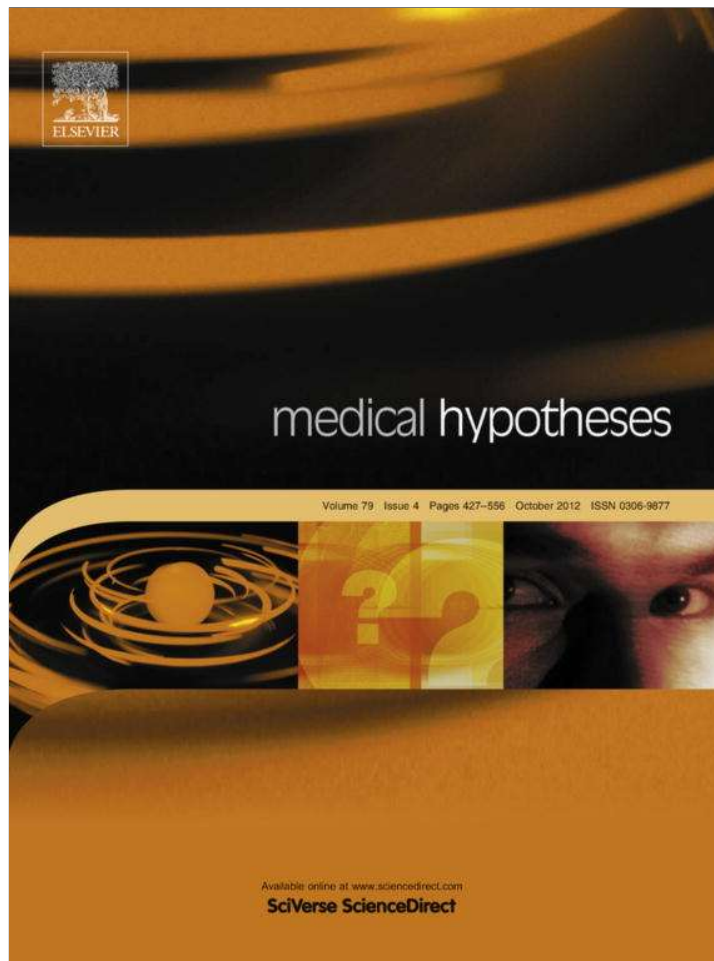


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# Medical Hypotheses

journal homepage: [www.elsevier.com/locate/mehy](http://www.elsevier.com/locate/mehy)

## The bio-energetic theory of carcinogenesis

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### ARTICLE INFO

#### Article history:

Received 1 February 2012

Accepted 22 June 2012

This paper is dedicated to the memory of our dear friend, colleague and mentor, Dr. Hugh D. Riordan

### ABSTRACT

The altered energy metabolism of tumor cells provides a viable target for a non toxic chemotherapeutic approach. An increased glucose consumption rate has been observed in malignant cells. Warburg (Nobel Laureate in medicine) postulated that the respiratory process of malignant cells was impaired and that the transformation of a normal cell to malignant was due to defects in the aerobic respiratory pathways. Szent-Györgyi (Nobel Laureate in medicine) also viewed cancer as originating from insufficient availability of oxygen. Oxygen by itself has an inhibitory action on malignant cell proliferation by interfering with anaerobic respiration (fermentation and lactic acid production). Interestingly, during cell differentiation (where cell energy level is high) there is an increased cellular production of oxidants that appear to provide one type of physiological stimulation for changes in gene expression that may lead to a terminal differentiated state. The failure to maintain high ATP production (high cell energy levels) may be a consequence of inactivation of key enzymes, especially those related to the Krebs cycle and the electron transport system. A distorted mitochondrial function (transmembrane potential) may result. This aspect could be suggestive of an important mitochondrial involvement in the carcinogenic process in addition to presenting it as a possible therapeutic target for cancer. Intermediate metabolic correction of the mitochondria is postulated as a possible non-toxic therapeutic approach for cancer.

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### Introduction

Most primitive life forms derive their energy from fermentation. Fermentation is the anaerobic metabolic breakdown of glucose without net oxidation. Fermentation does not release all the available energy of glucose; it merely allows glycolysis (a process that yields two ATP per mole of glucose) to continue by replenishing reduced coenzymes. Fermentation yields lactate as its final product. Glycolysis does not need oxygen as part of its biochemical reactions to proceed. Glycolysis serves as a first step in a variety of both aerobic and anaerobic energy producing pathways. It occurs in the cytoplasm of cells, not in specialized organelles. Glycolysis is the metabolic pathway found in all living organisms and the most primitive one.

