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Review Article

Evolutionary Metabolic Hypothesis of Cancer (EMHC)

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Abstract

This study introduces a hypothesis which is based on the Warburg Hypothesis and also lends further support to the metabolic theory of cancer put forth by Professor Thomas N Seyfried. As nearly all cancer cells have defective mitochondria they are unable to produce energy from oxidative phosphorylation. Instead, they generate ATP primarily from fermentation of glucose in the cytosol. We have done a three months' study based on the Special Keto-Diet plus Ozone therapy for each patients with 6 different cancer metastatic tumors at the Violet Cancer Institute (VCI) in Iran/Tehran. The results were the total significant reduction in cancer tumors and we conclude that the special Keto-Diet plus Ozone therapy would be one of the best treatment method for reducing the cancer tumor size and the possibility of the metastasis of malignant cancer tumors. Our latest study is put forth the correctness of the cancer as an Evolutionary Plus Metabolic disease. Understanding the significance of this landmark hypothesis offers oncologists and cancer biologists insight into evolutionary aspects of this disease and new directions for research and treatment strategies based on cancer cell vulnerabilities.

Keywords: *Warburg Hypothesis; Cancer Cells; Fermentation; Evolution*

Abbreviations

WE: Warburg Effect; VCI: Violet Cancer Institute; Keto-Diet: Ketogenic Diet; EMHC: Evolutionary Metabolic Hypothesis of Cancer; WHC: Warburg Hypothesis of Cancer; ATP: Adenosine Triphosphate; ROS: Reactive Oxygen Species; NADH: Nicotinamide Adenine Dinucleotide; NADPH: Nicotinamide Adenine Dinucleotide Phosphate

Introduction

Warburg effect in Plant physiology

The Warburg Effect (WE), is the decline in the photosynthesis rate by high oxygen concentrations [1,2]. Oxygen is an inhibitor of the carbon dioxide fixation by RuBisCO. Which initiates photosynthesis. Oxygen stimulates photo-respiration, which decreases photosynthetic result. These two mechanisms working together, are responsible for the Warburg Effect (WE) [3].

Warburg Effect in Oncology

The Warburg effect (WE) in oncology, says that cancer cells produce energy by a high rate of glycolysis followed by lactic acid fermentation in the cytosol [4,5], rather than by a comparatively low rate of glycolysis followed by oxidation of pyruvate in mitochondria [6-8]. The latter process is aerobic and uses oxygen. Malignant tumor cells have glycolytic rates 200 times higher than normal tissues of origin. This happens even if oxygen is plentiful and present as well. Otto Heinrich Warburg proved this change in metabolism is the prime cause of cancer [9].

