

Review Article

The Retrograde Signal: Dependency on Glucose Marks the Cancerous Phenotype

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Received: July 17, 2017; Accepted: August 31, 2017;

Published: October 16, 2017

Abstract

Nearly a century ago, Otto Warburg suggested that mitochondrial malfunction creates cytoplasmic fermentation resulting in increased anabolism leading to tumor genesis and decreased catabolism. Now, after focusing for more than 40 years on mutations in the human genome, oncological research is beginning to shift back toward cancer as a state of metabolic inflexibility. Evidence shows a chronic, metabolic shift toward non-oxidative energy production follows mitochondrial damage; impaired oxidative respiration is a hallmark of cancerous growth. Once the oxidative energy capacity of cells is impaired, metabolic signaling undergoes dramatic transformation; oncogenes are activated initiating uncontrolled proliferation. The anabolic shift is immune to homeostatic regulation. Cells are reprogrammed for aerobic glycolysis; this shift mediates a glucose dependency making sugar and glutamine/glutamate substrates of choice for dysregulated tumors. Likewise, increased cytoplasmic catabolism initiated through a ketogenic diet reduces glycolysis and restores oxidative phosphorylation (OXPHOS), therefore limiting tumor growth potential. The proposed bioenergetic model, utilizing a sustained ketogenic diet, fluxes the standard American diet (SAD) away from glucose (CHO) dependency to fatty acid (fats/protein) metabolism; the flux decreases basal insulin levels, bypasses the loop of non-oxidative glycolysis and restores homeostatic signals. In addition, benign dietary ketosis represses postprandial insulin secretion to mobilize fatty acids for beta-oxidation directly into the TCA cycle of the mitochondria. Restored mitochondrial function, activated mitochondrial biogenesis and increased synthesis of key oxidative enzymes, facilitated by a ketogenic protocol (increases intracellular oxygen transport), will inhibit cancer growth, repress glycolytic metabolism, increase ATP synthesis/respiratory chain activity and reduce acute nuclear metabolic stress. Thus, fatty acid metabolism promotes the catabolic inhibition of oncological pathways.

Keywords: Warburg effect; Cancer; Retrograde signal; Benign dietary ketosis

Abbreviations

SAD: Standard American Diet; ATP: Adenosine Tri-phosphate; Pentose Phosphate Pathway DNA: Deoxyribonucleic Acid; RNA: Ribonucleic Acid; mTOR: Mammalian Target of Rapamycin; AMPK: 5' AMP-Activated Protein Kinase; HIIT: High Intensity Interval Training

Introduction

All site cancers are growing at alarming rates in the U.S. Nearly 30% of new cancer cases of cancer for women in 2017 will be cancer of the breast while 19% will be prostate for men [1]. The lifetime probability of developing cancer for females is 1 in 3; 1 in 8 for breast cancer. Likewise, the lifetime probability of tumor genesis in males is 1 in 2; 1 in 8 will develop prostate cancer [1]. Survival rate predictions are equally grim for all site cancers at 69% [1]. The rate of incidence is far outpacing effective treatment options as trends continue to increase as well as the mortality rates.

Current oncological treatments are based on the nuclear gene origin of cancer theory, originated in 1914 from researcher Theodor Bonverri. Observed defects in cell division during chromosome

segregation in sea urchins and nematodes were foundational to the genome theory [2]. Although Bonverri's nuclear gene origin hypothesis gained credibility as the basis for the present day somatic mutation theory, there is no evidence that he directly experimented with the disease [2]. C.D. Darlington, a prominent British geneticist, challenged the notion that the origin of cancer had a nuclear basis. Rather, he argued that cytoplasmic defects (*plasmagenes*) led to the formation of tumor cells, namely the mitochondria [3]. The belief that cancer cells initiate in the cytoplasm rather than the nucleus is demonstrated by past and current research, yet the somatic mutation theory of cancer continues to drive the majority of research and treatment modalities in the U.S. Oncological solutions have not always been genetically driven [4-8]. In the early 1920's, the German biochemist, Otto Warburg, discovered that cancer cells have an increased uptake of glucose and secretion of lactic acid under normoxic environments as compared to normal cells; this shift to aerobic fermentation was termed the Warburg effect. Furthermore, Warburg's research demonstrated an associated decrease in the volume/density of mitochondria in cancer cells, supporting the theory that cancer has cytoplasmic origins [9].

