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[Perspective] Glucolipotoxicity: A Novel Different Perspective on the Causes of Cancer

Maher Akl[1], Amr Ahmed[2]

1 Mansoura University
2 Ministry of Health Saudi Arabia

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Abstract

The Warburg effect, characterized by increased glucose uptake and lactate production in cancer cells even in the presence of oxygen, has long been recognized as a hallmark of cancer metabolism. This metabolic alteration provides cancer cells with a growth advantage, facilitating their rapid proliferation. The underlying mechanisms driving the Warburg effect involve dysregulated glucose metabolism, upregulation of glucose transporters, and metabolic reprogramming favoring glycolysis. The resulting accumulation of metabolic intermediates, such as lactate, contributes to the acidic tumor microenvironment, promoting tumor progression. However, a novel perspective proposed by Maher Akl suggests that dysregulated glycolipid metabolism, particularly the accumulation of glycolipids within cells, plays a pivotal role in tumor development.

This glucolipotoxicity hypothesis offers a broader understanding of the primary causes of cancer, emphasizing the interference of accumulated glycolipids with cellular processes and the activation of oncogenic pathways. In this abstract, we summarize the mechanisms underlying the Warburg effect and glucolipotoxicity, highlighting their implications for tumor growth. Understanding these paradoxical conditions that activate tumor growth provides insights for the development of innovative therapeutic strategies targeting the primary cause of cancer.

Maher Monir. Akl[a,*]

Department of Chemistry, Faculty of Science, Mansoura University, 35516, Mansoura, Egypt.

ORCID iD: 0000-0001-5480-1688

Amr Ahmed[b]

The public health department, Riyadh First Health Cluster, Ministry of Health, Saudia Arabia.

ORCID iD: 0000-0003-3477-236X

[*]**Corresponding Author:**

Maher Monir. Akl

Department of Chemistry, Faculty of Science, Mansoura University, 35516, Mansoura, Egypt.

Phone: +201020432031

E-mail: maherakl555@gmail.com
ORCID iD: 0000-0001-5480-1688

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1. *Introduction*

Cancer, a devastating disease characterized by uncontrolled cell growth and invasion, continues to pose a significant challenge in the field of medicine. Understanding the underlying mechanisms that drive tumor development is crucial for the development of effective therapeutic strategies. [1] One such mechanism that has garnered considerable attention is the Warburg effect, named after Otto Warburg, a Nobel laureate who first described the altered metabolic phenotype of cancer cells. The Warburg effect refers to the phenomenon wherein cancer cells exhibit increased glucose uptake and lactate production, even in the presence of oxygen. This metabolic switch, favoring glycolysis over oxidative phosphorylation, has long been recognized as a hallmark of cancer. While cancer cells possess the ability to generate energy through the more efficient process of oxidative phosphorylation, they predominantly rely on glycolysis for their energy needs. [2] The paradoxical nature of the Warburg effect has intrigued researchers for decades. Why would cancer cells choose a less efficient energy production pathway, especially when oxygen is readily available? This question has led to numerous investigations into the molecular and cellular mechanisms that underlie the Warburg effect and its implications for tumor development. [3]

One proposed explanation for the Glucolipotoxicity effect [4] is the temporary closure of glucose transporters on cancer cell membranes. This closure is believed to be a result excess accumulation of glycolipids disrupts cellular homeostasis. [5] The closure of glucose transporters temporarily halts glucose uptake, allowing the cell to metabolize the excess glucose before resuming normal glucose uptake.[6][7][8] During this metabolic adaptation, cancer cells engage in anaerobic glycolysis, breaking down glucose into lactate even in the presence of oxygen. This metabolic shift leads to the production of lactic acid, creating an acidic microenvironment within the tumor. The acidic conditions not only promote tumor growth but also contribute to immune suppression, angiogenesis, and invasive behavior. [9] While Otto Warburg's work focused on the metabolic alterations associated with the Warburg effect [10], a more comprehensive perspective has been proposed by Maher Akl. Akl's theory suggests that the dysregulation of glycolipid metabolism, specifically the accumulation of glycolipids within cells, is the primary driver of tumor growth.

This perspective expands upon Warburg's findings and emphasizes the role of glycolipotoxicity in cancer developmentIn this comprehensive exploration, we will delve into the mechanisms underlying the Warburg effect and the dysregulation of glycolipid metabolism. By understanding these processes, we can gain insights into the primary causes of cancer and

potentially identify novel therapeutic targets. This Perspective aims to contribute to the growing body of knowledge surrounding tumor development and provide a foundation for further research in the field.

