The Bio-Energetic Theory of Carcinogenesis: The Origin of Cancer Revisited

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Abstract *The Bio-Energetic Theory of Carcinogenesis states that cancer originates from damage to the mitochondria. The view of cancer as a genetic disease has been an issue of confusion and is largely responsible for the failure in overcoming the disease. Most genomic defects found in cancer arise as secondary downstream effects of defective energy metabolism. Mitochondria provide the energy needed to maintain cellular differentiation. We believe that targeting the defective energy metabolism of tumor cells will eventually become the most effective approach to cancer management. This novel theory opens up many possibilities for new avenues of cancer treatment, such as the ketogenic diet, intravenous vitamin C, hyperbaric oxygen and mitochondrial correction therapy.*

Introduction

Eukaryotic mitochondria resulted from symbiotic incorporation of alpha-proteobacteria into ancient archaea species. During evolution, mitochondria lost most of the prokaryotic bacterial genes and only conserved a small fraction including those encoding 13 proteins of the respiratory chain. In this process, many functions were transferred to the host cells, but mitochondria gained a central role in the regulation of cell proliferation and apoptosis, and in the modulation of metabolism; accordingly, defective organelles contribute to cell transformation and cancer, diabetes, and neurodegenerative diseases. Most cell and transcriptional effects of mitochondria depend on the modulation of respiratory rate and on the production of hydrogen peroxide and other oxidative species released into the cytosol.

All cancer cells regardless of their tissue origin express a defect in mitochondrial energy metabolism. The view of cancer as a genetic disease has been an issue of confusion and is largely responsible for the failure in overcoming the disease. This view of cancer as a genetic disease is based on the flawed assumption that somatic mutations cause cancer. Although we should state that genomic instability is linked to respiratory insufficiency. The mitochondrial oxidative rate has to remain depressed for cell proliferation; even in the presence of O2, energy is obtained from increased glycolysis (Warburg effect) (Antico-Arciuch et al, 2012).

It is probable that the major impediment to the effective treatment of cancer has been the confusion surrounding its origin. Most of the confusion arises from the absence of a unifying theory that integrates all aspects of the disease. We propose the Bio-Energetic Theory of Carcinogenesis to fill this gap in the understanding of the origin of cancer (Gonzalez et al, 2012).

In general, the Bio-Energetic Theory of Carcinogenesis states that cancer originates from damage to the mitochondria that at the same time impairs the cell's capacity to generate energy with oxygen (oxidative energy production),

with a concurrent increase in energy generation without oxygen. In other words, this theory states that cancer is not a genetic disease, but rather a disease of metabolism.

This theory is based on the ideas proposed in 1924 by the Nobel Prize winning German biochemist Otto Warburg. These ideas were subsequently discarded when it was discovered that cancer cells had mutations to their DNA. So it was concluded that if cancer cells have mutations to the molecule that dictates all cellular function; then that must be the cause of the disease.

A healthy cell produces 89% of its energy using oxygen, and 11% through non-oxidative metabolism (non-oxidative metabolism is also known as fermentation). Oxidative energy production is far more efficient than fermentation. Almost 20 times more energy is released when glucose is completely oxidized, as opposed to when it is just fermented.

The Bio-Energetic Theory of Carcinogenesis explains that the disease begins with damage to the mitochondria. The cell is then forced to shift energy production to fermentation in order to survive. Two main characteristics of cancer are 1: damaged mitochondria; 2: increased fermentation which are present in all cancer types. Also the greater the degree of fermentation displayed by a given cancer, the more aggressive the cancer is. Because a tumor cell's mitochondria are damaged, and are therefore forced to generate energy by an inefficient pathway, they need to consume much more glucose to remain viable. A glance at a PET scan, which uses a radioactive labeled glucose analog to image cancer, provides stunning visual evidence of the necessity that tumor cells have for glucose compared to normal cells.

It is interesting that since 1885, Freund observed that patients with malignant disease can develop spontaneous hyperglycemia (Freund et al, 1885), there has been episodic interest in the association of the altered glucose metabolism with the path of nutrition and neoplasia (Marks et al, 1957). As early as 1924, Händel and Tadenuma summarized the findings in those days by the following statement: "A diet rich in carbohydrates has a pronounced stimulating impact on tumor growth" (Händel et al, 1924).