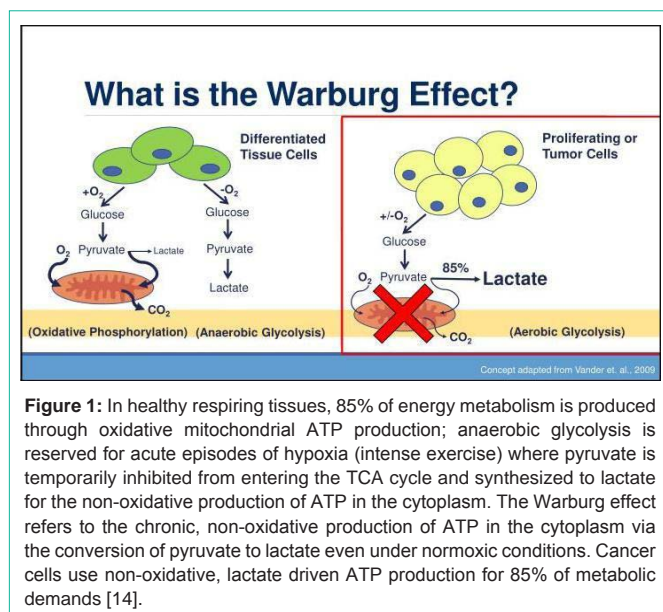


Figure 1: In healthy respiring tissues, 85% of energy metabolism is produced through oxidative mitochondrial ATP production; anaerobic glycolysis is reserved for acute episodes of hypoxia (intense exercise) where pyruvate is temporarily inhibited from entering the TCA cycle and synthesized to lactate for the non-oxidative production of ATP in the cytoplasm. The Warburg effect refers to the chronic, non-oxidative production of ATP in the cytoplasm via the conversion of pyruvate to lactate even under normoxic conditions. Cancer cells use non-oxidative, lactate driven ATP production for 85% of metabolic demands [14].

Metabolic theory of cancer

President Nixon declared war on cancer 46 years ago. Since the early 1980's, a mutation theory has guided oncological research; despite vast amounts of money, time, and energy devoted to cancer research, science is losing the war against the devastating disease. Sixteen hundred and fifty Americans die each day from cancer [10]. In 2000, the National Cancer Institute launched the Genome Atlas Project led by Michael Stratton and Peter Campbell. The project combined the knowledge of sequencing in the human genome with high throughput mutation detection techniques [11]. Its mission: "To systematically explore the entire spectrum of genomic changes involved in more than 20 types of human cancer" [11]. The goal of the project was to discover and sequence the genetic mutations responsible for cancer. However, the search for causative mutations has remained elusive. The data suggests that mutations are not central as was previously assumed; 'No mutation has yet to be identified that is reliably diagnostic of any type of cancer' [12]. The field of cancer research is slowly returning to the 1924 ideas of Nobel Prize honoree and German biochemist, Otto Warburg. Warburg is a great grandfather of the metabolic theory of cancer with the discovery of aerobic glycolysis or the Warburg effect (Figure 1). Warburg postulated that cancer cells, even under normoxic conditions, upregulate non-oxidative fermentation of glucose in the cytoplasm of the cell [9,13,14]. Although Warburg's research seemed to be lost for decades in translation, distinguished physicians and researchers such as Thomas Seyfried, MD, Dominic P. D'Agostino, PhD and other scientists trained in biochemistry are revitalizing the metabolic theory of cancer and pioneering innovative, novel therapies for the metabolic management, treatment and prevention [2]. Seyfried (2017) posits, "Emerging evidence indicates that cancer is a mitochondrial metabolic disease that depends on availability of fermentable fuels for tumor cell growth and survival. Glucose and glutamine are the most abundant fermentable fuels present in the circulation and in the tumor microenvironment" [15]. Pioneers like Warburg (1924) and Seyfried (2017), challenge the current view of cancer and define the disease as a cytoplasmic metabolic disturbance rather than a somatic

gene mutation. Innovative metabolic therapies aggressively target tumor cells via starvation of prominent glucose/glutamine substrates increasing the cells' vulnerability to oxidative stress and apoptotic death [16,17].