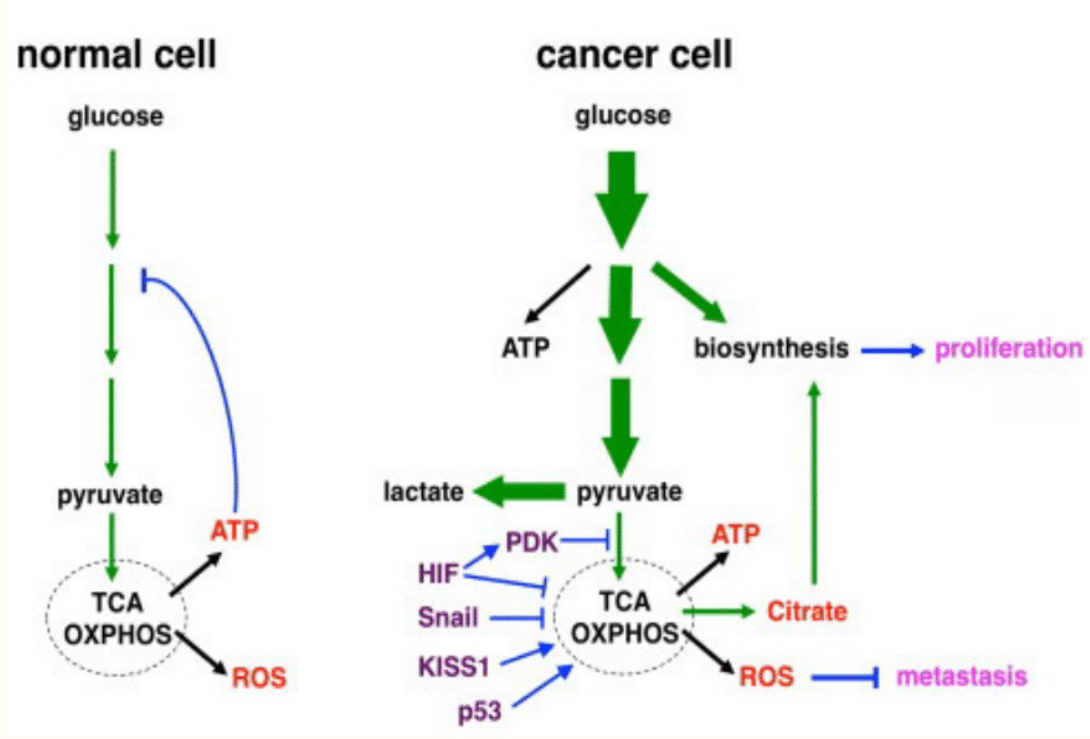

Figure 1: *The differences between cancer cells and normal cells as the explanation of the Warburg Effect (WE).*

Warburg Hypothesis of Cancer (WHC)

The Warburg Hypothesis of Cancer (WHC), explains that the real cause of tumorigenesis is an insufficient cellular respiration caused by insult to mitochondria [9]. Warburg Effect (WE) explains the observation that cancer cells, grown *in-vitro*, goes through the process of glucose fermentation even when enough oxygen is present for cell respiration. The Warburg Hypothesis of Cancer (WHC) shows that the Warburg Effect (WE) was the prime cause of cancer. The current popular opinion is that cancer cells ferment glucose and sugar molecules while keeping up the same level of respiration that was present before the process of carcinogenesis, and therefore, the Warburg effect would be defined as the observation that cancer cells exhibit glycolysis with lactic acid production and mitochondrial respiration even if the enough oxygen is present [10].

Warburg Hypothesis of Cancer (WHC) was discovered by the Nobel prize winner, Otto Heinrich Warburg in 1924 [11]. He hypothesized that cancer, malignant growth, and tumor growth are caused by the fact that tumor cells mainly generate energy as the form of adenosine triphosphate (ATP) by glycolysis. This is in contrast to normal cells, which produces energy from oxidative breakdown of pyruvate. Therefore, based on Warburg discovery, the cause of cancer cells should be interpreted as stemming from a lowering of mitochondrial respiration. Warburg reported a fundamental difference between normal and cancerous cells to be the ratio of glycolysis to respiration. This observation is also known as the Warburg Effect (WE). Cancer is caused by mutations and altered gene expression, in a process called malignant transformation, resulting in an uncontrolled growth of cells [12,13]. The metabolic differences observed by Warburg adapts cancer cells to the hypoxic conditions inside solid tumors, and results largely from the same mutations in oncogenes and tumor

suppressor genes that cause the other abnormal characteristics of cancer cells [14]. Hence, the metabolic change observed by Warburg is not so much the cause of cancer, as he claimed, but rather, it is one of the characteristic effects of cancer-causing mutations.

The prime cause of cancer is when the oxygen respiration changes in normal body cells by a fermentation of sugar [15].

Materials and Methods

We have done the treatment based on the special model of ketogenic diet and ozone therapy on the 54 cancer patients, including; Liver cancer, Colorectal cancer, kidney cancer, brain metastatic tumors, breast cancer, lung cancer.

This was a double blind controlled study which has done at the Violet Cancer Institute (VCI) in Iran/Tehran. 10 patients with the liver cancer, 5 patients with the kidney cancer, 11 with brain metastatic tumors, 18 patients with the breast cancer tumors, 5 patients with the lung cancer and 5 patients with colorectal cancer.

