Journal of Experimental and Basic Medical Sciences 2022;3(2):90-96

Review

The Warburg Effect on Cancer Formation and Progression

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ABSTRACT

The energy requirements of cell development are met by complete glucose catabolism, which utilizes mitochondrial oxidative phosphorylation to boost adenosine 5'-triphosphate production. While aerobic glycolysis can begin in tumor cells when respiration is compromised, anaerobic glycolysis starts when oxygen is not present. In cancer cells, aerobic glycolysis with oxygen results in enhanced glucose uptake and lactic acid production. The Warburg effect is an abnormal tendency of tumors to produce lactate in an environment with normal oxygen levels. Due to the reputation of early researchers and the lack of more advanced means to examine lactate metabolism, the notion that lactate generation originates from oxygen deprivation has survived. The purpose of this review was to discuss the Warburg effect's mechanism, clinical implications, and diagnostic uses in the context of the literature.

Keywords: Cancer, glucose, lactic acid, Warburg effect

The Warburg effect is a situation in which normal cells require mitochondrial oxidative phosphorylation, whereas malignant cells depend on aerobic glycolysis to produce the energy required for cellular functions. By showing that cultivated tumor tissues exhibit high rates of glucose uptake and lactate release even in the presence of oxygen, Otto Heinrich Warburg initially characterized this effect in 1924. The three factors that make up the Warburg effect are glucose uptake, lactate secretion, and oxygen availability.[1,2]

Most differentiated cells predominantly convert glucose to carbon dioxide when oxygen is present by oxidizing glycolytic pyruvate in the mitochondrial tricarboxylic cycle. The metabolic shift in cancer cells, particularly skin cancer cells, is constituted of enhanced glycolysis, activated anabolic pathways, including the generation of amino acids and pentose phosphate, and increased fatty acid biosynthesis.[3-6]

In this review, we aimed to discuss the effect of Warburg on cancer formation and progression in light of the literature.

LACTATE METABOLISM

High levels of lactic acid were first identified in the muscles of hunted deer in 1780 by Carl Wilhelm Scheele.[7] Since then, the glycolytic pathway and the notion that a lack of oxygen results in fermentation and the formation of lactate have come to be better-understood thanks to Pasteur[8], Meyerhof[9], and A.V. Hill.[10]

The concept that lactate is a waste product that must be eliminated from the muscles and blood-preferably by being converted to glucose in the liver via the *Escherichia coli* cell cycle-was developed as a result of this early research. When there is enough oxygen available, experiments have demonstrated that lactate is a potent fuel and signaling molecule that is often created and circulated in the body.[11] Despite this data, many medical schools continue to wrongly label lactic acid as a "hypoxic waste product."

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Cite this article as: Kılınç G, Sasani H, Erbaş O. The Warburg Effect on Cancer Formation and Progression. JEB Med Sci 2022;3(2):90-96.

doi: 10.5606/jebms.2022.1014

Received : July 15, 2022
Accepted : August 4, 2022
Published online : September 12, 2022

TUMOR METABOLISM

According to a research, axillary veins from chicken wings with sarcomas exhibited lower glucose levels and greater lactate levels than those from limbs without tumors. A similar strategy is used by Warburg et al.[12], who measured the arteriovenous differences between tumor beds in rat tumor models. They found that veins released more lactate and less glucose than arteries, which continuously supplied tumors, indicating that there may have been a net release of lactate in the normoxic tumor bed. The Warburg effect is an aberrant behavior of tumors to create lactate in a normoxic environment. Warburg did not discuss in detail the significance of lactate production and accumulation in cancer; however, later claimed that lactate is the end of glycolysis in cancer. The idea that lactate production results from oxygen deprivation have persisted due to the reputation of early researchers and the absence of more sophisticated techniques to study lactate metabolism.[13–15]

THE WARBURG EFFECT

According to this theory, the Warburg effect is related to poor mitochondrial function and energy metabolism. Contrary to the majority of healthy tissues, Warburg discovered that cancer cells frequently "ferment" glucose into lactate, even when there is enough oxygen present to enable mitochondrial oxidative phosphorylation. In other words, oxygen prevents the fermentation of sugars (the Pasteur effect), identifying glucose to lactate conversion as a predicted reaction to hypoxia. Thus, hypoxia may cause lactate production in cancers and malignancies may be hypoxic. Complete glucose catabolism employing mitochondrial oxidative phosphorylation to increase adenosine 5'-triphosphate (ATP) generation satisfies the energy needs of cell growth.[16–18]