Non-Oxidative energy pathways

Cancer has a sweet tooth; researchers, like Dr. Seyfried of Boston College and author of *Cancer as a Metabolic Disease* (2012), say cancer cells show a reversion to primitive forms of cellular metabolism – the fermentation of glucose, similar to a fungus, instead of oxidative respiration via the mitochondria, as in healthy differentiated cells. Cancer cells have a voracious appetite for sugar; glucose burned in the mitochondria with oxygen produces 36 molecules of energy (ATP). Glucose fermented in the cytoplasm produces only 2 molecules of ATP with excessive amounts of lactate waste. Non-oxidative energy metabolism requires the cancer cells to digest 20x as much glucose to yield the same energy as respiring cells. In addition to the cancer's increased consumption of glucose, excess lactate left in the wake of fermentation is recycled into supplemental glucose through hepatic gluconeogenesis. In addition, the recycled sugar produced via non-oxidative energy channels in the cytoplasm is shunted into cellular growth (PPP shunt) supporting the construct of RNA/DNA into 'daughter cells' leading to cancerous proliferation [17].

This "reserve" system of fermentation-lactate-gluconeogenesis was designed as an emergency energy system for acute states of hypoxia/ischemia like high intensity exercise where the muscles' demand for fuel exceeds the availability of oxygen. In hypoxia, the liver's production of new sugar is adaptive; and, the cycle of oxidative respiration is quickly restored once oxygen levels are restored. However, as Warburg suggested, cancer cells appear to shift to non-oxidative energy metabolism despite a normoxic environment. With increased energy production aberrantly programmed toward aerobic glycolysis and shifted away from cellular respiration, glucose and glutamate become the primary fuel substrates for dysregulated tumors. Current research suggests that the HIF-1/mTOR pathway triggered by disturbances in ATP availability induced by insulin resistant hypoglycemia and cellular starvation may be responsible for the energy shift toward non-oxidative energy metabolism and glucose dependency [18].

Aerobic glycolysis and anaerobic glycolysis are similar, lactic acid is synthesized in both environments; however, chronic and sustained aerobic glycolysis arises in cancerous cells due to compromised cellular viability, damaged respiration and a down regulation of key mitochondrial enzymes important for respiration, including cytochrome c oxidase (COX), α -ketoglutarate dehydrogenase complex, and pyruvate dehydrogenase complex. In addition to a reduction in oxidizing enzymes, cells with a sustained shift toward glycolysis show upregulation of PFKFB3, the master regulator of glycolysis, and PDK1, the primary inhibitor of pyruvate's entry into the TCA cycle for oxidative respiration. Anaerobic glycolysis is triggered in normal respiring cells from acute hypoxia. Restoration of oxygen quickly reduces anaerobic glycolysis and lactic acid production in healthy cells (Pasteur Effect); however, the continued production of lactic acid in the presence of oxygen represents an abnormal Pasteur Effect [18]. Likewise, the aforementioned reprogrammed shift toward non-oxidative energy metabolism creates

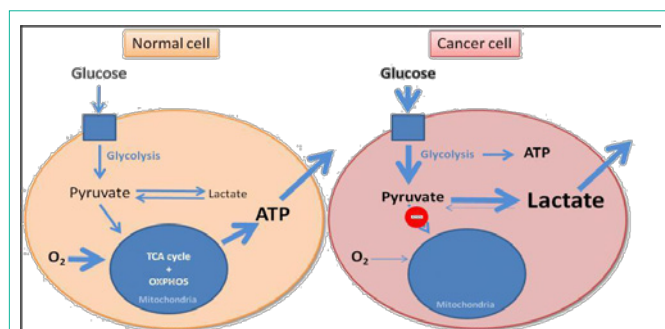


Figure 2: Hypoxia inducible factor 1 alpha (HIF-1a) triggered by insulin resistant cellular starvation stimulates the up-regulation of glycolytic enzymes; these enzymes inhibit pyruvate from entering into the TCA cycle and OXPHOS pathway for ATP production in the mitochondria as a survival mechanism resultant of energetic stress signaling. Non-oxidative, glycolytic synthesis of 2 moles of ATP for every molecule of glucose provides a consistent yet inefficient supply of non-oxidative ATP requiring increased glucose utilization and lactate production in the cancerous phenotype [22].