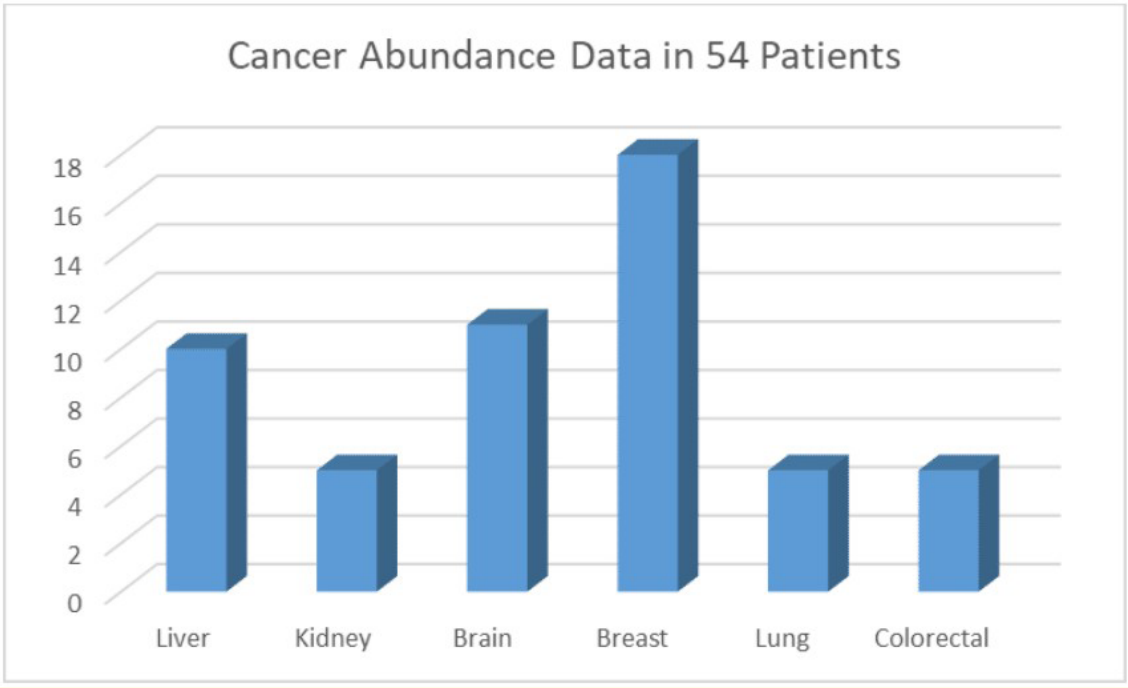

Table 1

The methodology of this study was based on 5 days of water fasting to make the normal cells go to the catabolism state, after 5 days we started the special Keto-Diet the 80 percent saturated fat including MCT and animal and coconut saturated fats. 15 percent protein powder with the lowest glutamine which we have produced at the Violet laboratory, and 5 percent complex carbohydrates with the highest fiber.

The Ozone therapy method was three days per week on each patient with 5% Ozone in 100 Mole Oxygen.

After 3 months of this study the average results of the reduction in cancer tumors by MRI device were:

1. 45 Percent decrease in tumor size in lung cancer tumors.
2. 25 percent decrease in tumor size in colorectal cancer tumors.
3. 75 percent decrease in tumor size in breast cancer tumors.
4. 62 percent decrease in tumor size in liver cancer tumors.
5. 54 percent decrease in tumor size in kidney cancer tumors.
6. 87 percent decrease in tumor size in brain cancer tumors.

