is now the second-leading cause of mortality among people in the developed world, exceeded only by heart disease.[17] By its nature and characteristics, cancer is the uncontrolled overgrowth of cells which we call a tumor. Normal cellular functions initiated by the mitochondria such as apoptosis, and cellular division/ replication are dysfunctional in a cancerous environment, due to loss of cellular membrane integrity, and an increasing acidic cellular environment, as stated above. When cellular functions no longer operate properly, the cell accumulates ROS and lactate, leaving the cell to depend on anaerobic glycolysis for energy, which generates only two ATPs.[10]

Our experience has revealed that conventional oncology believes that a significant proportion of cancers are the result of genetics, yet recent statistics inform us that genetics play a role in only 5% of cases.[18] We now know that mitochondrial activity/ function determines whether oncogenes get "switched on" or "off;" an alkaline diet appears to help keep these genes under control.

Otto Warburg, a German biochemist, was a pioneer in observing and publishing research into cellular respiration and the effects on cancerous cells/ tumor growth; he was awarded the Nobel Prize in Physiology in 1931 for his work. His research concluded that, unlike normal cells which depend on aerobic oxidative phosphorylation to produce ATP, cancerous cells instead use anaerobic respiration for energy production. As he wrote and lectured, "The prime cause of cancer is the replacement of the respiration of oxygen in normal cells with the fermentation of sugar. All normal cells meet their energy needs by respiration of oxygen, whereas cancer cells meet their energy needs in great part by fermentation. Thus, cancer cells are partial anaerobes." He added, "During cancer development aerobic respiration fails, fermentation appears, and highly differentiated cells are transformed into fermenting anaerobes, which retain only the now useless property of growth." He concludes, "Cancer is ultimately a problem of how cells use or misuse oxygen to burn sugars."[19] Sadly, this theory was discounted by the mainstream medical establishment, continued to be discounted throughout the 1960s when Warburg lectured internationally, and continues to be ignored by today's oncologists who refute the role of anaerobic glycolysis, sugar and ROS in the creation of cancerous conditions. Research done by Vaughn and Deshmukh demonstrate that it is "glucose metabolism which protects cancer cells from cytochrome C mediated apoptosis."[20] Albert Szent-Gyorgyi, who won the Nobel Prize in Physiology in 1937 for his work in discovering vitamin C elucidated what was the theory of cellular combustion (producing energy), i.e., that "the combustion of hydrogen is the real energy-supplying reaction."[25] Empirical experimentation with Hungarian paprika and lemons had a therapeutic effect on colleagues with damaged capillary blood vessels; the positive effect of vitamin C on blood vessel integrity and wound-healing is well-documented. Vitamin C is also a powerful RedOx agent and co-factor in many enzymatic reactions.[21]

Following on the research of Warburg and Szent-Gyorgyi, in the 1970s Linus Pauling conducted empirical studies of both oral and IV vitamin C on people with cancer and the common cold, reasoning that vitamin C therapy increased survival of cancer patients by four times compared to control groups. He co-wrote a book entitled "Vitamin C and Cancer" and with a colleague Ewan Cameron, but was still labeled a "quack" by the medical establishment. Gonzalez et al wrote that ascorbate (vitamin C) may preferentially target the mitochondria by increasing electron flux, thus increasing the production of ATP and thus, the "normalization" of the apoptosis function. They added that a greater amount of vitamin C optimizes the production of ATP as well as cell-to-cell communication and cell

differentiation.[16] Further research remains important with regards to both the dosage of vitamin C as well as the timing of application during oncologic therapies, as Vitamin C can have both antioxidant and pro-oxidant characteristics.[22] RedOx therapy may become the "medicine of the 21st century.

A recurring theme is that mainstream allopathic oncologists continue to deny the efficacy of vitamins, minerals, whole foods and antioxidants on prevention and treatment of chronic degenerative diseases and cancer. With the overview of biochemical processes involved in mitochondrial and cellular dysfunction as outlined in this paper, the evidence appears to be strong that an alkaline diet high in antioxidants (fruits and vegetables) would help prevent chronic degenerative disease and cancer, and lead to a better quality of life.