There is a predominance of glycolysis and the Cori cycle in cancer cells [1–3]. Warburg first discovered that cancer cells have a fundamentally different energy metabolism compared to normal cells [1]. Normal cells are obligate aerobes (oxygen-requiring cells)

and they usually meet their higher energy needs with oxygen requiring metabolic processes. All cancer cells are partial anaerobes (not requiring oxygen for their survival) and most of their energy needs can be met by fermentation. Although cancer may have an array of probable causes, one of these may be the replacement of respiratory oxygen processes by the non oxygen utilizing process of fermentation. This fermentation of sugar provides the proper environment for carcinogenesis. This increase in glycolytic flux is a metabolic strategy of tumor cells to ensure growth and survival in environments with low oxygen concentrations [3]. This glycolytic shift of energy explains why Positron Emission Tomography (PET Scan) can be successfully utilized to label malignant and fast growing tumors and metastases, since it utilizes labeled glucose as a marker for malignant tissue.

### Discussion

Increased anaerobic glucose fermentation to lactate in the presence of oxygen (aerobic glycolysis) and mitochondria independent ATP generation is a hallmark of aggressive cancer growth [3,4]. This metabolic shift results in increased lactate production via cycling through the pentose phosphate pathway (PPP) and may play an important role in tumor progression and resistance to immune attack, radiation and chemotherapy. The large amount of

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lactic acid produced by the fermentation of glucose from cancer cells is then transported to the liver. This conversion of glucose to lactate generates a lower, more acidic pH in cancerous tissues as well as overall lactic acid build-up [4]. Thus, larger tumors tend to exhibit a more acidic pH.

Glycolysis is an inefficient pathway for energy metabolism that yields only 2 mol of adenosine triphosphate (ATP) energy per mole of glucose, compared to 38 mol of ATP in the complete aerobic oxidation of glucose (oxidative phosphorylation). By extracting only about 5% (2 vs. 38 mol of ATP) of the available energy, cancer metabolism wastes energy and the patient becomes tired and undernourished. This vicious cycle increases body wasting. It is one reason why 40% of cancer patients die from malnutrition and/or cachexia.

Szent-Györgyi theorized that the cancerous condition is a reversal to a more primitive state of the cell. This phenomenon occurs because the oxidative electron flow breaks down and therefore not enough energy is available for the cell to maintain complicated structures and processes that keep cell division under control [5]. Cell division involves a complete rearrangement of the cellular interior, which is possible only in a semi-liquid state. So when dividing, the cell has to de-differentiate, dismantle part of its oxidative machinery, dissolve its nucleus, disintegrate its chromatin and rely more on fermentation during this time. These changes all mean a shift toward the earlier, more primitive, undifferentiated, anaerobic, proliferative state [5].

Cancer is a destructive condition incited and perpetuated by many factors which include mitochondrial dysfunction and anomalous oxygen signaling. It has seven principal characteristics: (1) respiratory to fermentative shift in ATP (energy) production (*anaerobic metabolism*); (2) production of large quantities of lactic acid (*low, acidic pH*); (3) formation of coagulated proteins around malignant cells that exclude the host immune cells and other immune defense molecules (*decrease immune reactivity*); (4) uncontrolled cellular replication (*increase in growth fraction*); (5) loss of cell to cell communication (*disruption of local tissue communication and architecture*); (6) colonization of distant tissues (*metastasis*); and (7) mitochondrial dysfunction (*changes in mitochondrial membrane potential and lower energy availability*). These characteristics were adapted from those presented previously by Kremer [6].

## Differentiation and cancer

As explained by Szent-Györgyi, the living state is an electronically desaturated state of molecules. The degree of development and differentiation of cells is a function of the degree of electronic desaturation. Electronic desaturation is an on-going redox state that favors electronic movement by means of resonance and temporary bond formation. It is the essence of life (electronic movement). Differentiation implies that a cell acquires certain structural and functional characteristics that enable it with the capacity to undertake a specialized task [7].

Differentiation is the process by which an immature cell becomes a more specialized cell type. It takes place in a developing embryo during pregnancy by which primitive, unspecialized embryo cells, as they multiply, change in form to the different specialized cells required to form the different organs of the body. At conception, when the egg and sperm unite to form one cell (zygote) which then subdivides and multiplies, the new cells, called embryonic cells, are all the same: they are primitive in form, largely anaerobic and multiply rapidly without constraint. Embryonic cells utilize the sugar of the ova as its main source of energy.

When the embryo attaches to the mother's circulatory system and begins to receive nourishment and oxygen from the mother's blood, the embryonic cells change and become fully aerobic,

(dependent on oxygen). As the embryo continues to grow, the embryonic cells change in form: they become different from each other in order to construct the different organs of the new body, so that they are identifiable as bone cells, muscle cells, skin cells and so on. They are differentiated as soon as the mitochondrion turns on and matures [8].

To understand cancer, a point to remember is that embryo cells are initially primitive, undifferentiated, and largely anaerobic and multiply rapidly without constraint [9], whereas fully differentiated, specialized cells in normal tissues are aerobic and their subdivision and growth is strictly constrained. In cytopathology the level (grade) of cellular differentiation is used as a measure of cancer progression. Grade is a marker of how differentiated a cell in a tumor is. Sequential stages of differentiation coincide with marked changes in metabolic and mitochondrial activity [10].