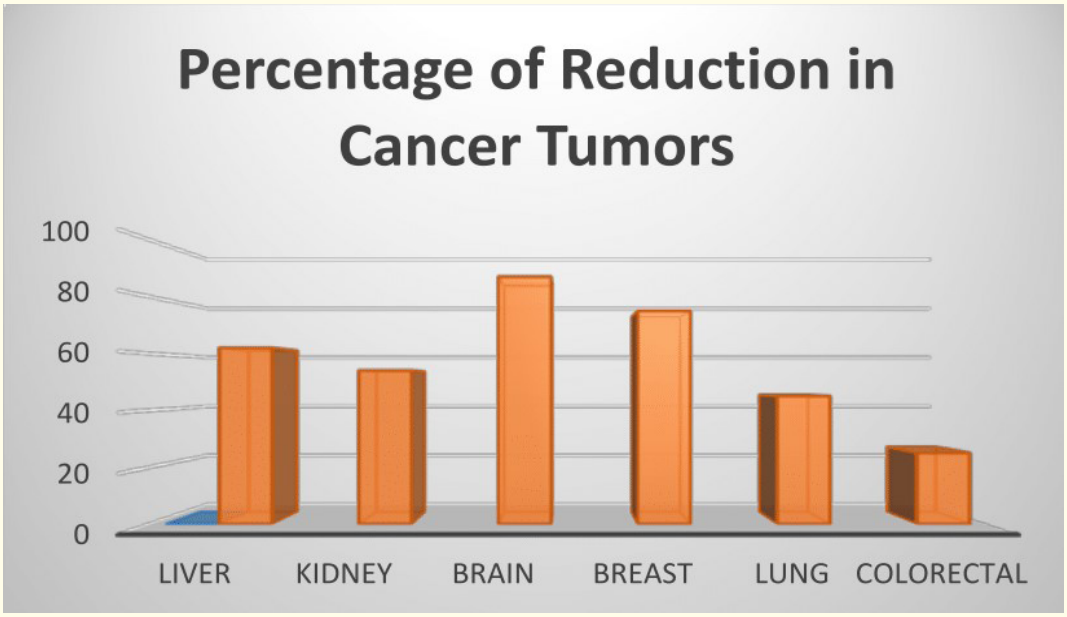

Table 2

Metabolic Mathematical Model as a Proof of EMHC Hypothesis

To properly understand or derive a mathematical model for cancer growth, we should understand the process of the ontogenetic development of an organism. This process is fueled by metabolism and follows a certain pattern which occurs primarily through cell division. mathematical model based on energy conservation was derived to model such growth and shows that regardless of the different masses and development times, all taxons share a common growth pattern [33]. It may be possible that cancer growth may be modeled in the same way. As the total energy that goes into the development of the organism either goes into the maintenance of existing tissue or the creation of new tissue, we can express this as

$$B = \sum_{C} \left[N_C B_C + E_c \frac{dN_C}{dt} \right]$$

B is the energy that an organism uses while at rest. The variables, Bc and Nc are the metabolic rate for an individual cell and the number of cells in a particular organism respectively; the NcBc term represents the energy to maintain existing tissue. Ecis the energy needed to create new tissue from an individual cell.

We assume that variables Ec, Bc and mc all remain constant during an organism's growth and is pertinent to a particular type of organism. Thus the total mass of an organism, m, can be determined from the mass of an individual cell and the number of cells, m = mcNc. By differentiating and substituting this into the equation, the result is:

$$\frac{dm}{dt} = B\left(\frac{m_c}{E_C}\right) - m\left(\frac{B_C}{E_C}\right)$$

Given that

$$B = B_0 m^{\frac{3}{4}}$$

where B0 depends on a particular taxon,

$$\frac{dm}{dt} = B_0 \frac{m_c}{E_c} m^{\frac{3}{4}} - \frac{B_c}{E_c} m$$

As the B0, mc and Ec terms are constant, we can express the above equation succinctly as

$$\frac{dm}{dt} = am^{\frac{3}{4}} - bm$$

where a ≡ B0mc/Ec and b ≡ Bc/Ec.

The 3/4 exponent is roughly the same for all organisms, whether they be mammals, birds, fish or plants. Thus the exponent describes the overall allometry of B from birth to maturity. As there is a tendency for natural selection to optimize energy transport, this has led to the evolution of a fractal-like distribution network. This exponent is related to the scaling in the total number, Nt of capillaries [33,34]. As we already know, the total number of cells is related to the organism's mass. This exponent has the profound implication in that it sets limits on the growth of an organism. Thus the point in which an organism stops growing, i.e. dm/dt = 0, we see that

$$M = \left(\frac{a}{b}\right)^4 = \left(\frac{B_0 m_c}{B_c}\right)^4$$

where M is the symptotic maximum body size. Thus the variation on M among different species within a taxon is determined entirely by the cellular metabolic rate, Bc, which scales to M-1/4. As cancer growth follows the same principles, blood and nutrients enter into and feed a tumor, we expect the same scaling principles to apply and thus by using this Universal Law for ontogenetic growth we hope to derive a similar universal law for cancer growth. As B0, mc and E_c are approximately constant, a is independent of M and b = a/M1/4. We can thus rewrite this equation as

$$\frac{dm}{dt} = am^{\frac{3}{4}}\left(1 - \left(\frac{m}{M}\right)^{\frac{1}{4}}\right)$$

by Solving this differential equation, the result is:

$$\left(\frac{m}{M}\right)^{\frac{1}{4}} = 1 - \left(1 - \left(\frac{m_0}{M}\right)^{\frac{1}{4}}\right) e^{\left(-at/4M^{\frac{1}{4}}\right)}$$

m0 is the mass of the organism at birth (t = 0). As a and b can be determined from fundamental parameters of a cell, a universal equation has been derived. We can see from the figures below that all growth curves follow the same path. We can infer that if similar considerations are made for cancerous cells, a similar growth curve will be obtained.