high tolerance for the acidic, low pH environment consequent of excessive/chronic release of lactate; the anomalous signaling fosters cellular immunity to homeostatic regulation. Warburg identified this renegade phenotype as an upstream metabolic shift occurring years, or decades, before cancer is detected [19]. Aerobic glycolysis, arising from damaged respiration, with aberrant signaling of glycolytic/oxidizing enzymes, is the most common phenotype in most cancer; research concludes, disturbances in ATP availability, common with insulin resistant states, compromises cell viability leading to signaling errors and defects in mtDNA caused by membrane swelling, collapse and deterioration of the inner mitochondrial bilayers; this cellular phenotype occurs in both the peripheral and brain systems [9,16,8,20-22] (Figure 2).

Retrograde signaling

The abnormal Pasteur Effect with cancerous reversion to non-oxidative energy metabolism is known to originate from signaling errors in the energy status of the cell occurring between the mitochondria and nucleus. Seyfried, and proponents of the metabolic theory, suggest an SOS survival signal is transmitted from the mitochondria in the presence of chronic deficits in oxidative ATP production co-occurring with hyperinsulinemia. The aforementioned energy deficits are common to insulin resistant pathologies characterized by defective glucose sensing/utilization, basal hyperinsulinemia, hyperglycemia/hypoglycemia and metabolic inflexibility [23]. Moreover, traditional treatments for hyperglycemia perturb the fed/fasted homeostatic signaling by raising plasma insulin levels and inducing hypoglycemia; metabolic inflexibility threatens the viability of hypoglycemic cells. The disturbed fast/fed signals set into motion a cascade of anabolic, chemical adaptations for survival led by the HIF-1/mTOR pathway resulting in oxidative stress, mtDNA defects, inflammatory cascades and sustained, non-oxidative energy metabolism [23]. Seyfried (2012) refers to the aberrant process as *retrograde* distress signals activating ancient pathways of cellular preservation. This archaic pathway of survival shifts the cellular metabolism away from mitochondrial respiration, via down-regulation of key oxidative enzymes, to a dependency on non-oxidative glucose metabolism, facilitated by an upregulation of master glycolytic enzymes [16]. In addition, this retrograde signal

has cascading effects within the nucleus; chronic survival adaptations activated by HIF-1 results in an over expression of oncogene proteins MYC/VEGF, which stimulate anabolic growth/proliferation, promote aerobic glycolysis and repress of the catabolic AMPK path responsible for apoptosis and the maintenance of cell polarity (LKB1/p53) [18]. Recent data suggest that the metabolic switch toward deregulation of glycolysis, common to all forms of metabolic syndrome pathologies, may be an early and fundamental event in tumorigenesis; metabolites of glycolysis are involved in epigenetic feedback loops creating a predisposition toward cancerous growth.

Furthermore, chronic PI3K/AKT/mTOR signaling supports the hypothesis of cancer as an “over healing wound.” Genes that orchestrate the anabolism of the wound-healing process are also key regulators of cancer growth and progression; in addition, mTOR activity inhibits cellular ‘housekeeping’ including autophagy, apoptosis and the maintenance of cell polarity. Likewise, the excess lactate production produced with non-oxidative metabolism, functions as an intrinsic inflammatory mediator that leads to increased interleukin (IL)-17A production within the microenvironment of tumors [20]. This chronic inflammation mirrors the exaggerated healing of a wound; the mTOR/HIF-1 path activates the oncogene protein expression of MYC and vascular endothelial growth factor (VEGF) initiating vascular-genesis and angiogenesis; the oncogenes propagate a “stem cell-like” growth potentiation activated in tissue repair and tumor proliferation [20].

The retrograde signal follows a maladaptive trajectory of cell survival activating oncogenes of growth and inhibition of apoptosis leading to proliferation of pre/cancerous cells [21,22,24]. In the scope of metabolic theory, cancer can be defined as an epigenetic shift toward non-oxidative modes of anabolic energy metabolism due to defective glucose sensing/utilization resulting in substrate inflexibility characterized by catabolic deficiency [25]. The theory supports Warburg’s original hypothesis on the origin of cancer, “cytoplasmic fermentation resulting in increased anabolism leading to tumor genesis and decreased catabolism” [9].