According to theory, a small organelle called the mitochondria creates the majority of the ATP needed by the body. According to Warburg's theory, mitochondria are not fully functioning and their function in cellular respiration is muted. In both aerobic and anaerobic glycolysis, lactic acid is generated. Anaerobic glycolysis develops in the absence of oxygen, whereas aerobic glycolysis can start in tumor cells when respiration is impaired. The presence of oxygen can cause an aberrant Pasteur effect since it usually causes anaerobic glycolysis and lactic acid generation to decrease in most normal cells. Glycolysis, a process that takes the place of breathing, may be a sign of cancer rather than its primary cause. The main source of nicotinamide adenine dinucleotide (NAD+) in hypoxic situations is lactate dehydrogenase, which turns pyruvate into lactate. Tumor cells are particularly prone to this response. In cancer cells, increased glucose absorption and lactic acid generation occur during aerobic glycolysis while oxygen is present. Most cancer cells have excessively expressed glycolysis-related genes.[17,18]

Factors Affecting the Warburg Effect

The high glycolytic rate used to fuel mitochondrial oxidation has a unique relationship to glucose metabolism and rapid cell proliferation (as in cancer cells and non-malignant cells). In contrast to benign carcinomas and normal tissues, aggressive malignancies have notably high levels of glycolysis in aerobic conditions.

Most cells absorb glucose and release some of the carbon back into the culture medium as lactate when growth agents encourage cell growth. In experimental models, glucose deprivation or inhibition of glycolysis frequently harms the proliferation and development of cancer cells.[19,20]

The discovery of the tumor-specific M2 pyruvate kinase (PK)[21] and the connection between tyrosine kinase signals and subsequent phosphorylation in the M2-PK inhibitor complete the metabolic portrait.[22,23]

Glycolysis in Cell Types

Aerobic glycolysis has been found to be more prevalent in testicular and retinal tissue, while respiration was suppressed in embryonic tissue. Additionally, exposure to cyanide and molecular nitrogen causes an increase in glycolysis by irreversibly suppressing respiration.[15,17]

The Warburg effect has an important role, especially in oncological imaging and treatment. In order to characterize lesions and separate disorders from one another, a variety of diagnostic techniques, particularly in MRS, are utilized in the diagnosis.

DIAGNOSTIC MODALITIES

Positron emission tomography: Aggressive cancer cells consume large amounts of glucose about 20–30 fold compared to normal cells and glucose fermentation is linked to aggressiveness in cancers. Metabolic profiling using the labeled substrate has shown that the carbon atoms of glucose predominantly occur in lactate, fatty acids, and nucleic acid-associated

ribose, reflecting both the high proliferation rate and the reduction of oxidative phosphorylation in aggressive cancer cells. Also, metabolic profiling revealed a progressive loss of respiration and an accompanying dependence on glycolysis for cell growth.[24,25] It is diagnostically exploited by the utilization of [18F]-fluoro-2-deoxyglucose positron emission tomography (FDG-PET).[26]

Magnetic resonance spectroscopy (MRS): The concept of nuclear magnetic resonance (NMR) spectroscopy, which makes use of radiofrequency waves to reveal information about magnetic nuclei (such as 1H, 31P, 13C, and 15N) in a magnetic field of a certain power, was first proposed in 1921. The nuclei start to resonate shortly after absorption, and during this process, the various atoms in a molecule vibrate at various frequencies. For kinetic and structural research on a variety of materials, including solids, liquids, and gases, NMR has been utilized. It is just one of many spectroscopic techniques that are used frequently in biology.[27–30]

The *in vivo* biochemical data provided by MRS includes the peaks on the spectra that correlate with different metabolites. On two-way axes, proton spectra are shown. The vertical (y) axis shows signal amplitude or concentrations, while the horizontal (x) axis displays the frequency chemical shift of the different metabolites (in parts per million, or ppm). The reading of a spectrum is from right to left. Depending on the echo time (TE), metabolites can be detected using proton MRS. Two kinds of spatial localization methods for MR spectroscopy exist (single-voxel and multi-voxel techniques).[31]

At 1.5 Tesla magnetic resonance imaging (MRI) scanner:

• Metabolites can be seen using intermediate to long TE (144-288ms): N-acetylaspartate (NAA), choline (Cho), creatine (Cr), and possibly alanine (Ala), and lactate (Lac).