2. *Glucolipotoxicity*

Glucolipotoxicity is a phenomenon that involves the toxic effects of elevated levels of glycolipids within cells. This condition arises due to an imbalance or dysregulation in lipid metabolism, particularly in the synthesis and degradation of glycolipids. Glycolipids are a class of lipids composed of a carbohydrate moiety linked to a lipid tail, and they play crucial roles in various cellular processes. [11] The occurrence of glucolipotoxicity can be attributed to multiple factors. One contributing factor is the excessive influx of glucose into cells, which leads to the overproduction of glycolipids. This increased synthesis overwhelms the capacity of the cellular machinery responsible for their degradation, resulting in the accumulation of glycolipids within the cell. Additionally, insulin resistance, a hallmark of conditions such as type 2 diabetes, can further exacerbate glucolipotoxicity. Insulin resistance impairs the ability of cells to respond to insulin, leading to elevated levels of glucose and fatty acids in the bloodstream. These excess nutrients are taken up by cells, promoting the synthesis of glycolipids and subsequent glycolipid accumulation. [12] The detrimental effects of glucolipotoxicity stem from the interference of accumulated glycolipids with vital cellular processes. One mechanism by which glycolipids induce cellular dysfunction is through the disruption of lipid bilayers in cellular membranes. Excessive glycolipid accumulation alters the physical properties of membranes, impairing their integrity and fluidity. This disturbance can affect the proper functioning of membrane-bound proteins and receptors, leading to aberrant signaling and cellular response. [13] Furthermore, glucolipotoxicity can induce endoplasmic reticulum (ER) stress, a condition characterized by the accumulation of unfolded or misfolded proteins within the ER. The presence of excessive glycolipids disrupts ER homeostasis, overwhelming the folding machinery and triggering a stress response. Prolonged ER stress can activate inflammatory pathways and initiate apoptotic signaling, ultimately leading to cell dysfunction or death. [14]

3. *Cellular Repair Mechanisms Following Glucolipotoxicity*

Glucolipotoxicity, the toxic effect of elevated levels of glycolipids within cells, triggers a series of cellular repair mechanisms aimed at mitigating the damage and restoring cellular homeostasis. One crucial aspect of this repair process involves the shutdown of glucose transporters and the utilization of alternative metabolic pathways to dispose of accumulated glucose in the absence of oxygen. This intricate mechanism ensures the cell's survival and prevents further glycolipid-induced dysfunction. Upon glucolipotoxicity-induced stress, cells activate a self-defense mechanism by downregulating glucose transporters, such as GLUT4, on the cell membrane. This downregulation limits the influx of glucose into the cell, reducing the substrate available for glycolipid synthesis.

By closing the gates for glucose entry, the cell aims to curtail further accumulation of glycolipids, thereby alleviating the toxic burden.[15][16] Simultaneously, in the absence of sufficient oxygen availability, cells resort to anaerobic metabolic pathways to dispose of the accumulated glucose. Glycolysis, a process that breaks down glucose into pyruvate, plays a

central role in this anaerobic sugar disposal mechanism. However, under normal circumstances, pyruvate would enter the mitochondria for further oxidation in the presence of oxygen. In the absence of oxygen, pyruvate is converted into lactate through the enzymatic action of lactate dehydrogenase. [17] The conversion of pyruvate to lactate serves two essential purposes: firstly, it allows for the regeneration of NAD+ from NADH, which is necessary for sustaining glycolysis. Secondly, lactate serves as a means to remove the excess glucose from the cell. Lactate is transported out of the cell through monocarboxylate transporters (MCTs), preventing further accumulation of glucose and reducing the glucolipotoxicity-induced burden. [18] While anaerobic sugar disposal offers a temporary solution, it is not without consequences. The accumulation of lactate in the extracellular environment can contribute to acidification, altering the cellular pH and potentially affecting various cellular processes. Furthermore, the reliance on anaerobic metabolism for prolonged periods can result in reduced energy production, as oxidative phosphorylation in the mitochondria is more efficient in generating ATP. [9][19]

4. *Accumulation of Lactic Acid: Cellular Response to Anaerobic Glucose Metabolism and the Role of Lactic Acid in Inhibiting Apoptotic Enzymes*