When bacteria, which are single primitive cell organisms are deprived of oxygen they are capable of survival by reverting to the process of fermentation in order to produce the energy they need. This process (glycolysis), used by primitive cells billions of years ago before oxygen became freely available in the sea and air; is still part of the aerobic respiratory process employed by oxygen utilizing cells of living organisms today.

Oxygen using (aerobic) cells still retain glycolysis in the initial stages of their respiratory cycle but are much more efficient because they are capable of taking the pyruvic acid resultant from glycolysis and combining it to the aerobic counterparts; the Krebs's cycle and the electron transport system. As a result of this metabolic deficiency, the cancer cells must take in large amounts of glucose for energy.

## Energy, cell membrane and cancer

Energy exchange is probably the most important form of cellular communication. It can only occur when an imbalance of electrons exists. This imbalance of electrons is the natural flow of biological energy that sustains life. Cell membranes are composed of a bilayer of highly mobile lipid molecules that electrically act as an insulator (dielectric). The insulating properties of the cell membrane lipids also act to restrict the movement of charged ions and electrons across the membrane, thus having an important role in cell communication.

All cells have an imbalance in electrical charges between the inside of the cell and the outside of the cell. This difference is known as the membrane potential. The membrane potential is created by the difference in the concentration of ions inside and outside the cell that creates an electrochemical force across the cell membrane. The cell membrane potential helps control cell membrane permeability. One common characteristic feature of both proliferating cells and cancer cells is that these cells have cell membrane potentials that are lower than the cell membrane potential of healthy differentiated adult cells and electrical connections are disrupted [11]. When the membrane potential drops, it leads to cell division and eventually causes cells to overpopulate. As electrons flow down the electron transport system, a very negative potential, is created. In fact, mitochondria are the most negatively charged organelles in the cell. The stored energy is used to synthesize ATP [12].

In coupled mitochondria, in the presence of excess calories and low cytoplasmic ADP, the very negative potential prevents further  $H^+$  pumping and the electron transport system is stalled. As electrons keep coming in, they cannot be oxidized and interact with molecular  $O_2$ , increasing reactive oxygen species production. In contrast, decreased calories and high levels of ADP result in  $H^+$  return into the matrix, decreasing the reactive oxygen species production. This might in part explain the fact that low calorie intake



and exercise have been associated with longevity and less cancer or cardiovascular disease [12].

When the electron donors of the respiratory chain NADH and FADH<sub>2</sub> release their electrons, hydrogen ions are also released. These positively charged hydrogen ions are pumped out of the mitochondrial matrix across the inner mitochondrial membrane creating an electrochemical gradient. At the last stage of the respiratory chain these hydrogen ions are allowed to flow back across the inner mitochondrial membrane and they drive a molecular motor called ATP synthase in the creation of ATP [13]. This normal energy production process utilizing electron transport and hydrogen ion gradients across the mitochondrial membrane is disrupted when cells become cancerous. Nevertheless, our current understanding of how cells produce the energy molecule ATP may be fundamentally flawed, and that may be the main reason why our efforts to find a cure for cancer have failed. We should point out that very high doses of ascorbic acid may produce an ergogenic effect by increasing electron movement in the mitochondria [14,15].

ATP production, according to Kremer [6], is not based on chemical energy release, but on the absorption of photons of light from the zero-point quantum medium. As explained by Kremer [6], all essential components of mitochondrial cell respiration are light absorbing molecules with characteristic frequency windows of absorption maxima from nearly UV spectrum to the longer wave yellow/orange spectral range of visible light. The currently accepted view is that energy production and storage in ATP is by means of chemical energy, stored in the phosphate bonds. The energy bond is then released by hydrolysis in the cytoplasm, where it is used to drive energetic and metabolic processes. Although hydrolysis only yields heat energy, which is not sufficient to drive all the various cell processes. The secret lies in the adenine groups of ATP which may absorb photons [6].

The essential components of mitochondrial cell respiration might as well be light absorbing molecules that react to frequencies from the near ultraviolet band down to the yellow/orange spectral range of visible light. Consequently, the human organism may not be governed by heat transfer but by a light frequency modulated energy transformation [6].

In oncogenesis, there is a functional disturbance in the enzyme complexes of the respiratory chain. These enzymes use O<sub>2</sub> as cofactor for the production of carbon monoxide (CO). In cases of long-term surplus production CO may have a crucial effect on cancer cell transformation. CO may activate a regulator protein for the stimulation of the cell division cycle without external growth signals. CO produces via enzymatic overactivation of the important secondary messenger cGMP that may inhibit or block the communication between neighboring cells. CO blocks programmed cell death by bonding onto the bivalent iron in important key enzymes [6].