• Metabolites can be seen using short echo-time acquisitions (TE<40 ms): Myo-inositol (Myo), glutamate and glutamine (Glx), glucose (Gc), some macromolecular proteins, and lipids.[32,33]

Lactate levels rise markedly in situations where anaerobic glycolysis takes control instead of aerobic oxidation, such as brain ischemia, hypoxia, convulsions, metabolic abnormalities, and when macrophages accumulate in the site of acute inflammation and it can accumulate in tissues with poor washouts such as cysts, necrotic tumors, and tumors with cysts, normal pressure hydrocephalus. It is detected at MRS as a doublet (twin peak) at 1.33 ppm. Variable projection of the peak at various TEs defines lactate. The doublet peak projects above the baseline for very short or very long TEs (30 or 288 ms), however, it is inverted below the baseline on acquisitions using intermediate TEs (135/144 ms).[32-37]

Diagnostic Applications

Mitochondrial disease: Production of ATP is hampered. Low ATP causes glycolysis to be upregulated, which causes an excess of pyruvate to be either transaminated to alanine or decreased to create lactate. The widespread consensus is that venous lactate acidosis, lactic acidosis, or high lactate is a clinically significant signal of mitochondrial dysfunction. Even in the context of normal venous lactate values, cerebrospinal fluid (CSF) lactate levels might be increased. Therefore, in patients with neurological symptoms, CSF lactate levels may be a more accurate diagnostic indicator of a mitochondrial problem than venous lactate. In both cerebral white and gray matter, the two most noticeable MRS signal abnormalities seen in mitochondrial diseases are NAA decrease and lactate deposition. Even in the absence of systemic lactic acidosis, patients with mitochondrial dysfunction show elevated lactate levels in their brain tissue. MRS lactate and Lac/Cr are increased in children with mitochondrial disease. Atrophy of the cerebrum is a frequent symptom as mitochondrial disease manifests in both childhood and adulthood. Leigh syndrome (subacute necrotizing encephalomyelopathy), the prototypical mitochondrial condition, is characterized by focal, bilateral, symmetric brain lesions affecting the basal ganglia and periaqueductal gray matter. It can also include vomiting, stiffness, brainstem dysfunction, dystonia, aberrant eye movements, and numerous organ involvements. Pathologically speaking, these focal brain lesions are necrotic and linked to demyelination, vascular growth, and gliosis. While bilateral lesions in the putamen and basal ganglia nuclei are the most common symptoms of some mitochondrial syndromes, other forms of the mitochondrial disorder may only affect one subregion of the basal ganglia, such as the globus pallidus or the substantia nigra and medulla with relative basal ganglia preservation.[38-47]

Neoplasia-tumors: Nearly all brain tumors have diminished NAA signals, as well as frequently elevated levels of Cho, which results in elevated Cho/NAA ratios. Given that NAA is thought to be predominantly of neuronal and axonal origin, the

reduction in NAA is frequently interpreted as the loss, malfunction, or displacement of normal neural tissue.[31] Rapid amounts of Cho are frequently seen in regions with high cellular membrane turnover and substantially increased relative cerebral blood volume (rCBV) indicating tumor neovascularization, even if brain biopsy remains the gold standard. According to a meta-analysis, tumor recurrence was associated with considerably higher average Cho/Cr and Cho/NAA ratios than radiation damage.[48–52]

Radiation necrosis: A variety of variables, including the total radiation dosage, the size of the radiation field and radiation fraction, the quantity and frequency of radiation doses, the combination of chemotherapy and radiation therapy, the length of survival, and the patient's age at the time of treatment, influence the course of the therapy. There are three phases of radiation injury: acute, early-delayed, and late-delayed. There have also been suggestions of effects on the immune system and fibrinolytic enzyme system. It has been demonstrated that oligodendrocytes are extremely susceptible to radiation. However, neurons are less sensitive. Early alterations in metabolic activity before the onset of neurocognitive symptoms or anatomic abnormalities visible on conventional MRI can be used to predict the structural deterioration in brain tissue after radiation treatment. It has been hypothesized that significant changes in brain metabolites, particularly a reduction in NAA, a neuronal marker, are caused by neuronal injuries, such as neuronal cell death from apoptosis or neuronal malfunction related to radiation exposure. In a study, it was found that the choline/creatine and Cho/NAA ratios were both significantly greater in radiation injury than in normal-appearing white matter, whereas the NAA/Cr ratios were significantly lower in radiation injury than in normal-appearing white matter.[53]