In the absence of oxygen, cells resort to anaerobic metabolism to generate energy from glucose. This metabolic adaptation leads to the accumulation of lactic acid as a byproduct of anaerobic glycolysis. The build-up of lactic acid plays a crucial role in cellular response and survival by inhibiting specific enzymes responsible for programmed cell death, known as apoptosis. Anaerobic glycolysis metabolism initiates with glycolysis, a process that breaks down glucose into pyruvate. In the presence of oxygen, pyruvate enters the mitochondria for further oxidation through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. However, under anaerobic conditions, pyruvate is converted into lactic acid through the enzymatic action of lactate dehydrogenase (LDH). [20] The accumulation of lactic acid serves two critical functions: metabolic and cytoprotective. Metabolically, the conversion of pyruvate to lactic acid allows for the regeneration of NAD+ from NADH, ensuring the continuous operation of glycolysis, which is dependent on NAD+ availability. This metabolic function helps sustain cellular energy production in the absence of oxygen. [21] Cytoprotective, lactic acid inhibits apoptotic enzymes, preventing programmed cell death. One enzyme affected by lactic acid is caspase-3, a key effector caspase involved in the execution phase of apoptosis. Lactic acid-induced acidification of the cytosol inhibits the activation of caspase-3, thereby preventing its proteolytic activity and the subsequent cleavage of cellular substrates required for apoptosis. [22][23] Moreover, lactic acid accumulation can alter the pH balance within the cell. The increased acidity inhibits other enzymes involved in apoptosis, such as caspase-9 and caspase-8, by disrupting their conformation and activity. These enzymes play crucial roles in initiating the apoptotic cascade, and their inhibition by lactic acid contributes to the cell's survival in oxygen-deprived conditions. [24][25] While lactic acid accumulation serves as an adaptive response to anaerobic glucose metabolism, prolonged acidification can have detrimental effects on cellular function.

Acidosis can disrupt protein structure, impair enzyme activity, and interfere with various cellular processes. Additionally, the reliance on anaerobic metabolism and lactic acid production for extended periods can result in reduced energy

production and compromised cellular viability. [26]

5. Glucolipotoxicity: Unraveling the Link between Metabolic Disturbances and Immune Dysfunction

Emerging evidence suggests a link between glucolipotoxicity and immune dysfunction. Our research findings reveal that elevated levels of glucose and fatty acids not only trigger detrimental effects on cellular function but also have implications for immune responses. Specifically, we have observed that the increased glucose and fatty acids induce DNA damage, caspase-dependent apoptosis, and mitochondrial respiratory dysfunction. These cellular alterations are attributed to the concept of glucolipotoxicity, which arises from enhanced production of reactive oxygen species (ROS) and subsequent oxidative stress. It has been proposed that this oxidative stress disrupts the normal functioning of mitochondria, affecting their membrane potential and bioenergetics. In addition to the impact on cellular processes, our investigations have unveiled modifications in cell signaling pathways that are crucial for immune regulation. The Nrf-2/NFk-B/AMPK/mTOR-dependent signaling cascade, known to play a role in immune responses, was found to be altered when cells were exposed to high glucose and palmitic acid. Moreover, a dysregulated inflammatory response characterized by elevated levels of IL6 and PGE2 was observed in these conditions. These findings indicate that glucolipotoxicity exerts a multifaceted influence, not only on cellular function but also on immune signaling and inflammatory processes. [27]

6. *The Paradoxical Conditions that Activate Tumor Growth: Unraveling the Warburg Effect and Elucidating the Mechanisms*

The phenomenon known as the Warburg effect, named after the renowned scientist Otto Warburg, refers to the observation that cancer cells exhibit a distinct metabolic phenotype characterized by increased glucose uptake and lactate production, even in the presence of oxygen. This metabolic switch, which favors glycolysis over oxidative phosphorylation, has been extensively studied and is now recognized as a hallmark of cancer. Understanding the paradoxical conditions that activate tumor growth through the Warburg effect is crucial for developing innovative approaches to target the primary cause of cancer [28], referred to here as the Maher Akl effect. The Warburg effect is driven by several interconnected mechanisms. Firstly, cancer cells upregulate glucose transporters, such as GLUT1 and GLUT3, on their cell membranes. This increased expression allows for enhanced glucose uptake, providing cancer cells with a continuous supply of glucose, a crucial substrate for rapid proliferation. Moreover, cancer cells exhibit dysregulated signaling pathways, such as the PI3K/Akt/mTOR pathway, which further enhance glucose uptake and promote glycolysis. [29]