Emerging evidence reveals that all hallmarks of cancer can be explained by mitochondrial damage followed by a shift to non-oxidative energy metabolism. Once the oxidative energy generating capacity of the cell is impaired, the cell undergoes a dramatic transformation; it is when oncogenes are switched on, initiating and propagating the uncontrolled proliferation that is the main hallmark of the disease.

Genetics and Cancer

Most genetic changes in tumor cells are irrelevant to the origin of cancer. They can be described as an epiphenomenon of the metabolical/physiological chaos of the less availability of cellular energy.

Genomic instability has been assumed to elicit the large number of mutations found in tumor cells, thus supporting the idea that cancer is a genetic disease. While genome changes participate in disease progression, they do not cause the disease. Cancer is a disease of defective cellular energy metabolism. Most genomic effects found in cancer arise as secondary downstream effects of defective energy metabolism (Seyfried et al, 2010).

Respiratory insufficiency precedes the genomic instability that further contributes to tumor development. Once established, this genomic derangement also contributes to further respiratory impairment, mutability and tumor progression. Metabolic derangements precede genetic changes. It starts as an epigenetic phenomenon that eventually changes the genotype.

Genetic sequencing data has been unable to implicate genetic mutations as cause of cancer, while in contrast metabolic dysfunction has been shown to be present in every type of cancer, regardless of tissue of origin. In an attempt to explain the random complexity of the thousands of mutations reported in cancer, researchers claim that cancer is a collection of over 200 different diseases. We believe that that cancer is one disease, a metabolic one. It is not a collection of over 200 different diseases as the genetic theory proposes.

The genetic mutational profile of any given cancer type looks different from person to person, rendering it impossible to claim that mutations are definitely responsible for the origin of the disease. To make this issue even more confusing, the mutational profile is different from cell to cell within the same tumor, rendering drug development to target mutations next to impossible. No mutation has yet to be identified that is reliably diagnostic of any type of cancer. So we definitely see genetic changes in cancer progression but

secondary to the metabolic problem which contributes to perpetuate the malignant state.

It is known that once a cell has impaired its ability to produce energy through oxidative pathways, genomic instability (increased potential for DNA mutations to occur) that accompanies tumor development, follows. The genetic mutations acquired following mitochondrial impairment unquestionably contribute to the tumor cell's features and aggressiveness but are not the cause of the disease. They appear to be of secondary consequence or an epiphenomenon to the metabolic dysfunction. While it's true that most of the agents known to cause cancer; chemical carcinogens, viruses, radiation, and inflammation can cause mutations to DNA, it is also true these agents damage cell membranes and especially the mitochondria. Once the mitochondrion is damaged, the cell reverts to fermentation to obtain energy, we can state that the cancer has begun. It is subsequent to the shift in energy metabolism that genomic instability and mutations occur (Seyfried et al, 2010).

To achieve real therapeutic progress, the true origin of the disease needs to be determined. All therapeutic progress, from prevention to treatment, must arise from a foundation of understanding of the disease.

A series of nuclear/cytoplasmic transfer experiments are exceptionally important in revealing the true nature of the disease. In brief, the experiments consist of transferring the nucleus of a cancer cell into a healthy cell that has had its nuclease removed prior. The newly created hybrid cell has the genetic material of a cancer cell, with all of its defects, but now has the healthy mitochondria of a normal cell. Intuitively, if the origin of cancer is indeed due to mutations to DNA, the newly created hybrid cells, that still retain all of the mutations of the cancer cell nucleus should be tumorigenic. But they were not. These experiments were carefully executed, with strict controls, and were found to be very reproducible. Experiments like these provide irrefutable evidence that DNA mutations are not the origin of cancer; the damaged mitochondria are. All cells require regulated energy homeostasis to maintain their differentiated state (Elliott et al, 2012).