Cancer is in part a result of the disturbance of the enzyme mediated transformation of that energy. The affected cells lose their ability to communicate with other cells around them and they change not only their way of making energy but they become, for all practical purposes, separate unicellular entities that must divide and form a colonies to survive. That colony is what we then see as the tumor, the visible manifestation of cancer. In other words, cancer is a cell survival mechanism to a hostile environment.

Cancer is a general phenomenon found in the entire spectrum of higher living organisms. The fact that carcinogenesis relates to particular energy changes in the cell suggests that energy resource changes may be the main carcinogenic mechanism. This hypothesis offers a new explanation and suggests new methods for the prevention and cure of cancer based on energy principles. Cancer cells are characterized as cells with low internal energy.

When a cell becomes cancerous, the following characteristics related to the internal energy of the cell are expressed:

- (1) The number of mitochondria is diminished, thus reducing the activity and energy level of the cell [16].
- (2) The ATP-producing function of oxidation–phosphorylation is diminished causing further reduction in available energy [16].
- (3) Anaerobic metabolism (glycolysis) increases, producing a smaller number of ATP molecules, resulting in limited energy production and reduced thermal energy [16].
- (4) The internal level of Na<sup>+</sup> ions is increased relative to the K<sup>+</sup> ions [17]. High internal Na<sup>+</sup> concentrations relative to external K<sup>+</sup> concentration impairs the efficiency of the Na/K pump that exchanges three internal Na<sup>+</sup> ions with two external K<sup>+</sup> ions [17], affecting cellular communication and cell membrane dynamics.
- (5) Na<sup>+</sup> has a large tendency for hydration; one Na<sup>+</sup> ion can bind at least one H<sub>2</sub>O molecule and water displaces internal thermal energy to the outside [17].

Although all five of these processes may be interrelated, they have in common the effect of reducing the internal energy resources of the transforming cell. This is manifested by; high internal Na<sup>+</sup> concentration causes a change in membrane potential from a normal healthy cell potential on the order of –50 to –70 mV to a typical cancer cell potential on the order of –15 mV [18].

A cell with such low membrane potential might be compared to a dying battery; the energy level of such a typical cancer cell is <5% of that of a normal, healthy cell [19,20]. Membrane potential (MP) or Transmembrane potential (TMP) is defined as the electrical potential between the negative interior of the cell membrane and the plasma environment (due to the presence of negative ions), with respect to the less negative or more positive potential of the exterior of the cell membrane and its tangential environment due to the presence of positive ions.

It has been reported that human cancer cell lines have a lower membrane potential compared to several non-cancerous cell lines, suggesting that this might be a hallmark of malignancy [11]. Since a significant proportion of cell energy production (70% or more) is channeled towards maintaining electrical integrity by supporting the ion pumps at the cell membrane, it becomes clear that this abnormal membrane potential of cancer cells is likely to be secondary to the cell being metabolically compromised.

Premature depolarization and mitosis leading to carcinogenesis may result from either a sustained increase in the intracellular concentration of Na<sup>+</sup> ions, or a surplus of negative ions. In the latter case, a secondary effect may be possible: since these charges would form a negative field or sheath around the cell, this would tend to repel negatively charged cells such as erythrocytes and lymphocytes, preventing oxygen and the immune system from destroying the tumor cells [6].

The transformed cancer cells remain trapped, dependent on the degree of malignancy, in a continuous cell division cycle and cannot switch back to the differentiated cell status due to its abnormal energy state. The cell symbiosis concept of Kremer postulates that when the cofactor O<sub>2</sub> is deficient then the even more effective mitochondrial inhibitor, cyanide gas (CN) is formed instead of CO [6]. CN is the strongest mitochondrial respiratory poison. This hypothesis can support the evolutionary-biological views of the cell symbiosis concept as cancer cells regress de facto to unicellular organisms (as a result of the loss of energy and cell to cell communication). Cancer cells represent in this sense a regression to the early eukaryotic stage of a single cellular protista colony and uses this change as a strategy for survival [6].

In general, healthy cells maintain, inside of themselves, a high concentration of potassium and a low concentration of sodium. Cancer cells exhibit both lower electrical membrane potentials and lower electrical impedance than normal cells [11]. The electri-

cal field across the membrane of a cancer cell will be reduced. The reduction in membrane electrical field strength will in turn cause alterations in the metabolic functions of the cell. Because cancerous cells demonstrate greater permittivity, which is the ability to resist the formation of an electrical field, they should resonate differently from normal cells. The ability to control cell functions by modulating bioelectric properties such as membrane potential would be an invaluable therapeutic tool.

