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Review Article

Warburg Effect in Oncology

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Abstract: The Warburg effect, defined by cancer cells' preference for aerobic glycolysis over mitochondrial oxidative phosphorylation for energy production, has been a central topic in cancer research since its identification in 1924. This process involves elevated glucose uptake and lactate production, even in the presence of oxygen, supporting rapid cell proliferation, immune evasion, and promoting angiogenesis and metastasis. In this review, we examine the molecular mechanisms underlying the Warburg effect, focusing on its impact on cancer progression and neurodegenerative disorders. High lactate levels play a critical role in metabolic reprogramming, contributing to tumor growth and survival. Diagnostic tools such as positron emission tomography (PET) and magnetic resonance spectroscopy (MRS) demonstrate increased glycolytic activity in aggressive cancers, while metabolic profiling provides deeper insights into cancer development. Mitochondrial dysfunction serves as a key link between cancer and neurodegenerative diseases, revealing shared metabolic pathways between these conditions. This review also explores the therapeutic potential of methylene blue, a long-established drug, in altering energy metabolism via mitochondrial pathways, offering promise for both cancer treatment and neuroprotection in conditions like Alzheimer's and Parkinson's diseases.

Keywords: Lactate metabolism, Diagnostic modalities, Diagnostic Applications, Neoplasia-cancers, Warburg Effect on Neurodegenerative Disorders.

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1. INTRODUCTION

The Warburg effect describes a metabolic shift in cancer cells where they favor aerobic glycolysis over mitochondrial oxidative phosphorylation for energy production. This phenomenon, first identified by Otto Heinrich Warburg in 1924, reveals that cancer cells exhibit increased glucose uptake and lactate production even when oxygen is present[1]. This metabolic reprogramming allows malignant cells to rapidly generate energy and biosynthetic precursors necessary for their high proliferation rates. In normal cells, glucose is primarily metabolized via oxidative phosphorylation in the mitochondria, where pyruvate from glycolysis is converted into carbon dioxide, producing a large amount of ATP. However, cancer cells divert pyruvate from the mitochondria to lactate production, a process known as aerobic glycolysis. This shift occurs despite the presence of oxygen and results in lower ATP production, but provides several advantages to cancer cells[2]. Initially, glycolysis is a faster process than oxidative phosphorylation, meeting the immediate energy demands of rapidly growing tumor cells. This metabolic pathway produces intermediates required for anabolic processes, including nucleotide, amino acid, and fatty acid synthesis, which are crucial for cell growth and proliferation[3]. The pentose phosphate pathway (PPP), a branch of glycolysis, further supports tumor growth by generating ribose-5-phosphate for nucleotide synthesis and NADPH for lipid synthesis and oxidative stress protection[4]. The increased lactate production associated with the Warburg effect contributes to a tumor-friendly microenvironment. Elevated lactate levels lower the pH of the surrounding tissue, which can inhibit immune cell function and promote immune evasion, aiding in tumor survival. This acidic environment also supports angiogenesis, the formation of new blood vessels, which is vital for tumor growth and metastasis[5]. The Warburg effect allows cancer cells to survive and proliferate in hypoxic conditions where oxygen is limited, thus providing a metabolic flexibility that supports growth in diverse and often hostile environments. The metabolic alterations observed in cancer cells extend beyond energy production. The Warburg effect is often accompanied by increased activity in other anabolic pathways, including the pentose phosphate pathway, amino acid synthesis, and fatty acid metabolism[6]. These pathways provide essential building blocks for rapidly dividing cells, further enhancing tumor growth and progression. Recent studies have linked the Warburg effect to genetic mutations in oncogenes and tumor suppressor genes. For example, MYC upregulates glycolytic enzymes and glutamine metabolism, while mutations in TP53 can impair mitochondrial function and drive glycolysis[7]. These genetic changes contribute to the sustained proliferation and survival of cancer cells by reinforcing their reliance on glycolysis[8]. This review aims to examine the impact of the Warburg effect on cancer growth and progression, drawing insights from current literature. By elucidating the molecular mechanisms underlying this metabolic shift, new therapeutic strategies can be developed to target the unique metabolic dependencies of cancer cells. The review also explores the Warburg effect influence on the tumor microenvironment, contributing to processes such as angiogenesis, immune evasion, and metastasis, and will consider its broader implications in other diseases, including neurodegenerative disorders.