Additionally, cancer cells undergo metabolic reprogramming that favors glycolysis, even under normoxic conditions. This metabolic switch involves the upregulation of glycolytic enzymes, such as hexokinase II and pyruvate kinase M2 isoform, which promote the conversion of glucose to lactate. The diversion of glucose towards lactate production, rather than entering the mitochondrial TCA cycle, is a key characteristic of the Warburg effect. [30] The consequences of the Warburg

effect extend beyond altered glucose metabolism. The high rate of glycolysis leads to the accumulation of metabolic intermediates, such as lactate and certain amino acids, which contribute to the tumor microenvironment's acidity. This acidic milieu provides a selective advantage for tumor cells by suppressing immune responses, promoting angiogenesis, and facilitating invasive behavior.[31]

The Maher Akl effect proposes a novel perspective on the primary cause of cancer, emphasizing the role of glucolipotoxicity in tumor development. Maher Akl suggests that the dysregulation of glyucolipid metabolism, particularly the accumulation of glycolipids within cells, plays a pivotal role in initiating and sustaining tumor growth.

This effect, similar to the Warburg effect, involves the interference of accumulated glycolipids with vital cellular processes, leading to cellular dysfunction and promoting oncogenic pathways.

7. *Discussion: Proposed Primary Cause of Cancer According to the Earlier Described Mechanisms*

The glucolipotoxicity hypothesis, as proposed by Maher Akl, offers a unique perspective on the primary cause of cancer, contrasting with the well-known Warburg effect. While the Warburg effect focuses on altered glucose metabolism and lactate production, the glucolipotoxicity hypothesis delves into the dysregulation of glucolipid metabolism and its implications in tumor development. In this discussion, we will explore the mechanisms underlying glucolipotoxicity, its impact on cellular function, and its potential role in tumor progression, while comparing the perspectives of Otto Warburg and Maher Akl. Glucolipotoxicity occurs when an excessive accumulation of glycolipids disrupts cellular homeostasis and impairs essential cellular processes. One of the key consequences of glucolipid accumulation is the temporary closure of glucose transporters, preventing further glucose uptake until the cell can metabolize the excess glucose. During this process, cells resort to anaerobic glycolysis, breaking down glucose in the absence of oxygen and creating an acidic environment due to the accumulation of lactic acid. The acidity resulting from anaerobic glycolysis in turn plays a role in tumor development. Acidic conditions within the tumor microenvironment promote tumor growth by inhibiting apoptosis, the programmed cell death process. The increased acidity inhibits enzymes responsible for initiating apoptosis, such as caspase-3, caspase-9, and caspase-8, ultimately leading to cell survival and tumor progression. Moreover, in the absence of oxygen, cells may adopt alternative metabolic pathways to sustain their energy demands. This metabolic adaptation includes the utilization of glucose through anaerobic glycolysis, which provides an advantage for cells with genetic alterations that favor their transformation into cancerous tumors. Otto Warburg extensively described this metabolic switch in his work on the Warburg effect, highlighting the role of altered glucose metabolism in cancer cell proliferation. However, Maher Akl's glucolipotoxicity hypothesis goes beyond the metabolic alterations described by Warburg. Akl suggests that the accumulation of glucolipids, resulting from dysregulated glucolipid metabolism, is the primary driver of tumor growth. The interference of accumulated glycolipids with cellular processes leads to cellular dysfunction and the activation of oncogenic pathways, ultimately promoting tumor development. In comparing the perspectives of Warburg and Akl, it is evident that both highlight the importance of altered metabolism in cancer development.

While Warburg focuses on the metabolic switch to glycolysis and its consequences, Akl emphasizes the dysregulation of glycolipid metabolism and its impact on cellular function. These differing perspectives contribute to a broader understanding of the primary causes of cancer and can potentially guide the development of innovative therapeutic approaches.

8. *Conclusion*

In conclusion, the proposed primary cause of cancer according to the glucolipotoxicity hypothesis involves the dysregulation of glycolipid metabolism and its implications for cellular function. Accumulated glycolipids disrupt cellular processes, promoting cell survival and tumor progression. Comparing the perspectives of Otto Warburg and Maher Akl allows for a more comprehensive understanding of the metabolic alterations in cancer and opens avenues for further research and therapeutic interventions.

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