The Protective, Preventive Action of an Alkaline Diet

Prevention of cancer involves two elements: consumption of the proper diet and the avoidance of substances that damage the mitochondria. Damage to mitochondria is known to have a key role in the pathogenesis of an extensive amount of disorders such as schizophrenia, dementia, Alzheimer's disease, epilepsy, strokes, neuropathic pain, Parkinson's disease, ataxia, transient ischemic attack, cardiomyopathy, coronary artery disease, chronic fatigue syndrome, fibromyalgia and diabetes among others. A proper diet must include sufficient nutrients to sustain efficient aerobic respiration. This includes the macronutrients that are the energy and macromolecules for functional and structure and function and the micronutrients that facilitate efficient functioning of the biochemical pathways to extract and transform energy into a biologically useful form. These micronutrients include the B-complex, various minerals, other cofactors such as CoQ_{10}, lipoic acid and acetyl L carnitine and the electrolyte balance to promote the conditions for an efficient physiological functioning.

Risk factors linked with chronic diseases (e.g., cancer, lung diseases), such as stress, tobacco, environmental pollutants, radiation, infection, cause damage to cells through excessive or uncontrolled generation of ROS.[23]

Xenobiotics that damage mitochondrial membrane include environmental toxicants and medications. Tobacco smoke reduces arterial oxygenation and increases oxidative stress and decreases cytochrome oxidase in complex IV if the mitochondria, 25% after 30 minutes of passive smoke and the enzyme activity continues to decrease with time.[24]

Because the mitochondria is crucial in energy production, the mitochondrial dysfunction can be related to various groups of diseases including the main killers in our society cancer and cardiovascular disease.[25] Other environmental factors include some insecticides and pesticides and fat soluble chemicals with benzene rings such as hair dye and paint fumes.

Research has demonstrated that medications are a major cause of mitochondrial damage, which may explain many adverse effects. These offenders include psychotropic drugs, anticonvulsants, anti-cholesterol medications, analgesics and anti-inflammatory agents, antibiotics, steroids, anticancer chemotherapy, Diabetes medications and HIV/AIDS medications. While certain nutritional cofactors might limit the damage caused to mitochondria by medications, there is still much research needed in this area.[26]

Chronic inflammation can stimulate all stages of tumorigenesis, (DNA damage, uncontrolled replication, inhibition of apoptosis, augmented angiogenesis and tissue invasion/metastasis. Chronic inflammation is prompted by environmental factors (e.g., infection, tobacco, asbestos) and host gene mutations factors (e.g., Ras, Myc, p53). Despite the extensive research published over the last decade, many of the precise molecular mechanisms are still in elucidation and discussion.

It has been proposed that activation of Ras, Myc, and p53 cause mitochondrial dysfunction, which then causes mitochondrial reactive oxygen species (ROS) production and consequent signaling transcription factors (eg, NFkappaB, STAT3, etc.) that promote inflammation-associated cancer.[27] However, the bioenergetic theory of carcinogenesis[28] proposes that mitochondrial dysfunction could

be the original insult that induces signaling that activates the oncogenes and transcription factors. Inflammation-associated cancers produced from signaling from the mitochondrial are being identified that may prove useful for developing innovative strategies for both cancer prevention and cancer treatment.

Diet and Biochemical Conditions

Neustadt suggests that because the major reason and root cause for mitochondrial dysfunction (and thus chronic disease and cancer) lies in a surplus of ROS that cannot effectively be neutralized, that RedOx therapy (IV vitamin C, alkaline diet, supplements, enzymes, etc) may be a viable lifestyle option for both prevention and treatment. Because research is still lacking in the dosage and timing of reductive therapy, the best way to determine vitamin and supplement needs is through urinary organic acid testing. Optimal mitochondrial function is dependent upon sufficient vitamins, minerals, enzymes, co-factors and all the nutrients necessary for optimal cellular function, all of which are found in a good alkaline diet.[1] Cancer cannot exist in an alkaline, oxygen-rich environment. To overcome cancer, we must change our internal environment.[9] This is the mitochondrial correction concept.