2. LACTATE METABOLISM

Elevated concentrations of lactic acid were initially discovered in the musculature of deer in 1780 by Carl Wilhelm Scheele[9]. Since then, the glycolytic route and the concept that oxygen deficiency leads to fermentation and lactate production have been elucidated, owing to the contributions of Pasteur, Meyerhof, and A.V. Elevation. The notion that lactate is a by-product requiring removal from muscles and blood ideally by conversion to glucose in the liver via the Escherichia coli cell cycle emerged from this preliminary study. When sufficient oxygen is present, investigations have shown that lactate serves as an effective fuel and signalling molecule often produced and distributed across the body.

3. THE WARBURG EFFECT'S ROLE IN CANCER DEVELOPMENT AND ADVANCEMENT

According to studies, axillary veins from chicken wings with sarcomas demonstrated reduced glucose levels and elevated lactate levels compared to those from limbs devoid of tumors. A comparable approach is employed by Warburg et al., who assessed the arteriovenous variations in tumor beds within rat tumor models[10]. It was shown that veins discharged a greater quantity of lactate and a lesser amount of glucose compared to arteries, which consistently fed tumors, suggesting a net release of lactate in the normoxic tumor microenvironment. The Warburg effect is an atypical trait of cancers to generate lactate in a normoxic setting[11]. Warburg did not expound on the significance of lactate production and accumulation in cancer; nonetheless, he subsequently claimed that lactate is the ultimate product of glycolysis in malignant cells. The belief that lactate production results from oxygen deficiency has persisted due to the early investigators and the absence of sophisticated techniques to examine lactate metabolism. The Warburg effect, according to this idea, is linked to impaired mitochondrial function and energy metabolism. Warburg observed that, unlike most healthy tissues, cancer cells frequently "ferment" glucose into lactate, even when ample oxygen is available for mitochondrial oxidative phosphorylation. Oxygen suppresses carbohydrate fermentation (the Pasteur effect), signifying that the transformation of glucose to lactate is a predictable reaction to hypoxia[12]. Consequently, hypoxia may induce lactate production in tumors, and malignancies may exhibit hypoxic conditions. The complete breakdown of glucose by mitochondrial oxidative phosphorylation enhances adenosine 5'-triphosphate (ATP) production, fulfilling the energy requirements for cellular development[13]. According to hypothesis, the mitochondria produces the bulk of the ATP required by the body. Warburg's theory posits that mitochondria are not completely operational and their role in cellular respiration is diminished. Lactic acid is produced in both aerobic and anaerobic glycolysis. Anaerobic glycolysis occurs in the absence of oxygen, but aerobic glycolysis can initiate in tumor cells when respiration is compromised. The presence of oxygen can induce an anomalous pasteur effect, as it typically reduces anaerobic glycolysis and lactic acid production in most normal cells. Glycolysis, a mechanism that substitutes for respiration, may indicate cancer rather than serve as its major causative factor. The primary source of nicotinamide adenine dinucleotide (NAD+) under hypoxic conditions is lactate dehydrogenase, which converts pyruvate into lactate[14]. Tumor cells are especially susceptible to this

reaction. Cancer cells exhibit increaed glucose uptake and lactic acid production during aerobic glycolysis in the presence of oxygen. Most cancer cells exhibit overexpression of glycolysis-related genes.

4. FACTORS INFLUENCING THE WARBURG EFFECT

The elevated glycolytic rate that supports mitochondrial oxidation has a distinct correlation with glucose metabolism and accelerated cellular proliferation, as shown in both cancerous and non-cancerous cells. In contrast to benign carcinomas and normal tissues, aggressive malignancies have significantly elevated levels of glycolysis in aerobic circumstances[15]. Most cells assimilate glucose and excrete a portion of the carbon into the culture medium as lactate when growth factors stimulate cellular proliferation. In experimental models, glucose restriction or glycolysis suppression often impairs the proliferation and growth of cancer cells. The identification of the tumor-specific M2 pyruvate kinase (PK) and the association between tyrosine kinase signals and subsequent phosphorylation in the M2-PK inhibitor results in the metabolic profile[16]. Aerobic glycolysis is more abundant in testicular and retinal tissues, whereas respiration is reduced in embryonic tissue. Furthermore, exposure to cyanide and molecular nitrogen enhances glycolysis by permanently inhibiting respiration. The Warburg effect plays a significant role, particularly in oncological imaging and therapy. To describe lesions and differentiate pathologies, many diagnostic tools, notably in MRS, are employed in the diagnosis.