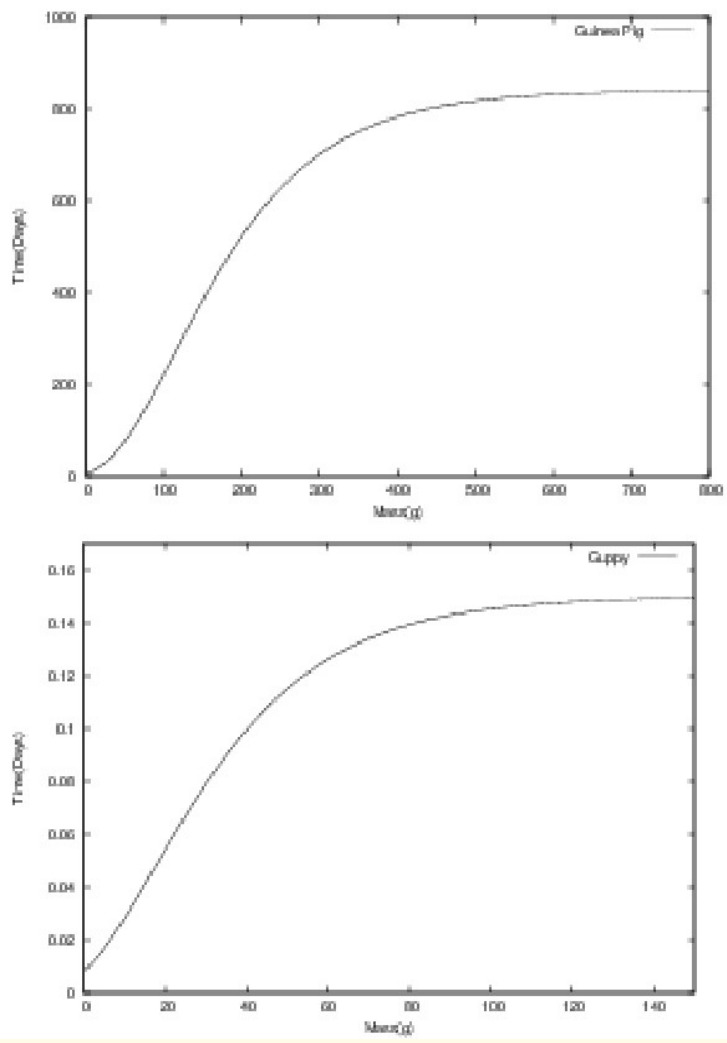

Figure 2

Results and Discussions

Introduction to the Evolutionary Metabolic Hypothesis of Cancer (EMHC)

The first living cells on Earth are thought to have arisen more than 3.5×10^9 years ago, when the Earth was not more than about 10^9 years old. The environment lacked oxygen but was presumably rich in geochemically produced organic molecules, and some of the earliest metabolic pathways for producing ATP may have resembled present-day forms of fermentation. In the process of fermentation, ATP is made by a phosphorylation event that harnesses the energy released when a hydrogen-rich organic molecule, such as glucose, is partly oxidized. The electrons lost from the oxidized organic molecules are transferred via NADH or NADPH to a different organic molecule or to a different part of the same molecule, which thereby becomes more reduced. At the end of the fermentation process, one or more of the organic molecules produced are excreted into the medium as metabolic waste products. Others, such as pyruvate, are retained by the cell for biosynthesis. The excreted end-products are different in different organisms, but they tend to be organic acids. Among the most important of such products in bacterial cells are lactic acid which also accumulates in anaerobic mammalian glycolysis, and formic, acetic, propionic, butyric, and succinic acids [29].

As we can see in the figure 3, the first cell on the earth before the entrance of the bacteria did contain nucleus and used the fermentation process to produce ATP for its energy. Then an aerobic proteo-bacterium enters the eukaryote either as a prey or a parasite and manages to avoid digestion. It then became an endosymbiont. As we observe, the fermentation process used the glucose or even glutamine to produce ATP, but the aerobic process used the glucose, fat and protein to produce more ATP than the previous one. The symbio-genesis of the mitochondria is based on the natural selection of Charles Darwin. Based on Otto Warburg Hypothesis and Seyfried Metabolic Hypothesis of cancer, in nearly all cancer cells, the mitochondrion are shut down or are defected and the cancer cell do not use its mitochondrion to produce ATP [9]. This process of adaptation is based on Lamarckian Hypothesis of Evolution and the normal cells goes back to the most primitive time of evolution to protect itself from apoptosis and uses the fermentation process like the first living cells 1.5 billion years ago. Therefore, cancer is an evolutionary metabolic disease which uses glucose as the main food to produce ATP and Lactic Acid.