Mitochondrial morphological alterations

Oxidative energy production occurs in the cellular organelle of the mitochondria. Healthy cells produce 89% of energy using oxygen with only 11% through non-oxidative metabolism. Oxidative energy production is more efficient than fermentation. Nearly 20 times more energy is synthesized when glucose is completely oxidized, as opposed to fermentation [26-28].

Mitochondria have a bilayer membrane. The outer membrane is smooth. The cristae or inner membrane is convoluted with folds. The folds of the cristae expand the inner membrane’s surface area. Nutrients activate with oxygen on the folds of cristae to produce ATP through OXPHOS. Within the inner and outer mitochondrial membranes, the TCA cycle and ETC complex I-IV centralize optimal energy production for the cell.

It is well documented that once cells have impaired pathways for oxidative energy production, genomic instability and a risk of tumor development inevitably follow [29,30] (Figure 3). Seyfried postulates that the genomic instability of the cell appears to be a secondary consequence, or an epiphenomenon, occurring after

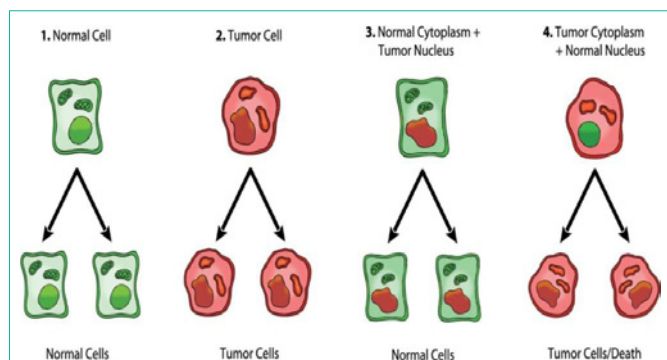


Figure 3: Role of the nucleus and mitochondria in the origin of tumors. This image summarizes the experimental evidence supporting a dominant role of the mitochondria in the origin of tumorigenesis as described previously. Normal cells are depicted in green with mitochondrial and nuclear morphology indicative of normal respiration and nuclear gene expression, respectively. Tumor cells are depicted in red with abnormal mitochondrial and nuclear morphology indicative of abnormal respiration and genomic instability. (1) Normal cells beget normal cells. (2) Tumor cells beget tumor cells. (3) Delivery of a tumor cell nucleus into a normal cell cytoplasm begets normal cells despite the persistence of tumor-associated genomic abnormalities. (4) Delivery of a normal cell nucleus into a tumor cell cytoplasm begets tumor cells or dead cells but not normal cells. The results suggest that tumors do not arise from nuclear genomic defects alone and that normal mitochondria can suppress tumorigenesis [18].

primary metabolic dysregulation. Once mitochondria assume a threshold of damage, metabolism chronically shifts into a reserve mode of non-oxidative ATP production; the cancerous phenotype is borne [2,16,17]. Adiele & Adiele (2016) suggest reductions in oxidative ATP results in enlarged and swollen mitochondria with discolored matrix and distorted cristae; the outer membranes are missing or partially intact with intra-mitochondrial inclusions [30]. Mitochondrial morphological alterations are linear to metabolic energy deficits supporting the early role of metabolic inflexibility and insulin resistance in the pathology of cancerous proliferation.

Emerging research demonstrates that the phenotype of cancer can be described by mitochondrial damage (mtDNA) resulting from chronically impaired oxidative respiration consequent to the inhibition of mitochondrial intermediates with an increased synthesis of glycolytic enzymes, thus, inhibiting pyruvate from entering the TCA cycle. Metabolic deficits in oxidative ATP, with corresponding shifts to non-oxidative energy production, are correlated to morphological damage to mtDNA [2,9,13,21,23,28,30]. As mitochondrial energy capacity is impaired, cells experience maladaptation to thwart starvation; powerful oncogenes are activated, key enzymes are chronically up/down-regulated and a cascade of oxidative stress/ROS initiates uncontrolled growth and proliferation of renegade cells. Impaired glucose sensing/utilization and consequential hyperinsulinemia, resultant of homeostatic dysregulation in pancreatic signaling, provide the hormonal backdrop for deficits in oxidative ATP; maladaptation from simultaneous signals of fed/fasted due to chronically elevated insulin will epigenetically trigger oncogene expression.