5. DIAGNOSTIC MODALITIES

Positron emission tomography (PET) reveals that, aggressive cancer cells metabolize glucose at a rate 20–30 times greater than that of normal cells, with glucose fermentation correlating with cancer aggressiveness[17]. Metabolic profiling utilizing labeled substrates has demonstrated that, the carbon atoms of glucose primarily manifest in lactate, fatty acids, and ribose associated with nucleic acids, indicating both increased proliferation rate and a diminished oxidative phosphorylation in aggressive cancer cells. Metabolic profiling indicates a gradual decline in respiration and a corresponding reliance on glycolysis for cellular proliferation. It is diagnostically utilized by the application of [18F]-fluoro-2-deoxyglucose positron emission tomography (FDG-PET)[18]. Magnetic resonance spectroscopy (MRS) is based on the principle of nuclear magnetic resonance (NMR) spectroscopy, which utilizes radiofrequency waves to obtain information about magnetic nuclei (such as 1H, 31P, 13C, and 15N) within a magnetic field of specific strength, a concept first introduced in 1921. The nuclei begin to resonate quickly after absorption, causing the different atoms in a molecule to vibrate at distinct frequencies. NMR has been employed for kinetic and structural investigations of several materials, including solids, liquids, and gases[19]. It is only one of the spectroscopic methods often employed in biology. The *invivo* biochemical data obtained by MRS comprises spectral peaks that correspond to several metabolites. Proton spectra are displayed on a two-dimensional graph, with the vertical (y) axis representing signal amplitude or metabolite concentrations and the horizontal (x) axis showing the chemical shift frequency of different metabolites, measured in parts per million (ppm). The spectrum is read from right to left. Metabolite detection via proton MRS depends on the echo time (TE)[20]. MR spectroscopy uses two spatial localization methods: single-voxel and multi-voxel techniques. With a 1.5 Tesla MRI scanner:

- Metabolites like N-acetylaspartate (NAA), choline (Cho), creatine (Cr), and potentially alanine (Ala) and lactate (Lac) can be detected using intermediate to long echo times (TE 144-288 ms).
- Short echo times (TE < 40 ms) reveal Myo-inositol (Myo), glutamate and glutamine (Glx), glucose (Gc), some proteins, and lipids.

Lactate levels rise when anaerobic glycolysis overtakes aerobic metabolism, such as in brain ischemia, hypoxia, seizures, metabolic disorders, and during macrophage activity at inflammatory sites. Lactate may accumulate in tissues with reduced clearance, such as cysts, necrotic tumors, tumor cysts, and in normal pressure hydrocephalus. In MRS, lactate appears as a doublet at 1.33 ppm. The peak behavior at different TEs distinguishes lactate, with the doublet rising above the baseline at very short or long echo times (30 or 288 ms) and inverting below the baseline at moderate echo times (135/144 ms)[21].

6. DIAGNOSTIC APPLICATIONS

Mitochondrial illness impairs generation of ATP. Lower ATP levels cause glycolysis to be upregulated, which accumulates pyruvate either reduced to create lactate or transaminated to alanine. Venous lactate acidosis, lactic acidosis, or raised lactate levels are generally agreed upon to be clinically significant markers of mitochondrial dysfunction. Cerebrospinal fluid (CSF) lactate levels may be raised even with acceptable venous lactate readings[22]. Therefore, in those with neurological symptoms, CSF lactate levels might be a more accurate diagnostic indication for mitochondrial failure than venous lactate levels. In both cerebral white and gray matter, the most notable MRS signal abnormalities seen in mitochondrial diseases are a decrease in NAA and lactate buildup. Even without systematic lactic acidosis, patients with mitochondrial dysfunction have increased lactate levels in their brain tissue. Children with mitochondrial disease had increased levels of MRS lactate and Lac/Cr[23]. cerebral atrophy is a feature of mitochondrial illness and commonly occur in both childhood and adulthood. Leigh disease, a classic mitochondrial disorder (subacute necrotizing encephalomyelopathy), is characterized by isolated, symmetrical brain lesions in the basal ganglia and periaqueductal gray matter. Symptoms may include vomiting, rigidity, brainstem dysfunction, dystonia, abnormal eye movements, and involvement of other organs. These brain lesions show necrosis, gliosis, vascular proliferation, and demyelination. In some mitochondrial syndromes, the primary feature is bilateral lesions in the putamen and basal ganglia nuclei, while maintaining the overall structure of the basal ganglia[24]. Other variants of mitochondrial diseases may selectively affect specific regions, such as the globus pallidus, substantia nigra, or medulla. MRI often reveals hyperintense signals on T2-weighted images in these regions[25]. Other variants of mitochondrial diseases may selectively affect specific areas, such as the globus pallidus, substantia nigra, or medulla, each presenting distinct imaging patterns that aid in differential diagnosis. Identifying these characteristic lesions is crucial for accurately diagnosing and distinguishing mitochondrial disorders from other neurodegenerative conditions.