### Mitochondria and cancer

Mitochondrial activities on cellular physiology are not restricted to ATP production. Mitochondria also produce reactive oxygen species (ROS) which are involved in the regulation of an array of physiological processes but which may be harmful to the cell if produced excessively. Mitochondria are also involved in the regulation of intracellular calcium homeostasis and in the regulation of cell death pathways [21]. Mitochondria may have a role in differentiation [15]. Mitochondria have been connected with cancer since the 1930s, when first noticed that these organelles dysfunction when cancer is present [22]. The destruction of the respiratory enzyme, cytochrome oxidase has also been implicated in carcinogenesis [23–25].

The mitochondria of rapidly growing tumors tend to be fewer in number, smaller and have fewer cristae than mitochondria from slowly growing tumors; the latter are larger and have characteristics more closely resembling those of normal cells [26]. A dysfunctional mitochondria in Cancer has also been proposed by John [26].

According to the prevailing cancer theories, mutations in the DNA in the nucleus of the cell, which are regarded as irreparable, are considered to be the primary cause of the disease. Standard therapy in oncology (surgery, chemotherapy and/or radiation therapy) is based on this assumption.

To understand the new concept of oncogenesis or carcinogenesis, we must take a look at the evolution of cells and organisms. Cells as present in today's organisms are the result of a fusion, in prehistoric times, of two different types of unicellular life forms into a unique symbiotic combination. A type of cell of the archaea family and another type of the bacteria family entered into symbiosis and formed what is now known as a protist. This is known as endosymbiosis. The cells of mammals including humans today contain genes from both original families. The bacterial symbionts have evolved together with the mitochondria which take care of energy production [6].

Under certain conditions where the cell cannot use oxygen properly, the mitochondria can dissolve their symbiosis with the cell host, and no longer function in harmony with the cell. This is called mitochondrial dysbiosis, and is a serious indicator for risk of cancer, as the cells revert to ancient survival mechanisms in which they use fermentation to make ATP, rather than oxidative phosphorylation [5]. In general, human cancers have a disturbed mitochondrial membrane potential, contributing to apoptosis resistance.

### The biochemistry of cancer

This loss of respiration leads to the accumulation of reduced nicotinamide adenine dinucleotide (NADH), oxaloacetic acid, succinyl-CoA, and citrate. The accumulation of NADH and succinyl-CoA will inhibit Krebs' cycle rate limiting enzymes, pyruvate dehydrogenase, citrate synthase and isocitrate dehydrogenase. This will limit the conversion of pyruvate to acetyl-CoA therefore limiting the Krebs' cycle. The failure to maintain high ATP production may be the direct consequence of the inactivation of these key enzymes.

Cancer cells have little or no superoxide dismutase (SD) in their mitochondria [27]. Without adequate protection from SD, superoxide, a normal, toxic free-radical by-product of the Krebs cycle of metabolism, would injure the genes or proteins in the mitochondria. This would impair the function of the Krebs cycle and prevent the entry of pyruvic acid into the mitochondria. Consequently, pyruvic acid must be converted into lactic acid instead of its normal breakdown into carbon dioxide and water.

Several of the enzymes involved in glycolysis are also important regulators of apoptosis and gene transcription, suggesting that links between metabolic sensors, cell death and gene transcription are established directly through the enzymes that control metabolism [28]. For example, hexokinase activation leads to a significant suppression of apoptosis; activated hexokinase translocates from the cytoplasm to the mitochondrial membranes where it interacts with and suppresses several key components of mitochondria-dependent apoptosis [29]. It is therefore not surprising that hexokinase is upregulated and activated in many cancers.

### Mitochondrial reactivation or intermediate metabolic correction

A relatively simple way to help re-activate the mitochondria and make them re-start normal energy production may be by using dichloroacetate or DCA. DCA, is a chemical compound with formula  $\text{CHCl}_2\text{COOH}$ . It is an acid, an analog of acetic acid in which two of the three hydrogen atoms of the methyl group have been replaced by chlorine atoms. Salts of DCA are used as drugs since they inhibit the enzyme pyruvate dehydrogenase kinase (PDK). PDK is a kinase enzyme which acts to inactivate the enzyme pyruvate dehydrogenase by phosphorylating it by using ATP. PDK participates in the regulation of the pyruvate dehydrogenase complex. Both PDK and the pyruvate dehydrogenase complex are located in the mitochondrial matrix of eukaryotes. The complex acts to convert pyruvate to acetyl-coA, which is then oxidized in the mitochondria to produce energy in the Krebs cycle. By downregulating the activity of this complex, PDK will decrease the oxidation of pyruvate in mitochondria and increase the conversion of pyruvate to lactate in the cytosol. So DCA by inhibiting PDK, will decrease the conversion of pyruvate to lactate [30]. It increases the flux of pyruvate into the mitochondria, promoting respiration over glycolysis. This may also reverse the suppressed mitochondrial apoptosis in cancer cells.