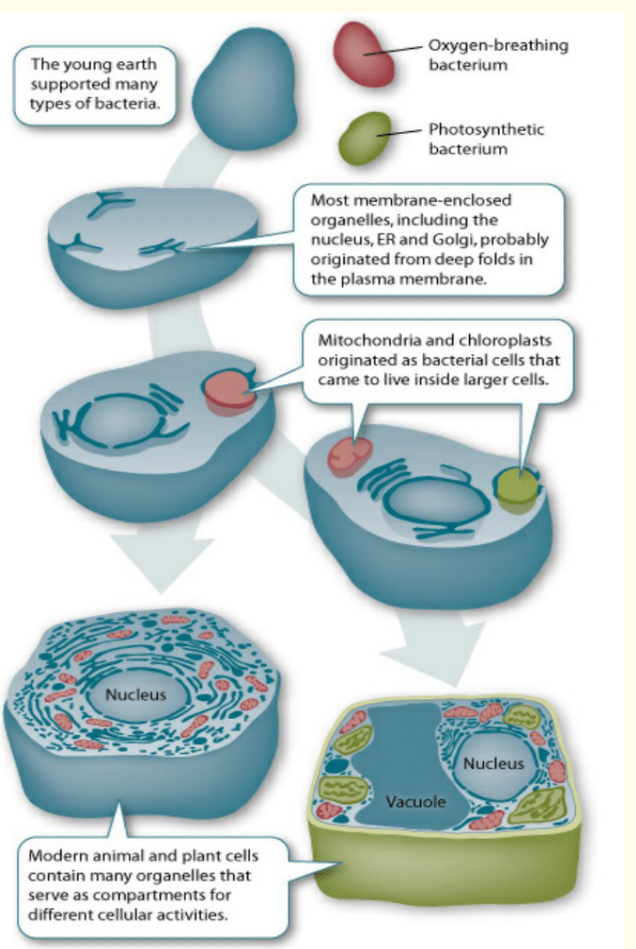

Figure 3: *Symbio-genesis of mitochondria [31].*

The prime cause of cancer is the abundance of Reactive Oxygen Species produced by mitochondria that is a threat to the living normal cell and causes mitochondrial damage mainly in its cristae [S. Niknamian., *et al*. 2016].

Research Studies as the Proof of Cancer as a Metabolic Disease

In a study by Michael Ristow and colleagues, colon cancer lines were modified to overexpress frataxin. The results of their research shows that an increase in oxidative metabolism induced by mitochondrial frataxin may inhibit cancer growth in mammals [16].

Studies published since 2005 have shown that the Warburg Effect (WE) may lead to a promising approach in the treatment of solid tumors. Alpha-cyano-4-hydroxycinnamic acid (ACCA, CHCA), a small-molecule inhibitor of mono-carboxylate transporters (MCTs) which prevent lactic acid build up in tumors, has been successfully used as a metabolic target in brain tumor pre-clinical research [17-20]. Higher affinity MCT inhibitors have been developed by Astra-Zeneca [21]. The chemical dichloro-acetic acid (DCA), which promotes respiration and the activity of mitochondria, has also been shown to kill cancer cells *in-vitro* and in some animals [22]. Our body, kills damaged cells by apoptosis most of the time, a process that involves mitochondria and is a self-destruction, Therefore, this mechanism fails in Malignant Cancer Cells (MCC) where the mitochondria are shut down or is damaged. The reactivation of mitochondria in cancer cells restarts their apoptosis program [23]. Besides human research at the University of Alberta led by Dr Evangelos Michelakis, other glycolytic inhibitors besides DCA that hold promise include Bromo-pyruvic acid, being studied at The University of Texas M. D. Anderson Cancer Center (ACC), 2-deoxyglucose (2-DG) at Emory University School of Medicine (EUSM), and lactate dehydrogenase A at Johns Hopkins University School of Medicine [24].

Cancer as a metabolic disease

Impaired cellular metabolism of energy is the characteristic of nearly all cancers regardless of cellular or tissue origin. Normal cells derive most of their energy from oxidative phosphorylation, Therefore, most cancer cells become dependent on substrate level phosphorylation to meet their energy needs. Many evidences are reviewed in the support of a general hypothesis that genomic instability and essentially all hallmarks of cancer, including aerobic glycolysis which is called Warburg Effect (WE), can be linked to impaired mitochondrial function and energy metabolism [25].