The co-factors necessary for complete Kreb's Cycle metabolism include cysteine, sulfur, iron, magnesium, manganese, lipoic acid, niacin, thiamin, riboflavin, and pantothenic acid, the last four of which are in the Vitamin B family. Supplementation with lipoic acid and acetyl-L-carnitine can improve mitochondrial function.[29] Carnitine is necessary to move Acetyl-CoA into the mitochondria with vitamin C as a co-factor. The ETS requires both CoQ_{10} and flavins which include riboflavin, iron-sulfur complexes, copper and heme molecules. Heme synthesis requires pyridoxine (B_6), riboflavin (B_2), iron, copper, and zinc. Glutathione is a major anti-oxidant which requires selenium as a co-factor for production. Deficiencies in any of these substances can cause increased ROS production and loss of cellular function. Antioxidant herbs and supplements include such substances as turmeric (curcumin), green tea, resveratrol, and garden herbs such as oregano. Anti-inflammatory substances include Omega-3 fish oil, flax oil, vitamin E, boswellia, and ginger.[1]

Alkaline vs Acidic Environment

Average adult humans eating Western diets have chronic, low-grade metabolic acidosis at a grade that can be estimated by the net rate of endogenous non-carbonic acid production (NEAP), which varies with diet. [30] Some age-related problems such as bone mass decline, osteoporosis, and decrease in muscle mass. Chronic, low-grade is in part caused by diet-dependent acidosis and may therefore be improved by diet modification and/or supplementation.

Our current "Standard American Diet" (SAD) is acidic, made so by over-consumption of high-glycemic foods, processed foods, sugar, meats, coffee and alcohol, and anything made with white flour. Stress and toxins also contribute to an acidic environment. Mitochondrial enzymes in the matrix work best in an alkaline environment, thus optimizing their metabolic processes.[31,32] According to Gonzalez, alkaline solutions absorb oxygen, whereas acidic environments expel oxygen, which explains why anaerobic organisms thrive in an acidic environment, and why tumorigenesis is also favored in an acidic environment. A lowered pH contributes to a lowered membrane potential which results in cellular dysfunction and lowered ATP production, again, favoring chronic disease progression and carcinogenesis.[16]

The ideal blood pH range is 7.35 to 7.45, with the majority of holistic health practitioners preferring the higher range, closer to 7.4. One of the chief ways the body creates homeostasis is to "steal" minerals from bones and other vital organs. This compensating mechanism, of course, contributes to loss of vital co-factors involved in important enzymatic reactions, which in turn decreases cellular and organ function eventually leading to chronic disease and/or cancer.

Concluding Remarks

Developing a healthy lifestyle, with an emphasis on increasing vegetables in the diet, would decrease ROS and provide the or-

ganism with a balance of nutrients that fosters a healthy biochemical environment that strengthens the composition and function of the mitochondria should be protective against chronic diseases such as cancer.

Competing Interests

The authors of this report declare that they have no competing interests.