Cytoplasmic transfer

Decades ago, Israel & Schaefer (1987) originated studies of cytoplasmic transfer demonstrating it was the mitochondria of the cell, not the nucleus (DNA) that initiates cancerous growth [31]

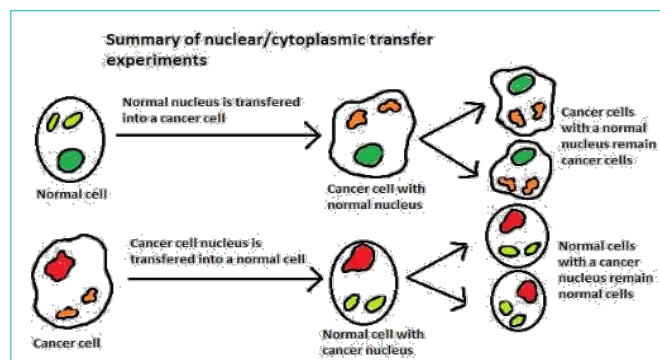


Figure 4: A diagram summarizing a series of experiments conclusively determining that it is the mitochondria, and not nuclear DNA, that causes cancer. A transplanted cancerous nucleus did not initiate cancer in a healthy cell [2].

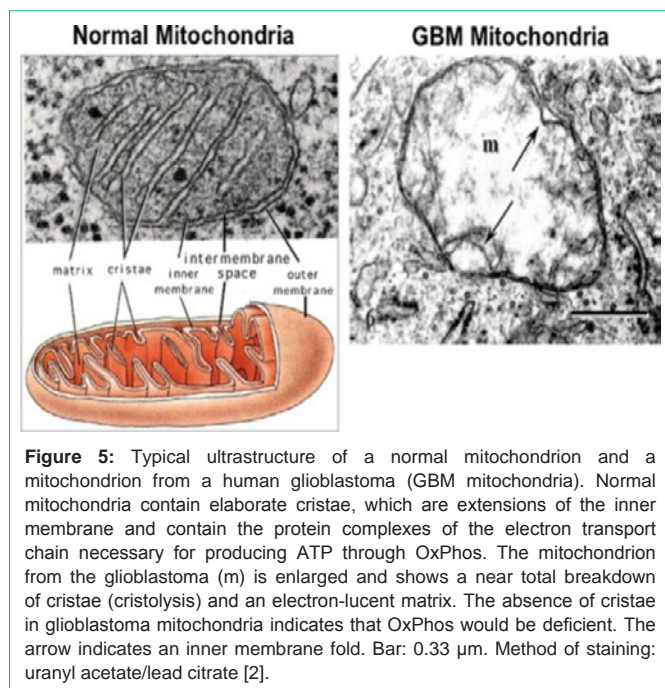
(Figure 4).

In brief, the Israel & Schaefer experiments consisted of transferring the nucleus of a cancer cell into a healthy cell that had its nucleolus removed. The newly created hybrid cell had the genetic material of a cancer cell, with all of its defects, but now had the healthy mitochondria of a normal cell. Intuitively, if the origin of cancer was indeed mutations to DNA, the newly created hybrid cells, that still retained all of the mutations within the nucleus, should be tumorigenic. But they were not; they were perfectly healthy. These experiments were carefully executed, with strict controls, and were found to be very reproducible. The research showed DNA mutations were not driving the cancerous growth; it was the mitochondria [31].

Mitochondriogenesis

All cells produce energy to survive; disturbances in ATP production compromise cell viability. Hans A. Krebs (1937) elucidated the process of energy synthesis, the Citric Acid Cycle (Krebs cycle). Oxidative respiration within the mitochondria provides 87% of the ATP required for an organism to function [2,16,17,21]. Mitochondria require oxygen. The utilization of oxygen by mitochondrial cellular respiration is a pro-survival mechanism.