7. NEOPLASIA-CANCERS

Most brain cancers exhibit reduced NAA signals and frequently elevated Cho levels, leading to increased Cho/NAA ratios[26]. Since NAA is primarily associated with neuronal and axonal activity, its decline due to cancer is often interpreted as the loss, dysfunction, or displacement of healthy brain tissue. Elevated Cho levels are typically found in areas of high cellular membrane turnover and significantly increased relative cerebral blood volume (rCBV), indicating tumor-driven neovascularization, though brain biopsy remains the definitive diagnostic method. A meta-analysis showed that tumor recurrence is linked to higher Cho/Cr and Cho/NAA ratios compared to radiation damage. Several factors influence radiation necrosis, including the total radiation dose, the size and fractionation of the radiation field, radiation dose timing and frequency, the combination of chemotherapy and radiation therapy, survival time, and the patient's age at treatment initiation. Radiation damage progresses through three phases: acute, early-delayed, and late-delayed[27]. Oligodendrocytes are particularly vulnerable to radiation, while neurons exhibit lower sensitivity. Metabolic changes before the appearance of neurocognitive symptoms or structural changes on standard MRI could signal early brain tissue deterioration following radiation therapy. Significant changes in brain metabolites, especially a decrease in NAA, a marker of neuronal health, are thought to result from neuronal injury or death due to apoptosis or dysfunction caused by radiation exposure. Research has shown that the choline/creatine and Cho/NAA ratios were significantly higher in radiation-induced damage compared to normal-appearing white matter, while the NAA/Cr ratios were significantly lower in radiation-damaged areas[28]. In cases of radiation necrosis, a distinct lipid-dominant peak, along with reduced Cho and NAA peaks, was observed in the non-enhanced central region.

8. THE WARBURG EFFECT ON NEURODEGENERATIVE DISORDERS

Glucose functions as the only energy substrate for the brain, which has a substantial requirement for energy metabolism. Decreased energy metabolism and glucose uptake in the brain are apparent in neurodegenerative disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS)[29]. Experimental and clinical research have demonstrated that metabolic issues are prevalent in several neurodegenerative disorders. Owing to their many ancestries and genomic instability, tumors have genetic commonalities, whereas cancer cells exhibit phenotypic variety. Tumors, such as glioblastoma, exhibit increased glucose use and rely on aerobic glycolysis for energy consumption. The Warburg effect supplies macromolecules for biosynthesis and growth when oxidative phosphorylation is substituted by a less effective aerobic glycolytic route. A common misconception is that cancer and neurodegeneration are separate clinical conditions with completely different causes and treatment approaches. Neurodegenerative diseases are marked by progressive neuronal death, whereas cancer is defined by enhanced resistance to apoptosis. Cancer has been shown to have an inverse relationship with neurological disorders, such as Alzheimer's disease. Recent data suggests that cancer and neurodegenerative diseases may have similar pathogenic pathways and treatment alternatives. Age constitutes the principal risk factor for both cancer and dementia[30]. Dietary restriction has been shown to be one of the most effective methods for extending lifespan and mitigating age-related diseases, such as cancer and neurological disorders. Cancer and neurological diseases can be effectively controlled with a variety of medications. Research indicates that the retinoid X receptor agonist bexarotene, employed in T-cell lymphoma therapy, diminishes amyloid beta (Aβ) plaques and improves cognitive impairments in Alzheimer's disease models[31]. The influence of carbohydrate metabolism inhibitors on cancer is considerable. Methylene blue facilitate the electron transfer from NADH to cytochrome C in the presence of complex I, providing an alternative pathway for electron transport[32]. According to the Journal of Experimental Biology and Medical Science, methylene blue enhances glucose uptake, reduces glycolysis, and boosts oxygen consumption in vitro. Following short-term treatment with methylene blue, it increases regional cerebral blood flow and glucose uptake in rats[33]. Methylene blue protects neurons and astrocytes from various stressors. Methylene blue also enhances mitochondrial oxidative phosphorylation, halts the glioma cell cycle in the S phase, and decreases glioma cell growth in glioblastoma cells, thereby countering the Warburg effect[34]. It inhibits downstream targets like acetyl CoA carboxylase and cyclin-dependent kinases while activating AMP-activated protein kinase[35]. Enhancing mitochondrial oxidative phosphorylation through alternative electron transport pathways may offer neuroprotective effects and slow cancer progression. In summary, energy metabolism and mitochondrial dysfunction are central to the Warburg effect. The synthesis and accumulation of lactate play pivotal roles in the intricate genetic and metabolic processes leading to cancer. Persistently, high lactate levels during carcinogenesis trigger abnormal cell signaling, which increases glucose uptake and glycolysis, promotes lactate production and release, and impairs mitochondrial function. This results in enhanced angiogenesis, immune evasion, cell migration, and metastatic potential, all driven by the overexpression of monocarboxylate transporters, creating a feedback loop that supports cancer development and progression(fig 1).