References

1. Neustadt J, Pieczenik S: Mitochondrial dysfunction and molecular pathways of disease. Exp Molec Pathol, 2006; 83: 84-92.
2. Birch-Machin M: The role of mitochondria in ageing and carcinogenesis. Clin Exp Dermatol, 2006; 31: 548-552.
3. Alexeyev MF: Is there more to aging than mitochondrial DNA and reactive oxygen species? FEBS J, 2009; 276(20): 5768–5787.
4. Cohen B, Gold D: Mitochondrial cytopathy in adults: What we know so far. *Cleveland Clin J Med,* 2001; 68: 625-642.
5. Alberts B, Johnson A, Lewis J, et al: *Molecular Biology of the Cell.* New York: Garland Publishing Inc. 1994; 32-36.
6. King A, Selak MA, Gottlieb E: Succinate dehydrogenase and fumarate hydratase: linking mitochondrial dysfunction and cancer. *Oncogene,* 2006; 25: 4675-4682.
7. Pham T, Loiselle D, Power A, Hickey AJ: Mitochondrial inefficiencies and anoxic ATP hydrolysis capacities in diabetic rat heart. *Am J Physiol Cell Physiol,* 2014; 307: C499-C507.
8. Hüttemann M, Lee I, Grossman LI, et al: Phosphorylation of mammalian cytochrome c and cytochrome c oxidase in the regulation of cell destiny: respiration, apoptosis, and human disease. *Adv Exp Med Biol,* 2012; 748: 237-264.
9. Clark D: Basic Science Aspects of the Mitochondria. Section X: Cancer, 2000; p.2,6. Retrieved from: *[http://healingtools.tripod.com/primecause1.html/]*
10. Kowald A: The mitochondrial theory of aging: Do damaged mitochondria accumulate by delayed degradation? *Exp Gerontol,* 1999; 34: 605-612.
11. Neustad J, Pieczenik S: *Foundations and Applications of Medical Biochemistry in Clinical Practice.* Bloomington, IN. iUniverse. 2009.
12. Wallace D: A mitochondrial paradigm of metabolic and degenerative diseases, aging and cancer: A dawn for evolutionary medicine. *Ann Rev Genet*, 2005; 39:359.
13. Karam J: *Apoptosis in Carcinogenesis and Chemotherapy.* Netherlands: Springer. 2009.
14. Belikova N, Vladimirov YA, Osipov AN, et al: Peroxidase activity and structural transitions of cytochrome C bound to cardiolipin-containing membranes. *Biochem,* 2006; 45: 4998-5009.
15. Birch-Machin M: The role of mitochondria in ageing and carcinogenesis. *Clin Exper Dermatol,* 2006; 31: 548-552.
16. Gonzalez MJ, Rosario-Pérez G, Guzmán AM, et al: Mitochondria, energy and cancer: The relationship with Ascorbic acid. *J Orthomol Med,* 2010; 25: 29-38.
17. CDC Centers for Disease Control and Prevention. Cancer prevention and control. Cancer statistics by cancer type. Retrieved from *[http://www.cdc.gov/cancer/dcpc/data/types.htm].*
18. Seyfried TN, Shelton LM: Cancer as a metabolic disease. *Nutr Metab* (Lond), 2010; 7: 7.
19. Warburg O: On the Origin of Cancer Cells. *Am Assoc Adv Sci,* 1956; 123: 309-314.
20. Vaughn AE, Deshmukh M: Glucose metabolism inhibits apoptosis in neurons and cancer cells by redox inactivation of cytochrome c. *Nat Cell Biol,* 2008; 10: 1477-1483.
21. Szent-Gyorgyi A: The living state and cancer. *Proc Natl Acad Sci USA,* 1977; 74: 2844-2847.
22. Padayatty S, Katz A, Wang Y, et al: Vitamin C as an antioxidant: evaluation of its role in disease prevention. *J Am Nutr,* 2003; 22: 18-35.
23. Gupta SC, Hevia D, Patchva S, et al: Upsides and downsides of reactive oxygen species for cancer: the roles of reactive oxygen species in tumorigenesis, prevention, and therapy. *Antioxid Redox Signal,* 2012; 16: 1295-1322.
24. Gvozdjak J, Gvozdjakova A, Kucharska J, Bada V: The effect of smoking on myocardial metabolism. *Czech Med,* 1987; 10: 47-53.
25. Yang Z, Harrison CM, Chuang GC, Ballinger SW: The role of tobacco smoke induced mitochondrial damage in vascular dysfunction and atherosclerosis. *Mutat Res,* 2007; 621(1-2): 61-74.
26. Neustadt J, Pieczenik SR: Medication-induced mitochondrial damage and disease. *Mol Nutr Food Res,* 2008; 52: 780-788.
27. Kamp DW, Shacter E, Weitzman SA: Chronic inflammation and cancer: the role of the mitochondria. *Oncology,* 2011; 25: 400-410.
28. Gonzalez MJ, Miranda Massari JR, et al: The bioenergetic theory of carcinogenesis. *Med Hypotheses,* 2012; 79: 433-439.
29. Hagen TM, Moreau R, Suh JH, Visioli F: Mitochondrial decay in the aging rat heart: evidence for improvement by dietary supplementation with acetyl-L-carnitine and/or lipoic acid. *Ann NY Acad Sci,* 2002; 959: 491-507.
30. Frassetto LA, Todd KM, Morris RC Jr, Sebastian A: Estimation of net endogenous noncarbonic acid production in humans from diet potassium and protein contents. *Am J Clin Nutr,* 1998; 68: 576-583.
31. Hansen SH, Andersen ML, Cornett C, et al: A role for taurine in mitochondrial function. *J Biomed Sci,* 2010; 17(Suppl 1): S23.
32. Minich D, Bland J: Acid-alkaline balance: Role in chronic disease and detoxification. *Altern Ther Health Med,* 2007; 13: 62-65.