Nutrition plays a critical role in the process of mitochondriogenesis (creation of new mitochondria); poor nutrition with resulting insulin resistance predisposes tissue to serious and chronic impairment. Metabolic deficits common to insulin resistant states (pre-diabetes or diabetes (T2DM)) dramatically reduce glucose-pyruvate entry into the TCA cycle to synthesize ATP. Chronic upregulation of master glycolytic enzymes, PFKFB3/PDK1, common with starvation signals initiated by insulin resistance (overfed/undernourished), inhibits pyruvate from entering oxidative respiration via the TCA cycle; enzyme inhibition serves as a mechanism of cell survival under scarce fuel supply. As a consequence of impaired mitochondrial functioning and aberrant signaling, diabetics/pre-diabetics depends heavily on the hepatic production of glucose (Cori Cycle). Hyperinsulinemia results in systemic elevations in respiratory quotient (RQ) and metabolic inflexibility preventing beta-oxidation in the fasted state. Metabolic inflexibility initiates inflammation and lipotoxicity, which accumulates more insults to mitochondrial membranes [24]. Likewise, research shows diabetic patients have a deficit of mitochondria that are reduced in size; the children of diabetics have



fewer and smaller mitochondria even if they are not diabetic. Studies suggest a robust genetic predisposition toward mitochondrial defects especially in the ‘pre-diabetic’ state [26,27]. Recent studies in humans confirmed the down-regulation of oxidative mitochondrial enzymes with co-occurring upregulation of glycolytic pathways in obesity and insulin resistance [15,18,22,24,30].

Beta-oxidation as regulator of oncogene expression

Evidence supports long-term calorie restriction and beta-oxidation to reduce plasma glucose, glutamate and insulin levels, thereby signaling hepatic production of ketone bodies as a primary fuel substrate [26,27]. A phenotypic characteristic of cancer is damaged mitochondrion with an absence of cristae; damaged cristae result in chronic, non-oxidative glucose dependency in the tissue with impaired ability to oxidize fatty acids (Figure 5). In contrast, beta-oxidation occurs directly in the TCA cycle of the mitochondria synthesizing ATP for healthy cells. Fat oxidation starves glucose-dependent cells with damaged cristae. In contrast to the relatively simple metabolism of fat, glucose must first be converted in the cytosol to pyruvate by glycolysis before entering the TCA cycle; this is a complicated process. With impairment of metabolic pathways common to insulin resistance, lactate conversion competes with oxidative energy production in the TCA cycle through the synthesis of the glycolytic enzyme PDK1. PDK1 will block pyruvate from entering into the mitochondrial chain of oxidative respiration. Beta-oxidation naturally inhibits this glucose dependency; chronic aerobic glycolysis is thwarted as mitochondrial enzymes (inner membrane and matrix) are synthesized and glycolytic enzymes are down regulated (Figure 5).

A decline in basal insulin is linear to a reduction of dietary CHO. As insulin falls, metabolic flexibility is restored and RQ declines; metabolism naturally fluxes to beta-oxidation via long-chain fatty acid fuel transporters [24]. Fatty acids are metabolized in the liver to the ketone body acetoacetate. Acetoacetate metabolize directly intra-

mitochondrially with conversion to two molecules acetyl-CoA, which enter the TCA cycle directly and signal a fed state (ATP synthesis) to the nucleus. The flux toward beta-oxidation has potentiation to starve cancerous growth by modulating glycolysis. Key oxidative enzymes, cytochrome *c* oxidase (COX), α -ketoglutarate dehydrogenase complex and pyruvate dehydrogenase complex, are synthesized during fat metabolism and naturally inhibit the expression/activation of glycolytic enzymes. In healthy cells, the restoration of oxidative respiration (OXPHOS) via fatty acid metabolism thwarts starvation signaling (ATP deficit) in the HIF-1/mTOR path and activates the AMPK pathway restoring mechanisms of cellular repair and homeostatic regulation; in addition, beta-oxidation has been shown to stimulate mitochondriogenesis, an innately restorative mechanism unique to fat oxidation [24,32,33].