Oncogenic Paradox

High variety of things from viruses, bacteria to radiation, chemicals and oxidation can damage DNA and cause mutations [One Renegade Cell: How Cancer Begins, Robert A. Weinberg]. There are hundreds of thousands of significant mutations are associated with tumors. One single colon cancer cell can contain 11,000 mutations [26]. The number and type of mutations found in cancer cells are so serious that they would cause a healthy embryo to spontaneously abort. The transformation of a healthy cell into a cancerous cell malignant transformation happens in the very same special way every time. There is not one example of a mutation that causes the same type of cancer. Even those mutations most strongly associated with certain cancers only cause cancer in certain humans. Cancer cells within the same tumor can have different mutation patterns. Mutated genes thought to be strongly associated with cancer oncogenes, sometimes do promote tumor growth, but sometimes they inhibit tumor growth, and sometimes they do both. If one transplants mutated cancer cell DNA into a healthy cell, the healthy cell almost never becomes cancerous. Only 2 out of 24 experiments were successful in transforming normal cells into cancer cells. This result is against the mutation theory of cancer, which explains why mutation theory of cancer is not right [27,28].

Damaged Mitochondria and Cancer

Billions of years ago, before plants took hold on the planet, earth's atmosphere had very little oxygen and living creatures used fermentation to generate energy. Organisms were very simple, without sophisticated controls to help them decide when to reproduce. They just reproduced as fast as they possibly could [25]. Mitochondria appeared about 1.5 billion years ago, about a billion years after oxygen

became available, and probably already had the ability to switch back and forth between fermentation and respiration, depending on how much oxygen was around. Many cells will simply extinct if their mitochondria are damaged, but if the damage is not too sudden or severe, some cells will be able to adapt and survive by switching back to fermentation to make energy [26]. Mitochondrial damage unlocks an ancient toolkit of pre-existing adaptations that allow cells to survive in low-oxygen environments. Mitochondria are so good at producing energy that their arrival on the evolutionary scene is thought to be largely responsible for the increase in complexity of living things. Building and supporting elaborate new creatures with specialized organs and capabilities takes a lot of energy. If an organism does not constantly pour energy into a living thing to maintain its form and function, it will gradually succumb to entropy or chaos. For cells, this means regressing which means DNA becomes unstable [27]. Cells lose their unique shapes, become disorganized and start reproducing uncontrollably. Any number of environmental hazards can damage mitochondria. These are the same kinds of things thought typically as damaging DNA and causing cancer. However, the previous lines in this research article proposed that damaged DNA is not the primary cause of cancer. It is the mitochondria that are responsible. Mitochondria take care of cells and DNA. Mitochondrial damage happens first, and then genetic instability follows. Even though there is plenty of oxygen around, damaged mitochondria have no choice but to resort to fermentation, which is primitive and wasteful. Cells cannot stay in shape and under control under these circumstances. They may be able to live, but it will not be normal. Cells with damaged mitochondria, only if they survive, are at high risk for becoming cancerous [28].

Cancer and Sugar

Nearly all tumors depend heavily on glucose for survival, which is how PET scans are able to find many tumors hiding in normal tissues. PET scans follow radioactive glucose as it travels through the bloodstream. Radio-labeled glucose accumulates in tumor tissue more than in the normal tissues surrounding it, and lights up on the scan. There is a strong connection between high blood sugar or hyperglycemia, diabetes, and cancer. It is well-documented that the growth of brain tumors is more accelerated and prognosis is worse in animals and humans with higher blood glucose levels [29]. Hyperglycemia is directly linked with poor prognosis in humans with malignant brain cancer and is connected to the rapid growth of most malignant cancers. High blood glucose raises insulin levels, which stimulates cancer cells to take in and use more glucose [30]. This makes it easier for cancer cells to nourish themselves. Insulin also turns up the activity of the fermentation pathway, and fermentation leads to additional cellular damage. High blood glucose also raises levels of another circulating hormone called IGF-I or Insulin-like Growth Factor I. Cancer cells with receptors on their surfaces for this hormone grow more rapidly. IGF-I turns on a chemical pathway that drives tumor cell growth. Which is the PI3K-Akt-HIF-1 alpha pathway. This pathway sets the stage for cells to multiply, escape apoptosis, and recruit their own angiogenesis. Angiogenesis is required for tumors to grow beyond 2 millimeters in size. The genes for this growth pathway are also turned up by the fermentation process. More glucose means more fermentation and more insulin and more IGF-I mean more tumor growth. Briefly, cancer is a disease of growth, and insulin is the mother of all growth hormones [9].

