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

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Potential competing interests: No potential competing interests to declare.

1. **Abstract**

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.

Comment 1.

From the reviewer's point of view, it is not at all clear what is new about the proposal.

1. **1. Introduction**

One proposed explanation for the Glucolipotoxicity effect 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.

Comment 2.T

he presentation of experimental evidence of this phenomenon is not mentioned in this submission.

1. **2. Glucolipotoxicity**

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[14] inflammatory pathways and initiate apoptotic signaling, ultimately leading to cell dysfunction or death.

Comment 3:

There is no presentation of observations that provide concrete evidence of "accumulation of unfolding and

misfolded proteins".

1. 3. Cellular Repair Mechanisms Following Glucolipotoxicity

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

Comment 4

Cancer does not occur if it leads to the 'Cellular dysfunction or death'. Observations of 'glucose transporter shutdown' and 'glucose accumulation during oxygen deprivation' need to be presented.

1. 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[17] through the enzymatic action of lactate dehydrogenase.

Comment 5

The above phenomenon is primarily a consequence of the Warburg effect, and does not follow from the logic that intracellular glucose accumulation occurs.

1.

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. Furthermore, the reliance on anaerobic metabolism for prolonged periods can result in reduced energy production, as oxidative phosphorylation in the mitochondria is more [9][19] efficient in generating ATP.

Comment 6.

You state, " the reliance on anaerobic metabolism for prolonged periods can result in reduced energy production, " but the rate of energy production is extremely rapid glycolysis. At that time, intermediate products are used to produce the next generation of cellular components (cell membranes, nucleic acids, etc.), not a decrease in energy efficiency.

1.

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).

Comment 7.

Cancer is "a cell that has been forced to choose a selfish survival path to avoid mitochondrial collapse under hypoxic conditions.

Once they acquire that trait, the significance is that they are forced to choose to live by glycolysis, even in the presence of oxygen.

1. 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 [22][23 required for apoptosis.

Comment 8.

The earliest trigger of apoptosis is in the mitochondrial endoplasmic reticulum.

It starts with the release of the electron transfer system 'cytochrome c' and the caspase pathway is not triggered, so the cancer does not die.

1. 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 [26] production and compromised cellular viability.

Comment 9.

The above condition is applicable to normal details and does not apply to cancer cells. Also, is this 'acidic' intracellular?

The pH in cancer cells is maintained at homeostasis to be alkaline. This situation cannot occur in cancer cells because "the pH in cancer cells is homeostatic so that it is alkaline.

1. In addition to the impact on cellular processes, our investigations have

unveiled modifications in cell signaling pathways that are crucial for immune regulation.

Comment 10.

There needs to be a 'presentation of data' that concretely shows the above state of affairs.

1. It has been proposed that this oxidative stress disrupts the normal functioning of mitochondria, affecting their

membrane potential and bioenergetics.

Comment 11.

As mentioned in comment 9, who is advocating this? It is a well known fact that oxygen deprivation is the first trigger in any cancer.

The evidence for this is that the first gene to move is HIF.

1. **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 [27] multifaceted influence, not only on cellular function but also on immune signaling and inflammatory processes.**

Comment 12.

The Nrf-2/NFk-B/AMPK/mTOR-dependent signaling cascade is a signal generated in the retrograde response when mitochondria send signals to the nucleus during oxygen deprivation, and is the first subocular signal, a cascade known to promote cancer.

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

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[28],

cause of cancer referred to here as the Maher Akl effect.

Comment 13.

The original source citing this is a conference abstract, not a widely recognized one. Also, this phenomenon is nothing new as it occurs under the conditions proposed by Warburg O.

1. **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.**

Comment 14.

All of these metabolic modulations are a phenotype of the Warburg effect, which avoids mitochondrial disruption and keeps the mitochondrial membrane potential at substrate-level phosphorylation.

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.

Comment 15.

It needs to be clearly stated which points are unique.

1. **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.

Comment 16.

Data needs to be explicitly presented on these phenomena, but they are only reported at the level of conference presentations.

Decision Rejection.

Although it may be offered as a hypothesis, it makes a comment with virtually no evidence and is an extremely misguided understanding of cancer cell metabolism. The article does not deserve to be published. As I commented above, it is built entirely on 'conference-level reports,' but I don't think it is a nearly correct interpretation of cancer metabolism.

A cancer is a cell that has been put in a situation where there is nutrition and no oxygen, initiates mitochondrial disruption, but OXPHOS can no longer be used, and selfishly begins to survive. The first gene to move in any cancer is HIF.

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