Dichloroacetate (DCA) can produce regression in several cancers, including lung, breast, and brain tumors [30]. Cancer mitochondria are hyperpolarized and have suppressed oxidative metabolism, both of which are reversed by DCA [30]. DCA causes efflux of pro-apoptotic factors from mitochondria and increases ROS production [30]. DCA activates electric channels in cancer cells by an  $\text{H}_2\text{O}_2$ -dependent mechanism [30]. DCA in the drinking water induces apoptosis and decreases tumor growth in vivo [30]. DCA has been used for decades to treat children with inborn errors of metabolism due to mitochondrial diseases. Dichloroacetate decreases lactate production by shifting the metabolism of pyruvate from glycolysis towards oxidation in the mitochondria. That is the main reason this substance has been used to treat lactic acidosis. The addition of coenzyme Q10, acetyl-L-carnitine, B-complex vitamins, magnesium and lipoic acid may further enhance this energy or metabolic correction action.

Moreover, this energetic derangement present in cancer cells, prevents the production of oxidation products in the mitochondria by oxidative respiration that normally leak out toward the cytosol and reach the nucleus. These oxidation products may influence gene expression in a way that promotes or favors differentiation [15]. In reference to differentiation, it should be pointed out that iron is imbedded in the center of the DNA double helix at certain

loci where it seems to function as an oxygen sensor to activate DNA in response to oxidative stress [31]. Because iron is a big molecule, it distorts the outer shape of the DNA helix. This distortion depends on the oxidation state of iron. Under non-oxidized (reduced) conditions, the iron is present in the ferrous state and the DNA helix is fairly tight around the iron atom. But when the iron is oxidized to the ferric state, it opens up the DNA so that it is more easily expressed so transcription into RNA and then into proteins can be accomplished. Most likely the proteins expressed are enzymes like SOD, catalase, glutathione peroxidase, heat shock proteins, plus other proteins that help mobilize and regulate the antioxidant defense system.

The ability of DNA to sense free radicals and oxidizing conditions in this way is an essential aspect of our capability to maintain homeostasis and adapt to stress. This temporary damage to DNA is a necessary bad and a small price to pay in order to be able to have an enhanced capacity for adaptability and increased survival. Moreover, it might be a mechanism of gene expression control of cell processes including cell division. It seems that in its activated state, the ferrous iron–DNA complex can react with vitamin C, dehydroascorbic acid, oxygen and/or hydrogen peroxide to produce reactive oxygen species (probably the hydroxyl radical) which can attack DNA at the iron binding site. This might be an explanation of how genes are regulated by oxidation–reduction reactions.

Nevertheless, this apparent mitochondrial dysfunction may in fact be reversible since the normalization of mitochondrial function resulted in a significant decrease in tumor growth both in test tubes and in animal models [21]. Inhibition of the mitochondria in normal cells spurs cancer growth [23] and if glycolysis is inhibited, cancer cells die off at a rapid rate.

Szent-Györgyi also thought that this apparent mitochondrial dysfunction is in fact reversible. He suggested that this fermentation energy is transferred to the mitotic mechanism, where it forces cell division. In other words, efficient oxidative energy production is associated with organized cell structure, whereas fermentation is associated with lack of structure and the inclination to cell division.

## Oxygen and cancer

Oxygen is the single most important substance taken into the body. Oxygen is a necessary component in every chemical reaction important to human physiology. Oxygen nourishes the cells, it provides the energy needed to metabolize carbohydrates, it allows chemical transport, breaks down waste products and toxins, regulates the pH of body chemistry, drives the desire to breathe and fights hostile organisms. Oxygen is our body's most important nutrient.

The appearance of oxygen on our globe induced profound changes in the nature of living systems which with enough energy available started to differentiate and build complex structures with complex functions. Oxidation was added to fermentation and proliferation was subjected to regulation. Fermentation demanded no structure, being the result of the action of a series of single molecules. Oxidation, with its electron flow, demanded structure and sequential electronic mobility. To produce meaningful structures and complex functions the action of the single molecules had to be integrated and organized [5] and this level of complexity needs high level energy.

Otto Warburg may have discovered the underlying cause for all forms of cancer about 90 years ago with his work showing that cancer is caused by a lack of oxygen respiration in cells. He stated in *The Prime Cause and Prevention of Cancer* that: "The cause of cancer occurs whenever any cell is denied 60% of its oxygen require-

ments. Cancer, above all other diseases, may have countless secondary causes. But, the prime cause of cancer is the replacement of the respiration of oxygen in normal body cells by a fermentation of sugar" [32].

As mentioned earlier, all normal body cells meet their energy needs by respiration of oxygen, whereas cancer cells meet their energy needs in great part by fermentation [33]. Since Warburg's discovery, this difference in respiration has remained the most fundamental physiological difference consistently found between normal and cancer cells.

White blood cells kill cancer cells by injecting them with oxygen ( $H_2O_2$ ), creating hydrogen peroxide in the cells. Looking at cancer in this light, it makes perfect sense for achieving a healthy status to drastically increase cellular oxygen levels and to detoxify the body so that more cells stay oxygenated. At the lab, if we want the cells to mutate, we turn down the oxygen. To stop them from growing, we turn the oxygen back up.