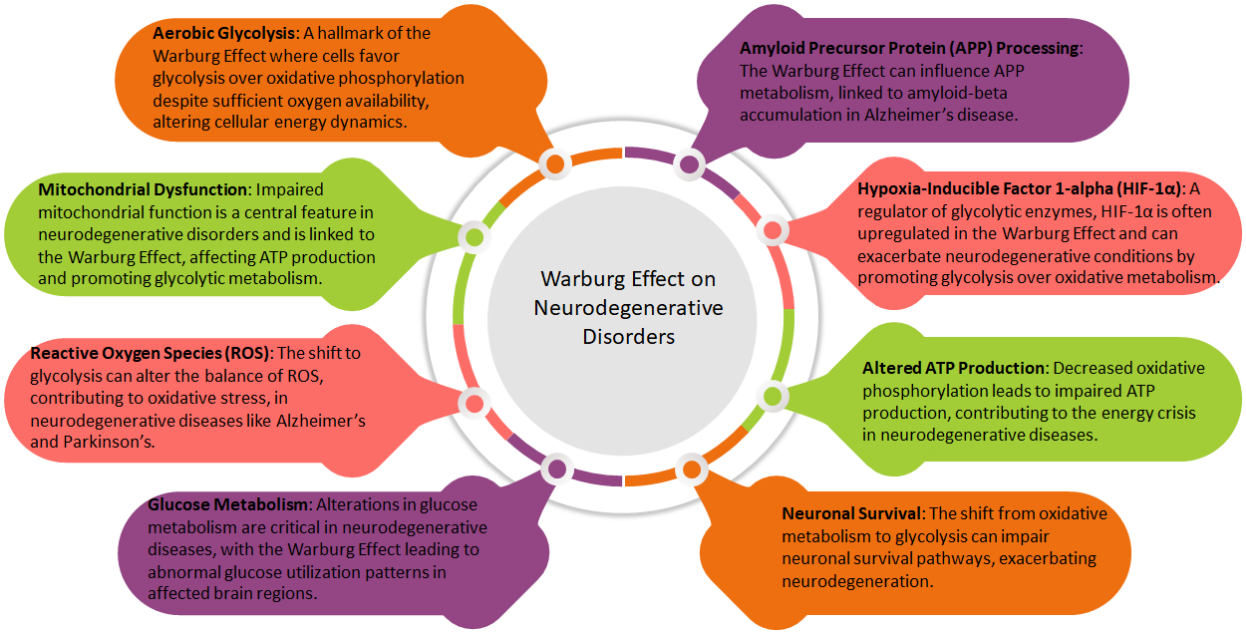

Fig 1: Warburg Effect on Neurodegenerative Disorders

9. CONCLUSION

The Warburg effect represents cancer metabolism, where a reliance on glycolysis over oxidative phosphorylation sustains cancer cell survival and growth. Elevated glucose uptake and lactate production, even under normoxic conditions, support a favorable tumor microenvironment by enhancing angiogenesis, metastasis, and immune evasion. The persistence of this metabolic alteration drives oncogenesis through the overexpression of key glycolysis-related genes and the accumulation of lactate, which further disrupts normal cellular signaling. Mitochondrial dysfunction is at the core of this metabolic reprogramming, linking cancer to neurodegenerative diseases through shared metabolic and cellular pathways. Advances in diagnostic imaging and therapeutic interventions, particularly those targeting mitochondrial oxidative phosphorylation, hold promise in curbing cancer progression and offering neuroprotective effects in conditions like Alzheimer's and Parkinson's diseases. Methylene blue, through its ability to enhance mitochondrial function, emerges as a potential therapeutic agent that could influence both cancer and neurodegenerative disease outcomes by mitigating the Warburg effect and restoring metabolic balance.

10. AUTHORS CONTRIBUTION STATEMENT

Dr. T. Shehnaz Begum, Prof Dr. Ammar A. Razzak Mahmood and Dr. Vanitha Innocent Rani wrote the initial draft. Maya Prabhakaran Pillai V, Amutha Chellathurai , Dr. John Abraham and Dr. Somenath Ghosh contributed to critical revision and supervision. All authors reviewed the manuscript.

11. CONFLICT OF INTEREST

Conflict of interest declared none.

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