Restoring mitochondrial ATP synthesis and correcting homeostatic signaling via a reduction in systemic RQ, thereby increasing metabolic flexibility in the tissue shows promise in the prevention and treatment of cancer. Induced and controlled dietary ketosis is a proven regulator of metabolic syndrome pathologies, including hyperglycemia and hyperinsulinemia, which contribute to tumor genesis [24,34-37]. Ketogenic metabolic therapy (KMT), as proposed by Winter. et al., has also demonstrated an anti-neoplastic effect in malignant glioma as well as advances in neuro-oncology [38]. In addition, systemic reductions in RQ with restoration of metabolic, substrate flexibility, shows promise to impede neuron degeneration in cerebral hypometabolism, universal to mild cognitive impairment (MCI) and Alzheimer’s disease (AD) [30,39,40]. Restored mitochondrial ATP synthesis inhibits cancer cell growth, increases ATP synthesis/respiratory chain activities and reduces acute nuclear metabolic stress. Altogether, fat metabolism starves cancer.

Benign dietary ketosis with glycolysis inhibitors

On the forefront of metabolic research/treatment of cancer management is “Press-pulse” therapy for the systematic elimination of cancer cells. Seyfried, et al. (2017) use press-pulse therapy to create chronic oxidative stress on tumor cell metabolism while restricting glucose and glutamine availability [15]. Benign dietary ketosis sits as the cornerstone of the specialized treatment, which facilitates the eradication of tumor cells by optimal dosing of glycolysis inhibitors, via the press-pulse protocol. The aforementioned environmental, cellular stress activated by a fat oxidizing, ketogenic diet acts as the “press” disturbance in the cytoplasm. “This energy stress...would be greater in the tumor cells than normal cells due to their dependency on fermentation energy metabolism, mitogens, anabolic signaling (IGF-1, mTOR, etc.), elevated redox stress, and mutational load” [15]. The “pulse” disturbance occurs by dosing specific pharmacological agents that target glucose and glutamine availability to create an acute reduction of tumor-dependent fuel substrates [15]. In essence, the Press-pulse therapy magnifies the natural, anti-tumor effects of a ketogenic diet by amplifying ROS disturbance within in the quasi-stable microenvironment of cancerous tissue, while synthetically restricting glucose and glutamine substrate availability.

Conclusion & Discussion

When cancer is viewed through a metabolic lens rather than a genetic construct, a bioenergetic model of treatment emerges to target mitochondrial dysregulation by reducing/eliminating fermentable

fuel substrates essential to tumor survival. Current research suggests that cancer is a metabolic disease surviving on glucose and glutamine/ glutamate in a non-oxidative environment initiating tumor genesis and promoting proliferation [2,15,16,23,24,30,38]. It has been shown that nutritional protocols used to reduce hyperinsulinemic states will also reduce inflammation in tumor microenvironments by correcting aberrant cell signaling in homeostatic pathways. Ketogenesis represses insulin while mediating hyperglycemia, thus restoring the homeostatic crosstalk between the mitochondria and nucleus by inhibiting 'overfed/undernourished' starvation signals and activating a 'fasted/nourished' state; this modulation is cancer preventative. It is well known that current treatments for hyperglycemia perturb homeostatic signaling and exacerbate hypoglycemia due to elevations in plasma insulin; common diabetic protocols disturb fed/fasted signaling and increase the risk of malignancy [24]. In contrast, homeostatic correction deactivates the reactionary HIF-1/mTOR path, restores oxidative ATP synthesis and epigenetically modulates oncogene expression by inhibiting the expression of MYC and VEGF proteins; fat oxidation starves cancerous growth and proliferation. Ketogenic nutritional research demonstrates the anti-cancer and neuroprotective effect of metabolic fuel substrate flexibility in patients with cancer, diabetes (T2DM), Alzheimer's disease and metabolic syndrome pathologies; the protocol promises robust health benefits without toxic side effects or long-term signal dysregulation. Restoration of metabolic flexibility, in both peripheral and cerebral tissue, is the apex of bioenergetic research on degenerative disease.

Acknowledgement

The author exclusively prepared this review.

Authorship Statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept. There is only one author for this review: Dr. Kelly J. Gibas.

Ethics Committee Approval and Informed Consent

Human subjects were not involved in the review; therefore, ethics committee approval and informed consent were not necessary.

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