Every year we lose more oxygen from our atmosphere and every year the incidence of cancer increases. In the beginning, the earth's atmosphere was 37% oxygen. Now the atmosphere is nearly 20% oxygen. It is difficult for cancer to exist in an alkaline, oxygen-rich environment. Hypoxia induces the expression of several genes, related to cancer including the glucose transporter gene and the hypoxia inducible factor-1 (HIF-1) [34].

To overcome cancer we must change your internal environment to one in which cancer cannot thrive or survive. All too often our cells are lacking in oxygen. Fortunately it is possible to increase the level of oxygen in cells, thus, making our body's internal environment a place where cancer survival is difficult. Cancer also needs an acidic environment to grow and does not survive well in an alkaline, oxygenated body.

## Acidity vs. alkalinity

When the internal milieu is disrupted, (the internal environment) the degenerative processes originate. This environment is the ocean that surrounds each and every cell. The one way this internal environment becomes acid is from the over consumption of protein. Protein is converted into strong acids by the body and these acids leach the minerals out of the body. In the long run, the best way to replace these lost minerals is to eat more fruits and vegetables and less acid producing foods.

Alkali solutions (pH over 7.0) tend to absorb oxygen, while acids (pH under 7.0) tend to expel oxygen. Therefore, when the body becomes acidic by dropping below pH 7.0, oxygen is driven out of the body thereby favoring carcinogenesis. Stomach fluids must remain acidic to digest food and urine must remain acidic to remove wastes from the body. Blood is the exception. Blood must always remain at an alkaline pH 7.4 so that it can retain its oxygen. When there is adequate mineral consumption in the diet, the blood is supplied the crucial minerals required to maintain an alkaline pH of 7.4.

Changes in pH may create membrane potential differences (voltage) that may result in cellular dysfunctions such as abnormal electron and proton efflux, electrical uncoupling and loss of inter-cellular communication [35].

However, when there is insufficient mineral consumption in the diet, the body is forced to rob other body fluids of their minerals to pay the blood. In doing so, it removes crucial minerals, such as calcium, from the body, in order to maintain the blood at pH 7.4. This causes the de-mineralized fluids and organs to become acidic and therefore anaerobic, thus favoring not only cancer, but a host of other degenerative diseases [36].

We propose that cancer cells have damaged their mitochondria and cannot utilize the Krebs cycle. Kidd and Burk [38] provided



further evidence that cancer cells have defective mitochondria. When they added succinate to various cancer cell lines, there was little or no increase in respiration, in contrast to the considerable increases obtained with normal tissues. Succinate is a normal intermediate substrate of the Krebs cycle metabolism.

Normal and malignant cells undergo mitosis between a pH range of 6.5–7.5 and the mitosis rate slows as the intracellular pH approaches the extremes of this range. If a cell can be forced into a pH outside of this range cell division ceases [38].

Foods considered to be alkaline forming are: Almonds, Aloe vera, apples, apricots, cabbage, cantaloupe, celery, carrots, cucumbers, dates, figs, honey, lettuce, peaches, pineapple, sprouted seeds, and mineral water. The consumption of these foods should be encouraged in cancer patients, as well as a diet low on refined and simple carbohydrate foods.

The bioflavonoid quercetin has been found to inhibit the synthesis of heat shock proteins in tumors and to block the export of lactate from tumors [39].

Respiratory rate and breath holding ability are key indicators of the pH of blood. The body uses carbon dioxide levels as a primary way to regulate blood pH. When you dissolve carbon dioxide in the blood, you get carbonic acid. If there is too much carbonic acid, the respiratory center in the brain will send signals to the respiratory muscles that they must breathe to get rid of excess carbon dioxide. If there is too little carbonic acid, the respiratory center will send out a message to reduce respiration to conserve carbon dioxide.

Many of the enzymes that facilitate metabolic reactions operate optimally only in solutions of specific alkalinity. When there is a deviation from this level of alkalinity, problems can occur. These problems are manifested by slower enzymatic reactions, and thus a decrease in synthesis of specialized molecules. There is also an impairment in the production of ATP.

### Warburg's cancer legacy

Warburg's hypothesis also ties in with a less mainstream theory that connects cancer and acidity. For years, alternative cancer therapists have recommended an alkaline diet to fight cancer. The Warburg effect provides a possible explanation, since the major by-product of glycolysis is lactic acid. In cancer patients we favor the supplementation of vitamin C, B-complex [41], quercetin, fish oils, magnesium, Coenzyme Q10, lipoic acid and acetyl-L-carnitine, all promoters of aerobic metabolism [40]. In addition, the use of baking soda (sodium bicarbonate), as part of a therapeutic protocol makes sense because of its alkalizing effect; also a complex carbohydrate vegetarian diet, oxygen therapies and IV Vitamin C may be part of a sensible therapeutic protocol. Although Warburg did not mention it, exercise increases blood oxygenation and should be of benefit to the cancer patient.