Cell Energetics

In order for cells to remain viable and to perform their programmed function they must produce energy. Membrane pumps require constant energy to maintain functionality. Most cell functions are linked to the membrane potential and to the Na+/K+/Ca+ gradients. Availability of ATP to the pumps maintains these ionic gradients. If these pumps are disrupted cellular dysfunction will ensue. Regardless of cell type or tissue origin, cancer cells share a singular characteristic and that is abnormal energy metabolism. Energy dysregulation is the hallmark of malignant cells. Tumor cells differ from normal cells in the origin of the energy produced rather than in the amount energy produced.

We truly believe that targeting the defective energy metabolism of tumor cells will eventually become the most effective approach to cancer management.

Warburg Hypothesis

Aerobic fermentation involves elevated glucose uptake with lactic acid production in the presence of oxygen. Warburg stated that irreversible damage to respiration was the prime cause of cancer (Warburg et al, 1931; Warburg et al 1956; Warburg et al, 1969). Warburg was the first to describe in detail the dependence of cancer cells on glucose and glycolysis in order to maintain viability following respiratory damage (Warburg et al, 1931; Warburg et al 1956; Warburg et al, 1969). Warburg considered energy as the central issue of carcinogenesis. Warburg considered fermentation as the formation of lactate from glucose in the absence of oxygen. This type of energy pathway is also utilized in mammalian embryos and muscle cells during strenuous exercise. Here pyruvate instead of entering the TCA cycle is reduced to lactate in the absence of oxygen. Lactate fermentation generates NAD+ that can be used as an electron acceptor. In cancer cells this fermentation occurs even in the presence of oxygen.

Lactate is basically a metabolic waste from incomplete oxidation of glucose; nevertheless it can be recycled at a high energetic cost in the Cori cycle. The Cori cycle produces 2 ATPs at a cost of 6 ATP's, which in part explains the cachexia syndrome in patients with advanced cancer. Most lactate enters the bloodstream where it is used to synthesize glucose in the liver. Warburg attributed this aerobic fermentation in tumor cells to respiratory damage or respiratory insufficiency. In other words damaged mitochondria.

One relevant issue pertaining the Warburg

hypothesis is that mitochondrial amino acid fermentation confuses the boundaries between normal respiration and fermentation; this particular issue can bring light to much of the controversy surrounding this hypothesis.

Cancer cells that rely on glutamine for energy production and are able to produce ATP through non -oxidative processes in the mitochondria. Glutamine metabolism increases ammonia in the extracellular environment. Ammonia can neutralize acidity from glycolytic lactate production (Baggetto et al, 1992; Kelly et al, 1974). Caution is therefore necessary in using pH as an indicator of lactate production (fermentation) in cancer cells that use glutamine as fuel. This type of pseudo-respiration has the biochemical characteristics of normal respiration but does not involve ATP synthesis through oxidative phosphorylation (OxPhos). The energy is derived from amino acid fermentation. Glucose and glutamine interact synergistically to drive tumor cell fermentation (Seyfried et al, 2010; Seyfried et al, 2011).

Mitochondria and Differentiation

Mitochondria provide the energy needed to maintain cellular differentiation. The total number of mitochondria in tumor cells is significantly lower that the number of mitochondria in normal cells (Seyfried et al, 2010). The total respiratory capacity of tumor mitochondria is lower than that of mitochondria of normal cells (Seyfried, 2010; Seyfried et al, 2014). Abnormalities in mitochondrial size and shape are correlated with mitochondrial dysfunction (Benard et al, 2008; Shapovalov et al, 2011; Matés et al, 2009). Highly malignant tumors do not have mitochondria of normal morphology and number (Seyfried et al, 2010). The greater the degree of mitochondrial morphological abnormality, the greater the degree of malignancy (Pedersen et al, 1978). Respiratory impairment requires enhanced fermentation to prevent apoptosis (Seyfried et al, 2010), moreover enhanced fermentation prevents differentiation and is linked to uncontrolled cell proliferation (Seyfried et al, 2010).

Mitochondrial Uncoupling and Cancer

Uncoupling involves dissipation of the mitochondrial proton gradient. Uncoupling produces heat instead of ATP. Heat production is greater in less differentiated tumor cells (Seyfried et al, 2010). The greater heat production in the less differentiated cells supports the hypothesis that mitochondrial uncoupling is greater in cancer cells that are more malignant. Moreover, heat production is correlated with increased glucose consumption and lactic acid production (Nittinger et al, 1990). The greater the uncoupling, the greater will be the need to produce energy through substrate level phosphorylation (aerobic glucose fermentation).