Regardless of which type of cancer one may have, what grade or stage it might be, or which mutations or genetic markers it might have, the hallmark of all cancer cells is damaged mitochondria. Cancer is not a collection of unrelated diseases that each need to be treated individually, cancer is one disease which is a mitochondrial disease, and diseased mitochondria prefer glucose and glutamine for fuel. Healthy cells with healthy mitochondria are flexible and can adapt to just about any fuel source, but not cancer cells. In fact, the majority of cells function best when they burn fat for energy. Cancer cells are bad at burning fat, because fat burning requires respiration, which requires healthy mitochondria [31].

Cancer Treatment Based on Evolutionary Metabolic Hypothesis of Cancer

If food is restricted enough to lower blood glucose, then insulin and IGF-1 levels will also be lower, quieting the tumor driving genes and pathways which is described in previous lines. This means that fermentation becomes harder for tumors to recruit new blood vessels, and tumor growth slows. Under low blood glucose levels, glucagon comes in. this is the opposite of insulin hormone. Glucagon stimulates fat burning, which raises ketones and fatty acids in the blood. Ketones and fatty acids are just breakdown products of fats [32].

Ketone bodies and fatty acids cannot be fermented, thus, cancer cells cannot utilize them for fuel. Glucose restriction stresses cancer cells. However, most healthy cells prefer to use fatty acids and ketones for energy. Glucose restriction is good for healthy cells. Glucagon also keeps blood sugar from dropping too low by turning on a process in the liver called gluconeogenesis. This is why humans never need to eat any carbohydrates. Humans are always able to make all the glucose they need out of proteins and fats [33]. The brain cannot burn fatty acids but it can burn ketones, and under low glucose conditions, the brain gradually shifts from burning mostly glucose to burning mostly ketones. The brain may still require a small percentage of glucose to function at its best, but there is always enough glucose in the bloodstream because of glucagon, and most other organs will pass up glucose under these conditions in order to let the brain have first dibs. Cancer cells and healthy cells both have a molecule on their surfaces called GLUT-1 [34]. This glucose transporter ushers glucose out of the bloodstream and into cells. Under low glucose conditions, healthy cells will create more of these transporters and display them on their surfaces so as to optimize their ability to obtain glucose. Cancer cells, which are damaged, and therefore less flexible and adaptable, are not able to do this. In fact, when glucose levels are low, cancer cells are even weaker than usual. Not only can they not raise their GLUT-1 levels, their GLUT-1 levels actually drop. This is one more way that glucose restriction impairs cancer cells. Even though there is always some glucose in the bloodstream because of gluconeogenesis, cancer cells are less able to access it than healthy cells because they are damaged [35].

When ketones are burned for energy instead of glucose, fewer reactive oxygen species (ROS) are generated. These are free radicals that cause oxidative damage. This means that shifting the body from being a carbohydrate-burning machine to becoming a fat-burning machine reduces oxidative damage, and therefore potentially reduces risk for numerous chronic diseases. Diets that raise blood levels of ketones are considered to be neuroprotective. That is they protect brain cells from harm. Glucose burning is neurotoxic and burning ketones instead simply restores the natural, healthy level of disease resistance humans inherited from their ancestors. One reason why ketogenic diet is under consideration for the treatment of so many neurological diseases, from autism to Alzheimer's to multiple sclerosis and epilepsy to Parkinson's Disease, is that the transition from glucose burning to ketone burning is powerfully anti-inflammatory. There is no drug therapy can target as many pro-inflammatory mechanisms in the microenvironment as can dietary energy restriction. Real progress in tumor management will be achieved once patients and the oncology community come to recognize this fact. In fact, it is inflammation which damages mitochondria and respiration, and thus, inflammation may be the true cause of cancer [36-46].

Conclusion

Evolutionary Metabolic Hypothesis of Cancer (EMHC) explains the process of changing the normal cells into cancer cells as an evolutionary aspect. As this article explains, increasing the amount of Reactive Oxygen Species (ROS) results in the damage of mitochondria inside the normal cell which uses the oxidative phosphorylation to produce ATP and shutting down or damages in the mitochondria will result in the change of metabolic process of the normal cell to produce its energy from fermentation process in the cytosol. 1.5 billion years ago these process were the normal respiration of the cells, which did contain the nucleus, before the entrance of the mitochondria as an endosymbiont. Therefore, cancer cells are the eukaryotes in the primitive life were the oxygen have not been present. The special Keto-Diet plus Ozone therapy can be a methodology of treatment of cancer tumors and could be a basic treatment in less time in most cancer patients.

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Conflict of Interests

There is no conflict of interests between the authors of this article.

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