### Ascorbate and cancer

Ascorbate or vitamin C has many known metabolic functions; nevertheless it may serve yet another metabolic and physiological function by providing reductive energy, the electrons necessary to direct energy pathways in the mitochondria [14,15]. Interestingly, ascorbate has been detected in the mitochondria and also found to be regenerated internally there. Vitamin C may participate in the transport of oxidation potential to the mitochondria and thus help facilitate the operation of the respiratory chain, with all its anticancer implications. This oxidation transport capability might be the major explanation as to why large doses of vitamin C seem to have powerful, general health benefits in cancer patients. It could be providing more energy to every cell [41]. Basically, the vitamin C transported to the cells where it diffuses to the mitochondria and

delivers its oxidation potential, powering the respiratory chain. Moreover, ascorbate has a cytotoxic action on cancer cells when given in high doses [42,43].

Oxygen, the final electron acceptor is of great importance to the ascorbate induced cytotoxic action on cancer cell proliferation by interfering with anaerobic respiration (fermentation), a commonly used energy mechanism of malignant cells. A problem in electron transfer activity might well be coupled to a defective mitochondria and vitamin C may help correct this electron transfer problem. Also ascorbate and oxygen may produce hydrogen peroxide that may kill cancer cells [43].

It is conceivable that other energy intermediates will prove of benefit against cancer either by interacting directly with ascorbate (redox) or by stimulating/improving and/or correcting aerobic metabolism in the mitochondria. This information supports the hypothesis that certain oxidation intermediates and/or aerobic metabolism cofactors originating from nutrients can act as active antineoplastic agents. Moreover the molecular structures of ascorbic acid and its oxidized form dihydroascorbic acid are similar to that of glucose. Actually many cell types transport ascorbate solely in its oxidized form, through facilitated glucose transporters [44]. To ascorbate's advantage, tumor cells have an increased requirement for glucose [45]. To compensate for this increased need for glucose, tumor cells increase their quantity of glucose transporters [44,45]. This action greatly enhances the entrance of either ascorbate or its oxidized form, dehydroascorbate into the cancer cell. Thus, facilitating action of ascorbate as a selective, non-toxic chemotherapeutic agent.

### Ascorbate and differentiation

Ascorbate can act both as an antioxidant and as an oxidant, depending upon the environment in which the molecule is present and its concentration. Millimolar concentrations of ascorbate induced apoptotic cell death, characterized by cell shrinkage, nuclear fragmentation and internucleosomal DNA cleavage, in human myelogenous leukemic cell lines [46]. Ascorbate derivatives, can induce apoptosis, produce radicals, elevate oxidation potential and stimulate methionine oxidation. This suggests that ascorbate may induce apoptosis by its prooxidant action. All these activities suggest an active role of ascorbate in gene expression regulation and cell differentiation.

It has been reported that osteoblast cells treated with Ascorbic acid had a fourfold increase in respiration and a threefold increase in ATP production that provided the necessary energy for cell differentiation [47]. Ascorbate causes a consistent and remarkable specific DNA demethylation of 1847 genes in human embryonic stem cells [48]. Also ascorbic acid promotes Schwann cell myelin formation by enabling the Schwann cell to assemble a basal lamina, which is required for complete differentiation [49]. Ascorbate may have an important role in cell differentiation.

### Conclusion

Cancer cells have an altered metabolism. These bioenergetic and metabolic changes permit the survival of the cancer cells under adverse conditions such as hypoxia but enables their proliferation, progression, invasiveness and metastasis [50]. Malignant transformation is associated with increase glycolysis, reduced pyruvate oxidation and increased lactic acid production. In addition, cancer cells have increased gluconeogenesis, increased glutaminolytic activity, reduced fatty acid oxidation, increased de novo fatty acid synthesis, increased glycerol turnover, modified amino acid metabolism and increased pentose phosphate pathway activity [50].

Toxic compounds that disrupt the electrical potential of cell membranes and the structure of mitochondrial membranes will deactivate the electron transport chain and disturb oxygen-dependent energy production. Cells will then revert to fermentation, which is a less efficient primeval form of energy production.

Improvement in cellular bioenergetics may be enhanced nutritionally by use of certain nutrients that help provide structural materials for membrane repair, repolarization and facilitation of mitochondrial enzyme production of ATP. We believe this hypothesis can have a major public health impact such as an increase in cancer survival rates.

We present a hypothesis and evidence to support the contention of a bio-energetic theory of carcinogenesis; that cancer cells originate because of dysfunctional mitochondria. Confirmation of this hypothesis will dramatically affect the development of future treatments for cancer.

### Conflicts of interest statement

None declared.

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