Additionally, in cases of radiation necrosis, a strong lipid-dominant peak, together with a low Cho peak and a low NAA peak, was seen from the center nonenhanced region. For the diagnosis of radiation necrosis, the positive predictive values of a Cho/Lipid or Lac ratio of 0.3 and a Cho/Cr 2.48 were 100% and 71.4%, respectively. A broad peak between 0 and 2 ppm in radiation necrosis may be visible, which is likely caused by cellular debris that contains amino acids, lactate, and fatty acids.[54-64]

THE WARBURG EFFECT ON NEURODEGENERATIVE DISORDERS

Glucose is the only energy source used by the brain, which has a high need for energy metabolism. Decreased energy metabolism and glucose uptake in the brain are observed in neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS).[65–68] Despite the variety, experimental and clinical research has demonstrated that metabolic abnormalities are prevalent in a wide range of neurodegenerative disorders.[69] Since tumors have many ancestries and genomic instability, cancer cells are similar genetically and phenotypically diverse.[70] Tumors, such as glioblastoma, ingest more glucose and rely on aerobic glycolysis for energy metabolism. The Warburg effect offers macromolecules for biosynthesis and growth when oxidative phosphorylation is switched to a less effective aerobic glycolytic route. There is a common misconception that cancer and neurodegeneration are two separate clinical conditions with completely different etiologies and treatment options. The hallmark of neurodegenerative disorders is progressive early neuronal death, whereas cancer is defined by greater resistance to cell death.[71] Cancer has been proven to have an inverse relationship with neurological disorders including AD.[72,73] However, there is increasing data that suggests cancer and neurodegenerative disorders may have similar pathogenic processes and treatment targets. Age is the main risk factor for both cancer and dementia.[74] Dietary restriction has been proven to be one of the best treatments for extending the life and preventing age-related disorders, including cancer and neurological disorders.[75–78] Cancer and neurodegenerative disorders can both be effectively treated with a wide variety of medications. For instance, it has been demonstrated that the retinoid X receptor agonist bexarotene, which is used to treat T-cell lymphoma, decreases amyloid beta (Aβ) plaques and improves cognitive impairments in AD models.[79–81]

USE IN TREATMENT

The effects of carbohydrate metabolism inhibitors on tumorigenesis are extremely potent.[82–84]

Methylene blue, a long-used medication, may be able to absorb electrons from NADH in the presence of complex I and give them to cytochrome C, thus offering a different route for electron transport.

In vitro, methylene blue improves glucose absorption while decreasing glycolysis and increasing oxygen consumption. Following acute therapy, methylene blue enhances rats' regional cerebral blood flow and glucose absorption. Additionally, *in vitro* and in rat models of AD, PD, and HD, methylene blue protects neurons and astrocytes from a variety of stresses. Methylene blue promotes mitochondrial oxidative phosphorylation, stops the glioma cell cycle in the S phase, and reduces glioma cell growth in glioblastoma cells to reverse the Warburg effect. Therefore, methylene blue inhibits downstream acetyl-CoA carboxylase and cyclin-dependent kinases while activating AMP-activated protein kinase. Mounting data shows that increased mitochondrial oxidative phosphorylation via alternate mitochondrial electron transport may have protective benefits against neurodegenerative disorders and slow the spread of cancer.[71]

In conclusion, energy metabolism and mitochondrial dysfunction are linked to the Warburg effect. Lactate generation and buildup are important factors in the complex sequence of genetic and metabolic processes that lead to carcinogenesis. In particular, aberrant cell signaling brought on by excessively and chronically high lactate levels during carcinogenesis increases glucose uptake and glycolysis, boosts lactate generation, accumulation, and release, and affects mitochondrial function. It is believed to lead to an unsuitable positive feedback loop that the upregulation of angiogenesis, immune evasion, cell migration, and metastatic support due to the expression of monocarboxylic acid transporters contributes to oncogenesis and the development of cancer.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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