ATP synthesis through mitochondrial fermentation involving substrate level phosphorylation could give the false impression that tumor mitochondria is producing ATP through respiration (Seyfried et al, 2010). The failure to recognize this type of ATP production by a non oxidative process in tumor mitochondria contributes to the confusion surrounding the Warburg hypothesis of cancer and explains the basis of its rejection (Denny et al, 2010).

While reduced oxygen uptake may be indicative of reduced OxPhos, increased oxygen uptake may or may not be indicative of increased OxPhos and ATP production (Jahnke et al, 2010; Samudio et al, 2009; Ramanathan et al, 2005). In this sense, oxygen consumption in tumor cells could provide misinformation of the true respiratory capacity of these cells.

Lipids and Cancer

OxPhos capability is linked the structural integrity of mitochondrial cristae (Frey et al, 2000; Putignani et al, 2008; Paumard et al, 2008). Lipids maintain the integrity of biomembranes. Abnormalities in lipids can compromise mitochondrial function. Mitochondrial lipid abnormalities are common in all tumors. Altered mitochondrial lipids reduces the efficiency of OxPhos, requiring increased energy production through substrate level phosphorylation.

Phospholipids and Cancer

Cardiolipin is known as the signature phospholipid of mitochondria. It is responsible for a wide range of mitochondrial functions. Abnormalities in the structure of cardiolipin have been identified in tumor cells (Seyfried et al, 2014).

It is important to clarify that the in vitro growth environment produces lipid and electron transport abnormalities in mitochondria in both tumorigenic and non-tumorigenic cells (Kiebish et al, 2009). A failure to recognize this fact

could confuse data interpretation related to energy metabolism. Caution should be taken when comparing energy metabolism of malignant versus nonmalignant cells in tissue culture environments since they do not truly replicate the *in vivo* environmental growth conditions. This could be a problem interpreting key experiments defining the metabolic origin of cancer.

Conclusion: A Protocol for Cancer

If we are correct that cancer is truly a metabolic disease, the therapeutic implications are huge. First, if we are correct, it would explain why virtually no progress has been made in reducing the death rates from cancer since 1950. Second, it opens up many possibilities for new avenues of treatment. The first place to start is by implementing a low carbohydrate diet (Paleolithic or ketogenic diet), starving the cancer cells of glucose. In virtually every experiment in which the ketogenic diet has been tested in mice, tumor growth rates have slowed dramatically. It appears that the ketogenic diet is able to put cancer cells under significant metabolic stress allowing additional non- toxic therapies, like intravenous vitamin C, hyperbaric oxygen, mitochondrial correction to push the cells further over the edge. We propose that combining these non-toxic treatments would provide a powerful, synergistic anticancer effect.

Potential concern may arise regarding the use of a diet therapy for cancer patients susceptible to cachexia. While low carbohydrate or ketogenic diets promote weight loss in overweight individuals, they are also known to spare muscle wasting during conditions of energy restriction and starvation (Manninen et al, 2006; Cahill et al, 2006; Veech et al, 2004; Volek et al, 2002).

The anti-cachexia effects of the ketogenic diet are not surprising when considering a metabolic switch to fat metabolism and subsequent ketosis evolved as a method of sparing protein during prolonged fasting or starvation (Veech et al, 2001; Wu et al, 1988). It makes sense that dietary-induced therapeutic ketosis in a cancer patient would prevent muscle wasting similarly as it does with athletes undergoing intense exercise (Paoli et al, 2012).

Human studies of high-dose IV Intravenous Vitamin C in patients with cancer have shown improved quantity and quality of life, as well as improvements in physical, mental, and emotional functions, symptoms of fatigue, nausea and vomiting, pain, and appetite loss (Gonzalez et al, 2014)

In relation to hyperbaric oxygen, there are a substantial number of studies indicating that hyperbaric oxygen can induce marked anticancer effects in vitro and in animal and human studies alike (Daruwalla et al, 2006; Moen et al, 2012; Al-Waili et al, 2005).

Competing Interests

The authors declare that they have no competing interests.

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