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International Journal of Clinical Case Reports and Reviews
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Review Article

Oncoadictology: Glucose and Glutamine Addiction in Cancer

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Received Date: July 19, 2023 | **Accepted Date:** July 31, 2023 | **Published Date:** August 08, 2023

Citation: M.A. Nagy, M.M. Mahmoud, (2023), Oncoadictology: Glucose and Glutamine Addiction in Cancer, *International Journal of Clinical Case Reports and Reviews*, 14(3); **DOI:10.31579/2690-4861/325**

Abstract:

The most obvious behavior in oncology or cancer biology is the addiction of cancer cells to some nutrients or metabolites as glucose and glutamine in their reprogrammed metabolism. Studying and blocking the metabolic pathways of glucose or glutamine or both is a therapeutic target and also has clinical diagnostical importance. This is not just a remark or an approach but I think it will be a promising branch of oncology that will be called Oncoaddictology as the first time.

Key words: oncoaddictology; addiction; glucose; glutamine

Introduction

Carbon and nitrogen are essential elements for life. Glucose as a carbon source and glutamine as a nitrogen source are important nutrients for cell proliferation. The metabolism of neoplasms has evolved to meet the demands of their high proliferative activity and growth in adverse conditions of hypoxia, nutrient shortage, and immunological pressure of the host. The reprogrammed metabolism of neoplasms, eventually adapting them to specific growth requirements and conditions, involves addiction to glucose (the Warburg effect, oxidative glycolysis) and/or glutamine (Liberti and Locasale. 2016).

Addiction of Glucose

About 100 years ago, it was discovered that cancer cells that have acquired unlimited proliferative capacity and undergone malignant evolution in their host manifest a cancer-specific remodeling of glucose metabolism (the Warburg effect). (Manabu Kodama and Keiichi I Nakayama, 2020).

Increased uptake of glucose by cancer cells with subsequent lactate production irrespective of oxygen availability was described almost 100 years ago. Known today as the Warburg effect, most of (if not all) the hallmarks of cancer could be the consequence of the Warburg's effect which. To compensate the reduced energy yield, there is massive glucose uptake, anaerobic glycolysis, with an up-regulation of the Pentose Phosphate Pathway resulting in increased biosynthesis (Schwartz et al22017). This metabolic phenotype is exploited clinically in the form of PET scanning with the glucose analog 18F-2-fluoro-2-deoxy-D-glucose (FDG) for cancer staging Michael and Robert Leone (2022).

NADH shuttles, including malate-aspartate shuttle (MAS) and glycerol-3-phosphate shuttle, can shuttle the reducing equivalents of cytosolic NADH into mitochondria. It is widely accepted that the major function of NADH shuttles is to increase mitochondrial energy production. the novel major function of NADH shuttles in cancer cells is to maintain glycolysis by decreasing cytosolic NADH/NAD (+) ratios instead of increasing mitochondrial energy metabolism. (Piet Borst., 2020)

Glucose addiction in glioblastoma

Tumor cells need glucose to ensure their survival and growth, so the type of transport proteins like GLUT are critical for them. Previous studies have shown that GLUT-1 and GLUT-3 may play an important role in the development of some types of malignant tumors, including glioblastoma (Beylerli et al.,2022).

Glucose addiction in Hepatocellular carcinoma (HCC)

carbohydrate responsive element binding protein (CHREBP) is acentral player in the regulation of lipid and glucose metabolism in the liver, on the development of HCC in in vitro and in vivo models. It is found that genetic deletion of CHREBP (that will be referred to as CHREBPKO mice) strongly delays or impairs hepatocarcinogenesis driven by AKT or AKT/c-Met overexpression in mice, respectively. In contrast, HCC development was found to be completely unaffected by CHREBP depletion in mice co-expressing AKT and N-Ras protooncogenes. In mouse and human HCC cell lines, suppression of CHREBP via specific small interfering RNAs (siRNAs) resulted in decreased proliferation and induction of apoptosis. Of note, these cellular events were strongly augmented by concomitant inhibition of the mitogen-activated protein kinase (MAPK) pathway (Ribback ET AL.,2018).

Glucose addiction in ovarian cancer

Cyclin E1 (CCNE1) gene amplification occurs in approximately 20% of ovarian high grade serous carcinoma (HGSC) and is associated with chemotherapy resistance and, in some studies, overall poor prognosis.

The role of cyclin E1 in inducing S phase entry relies upon its interactions with cyclin dependent kinases (CDK), specifically CDK2 (Kanska et al.,2016). Cyclin E-driven OVCA cells appeared addicted to glucose metabolism via TCA. Combined CDKI with modalities targeting TCA, like SDHA inhibition showed promising effects for this genotype.

Glucose addiction in breast cancer

The glucose uptake by mammalian cells is facilitated by GLUT family members. Of the 14 isoforms, GLUT-1 is the primary mediator of glucose uptake by mammary cells. GLUT-1 expression in breast cancer was associated with high proliferation and total histologic score (Roy et al.,2019).

Glucose addiction in lung cancer

Orchestrated activation of glucose absorption and metabolism towards anaerobic pathways characterize the majority of non-small cell lung cancer (NSCLC) and this phenotype is strongly linked with an aggressive clinical behavior. This glycolytic addiction of lung cancer cell is revealed as a key therapeutic target (Giatromanolaki et al.2017).

Glutamine

Glutamine is a nonessential amino acid that can be synthesized from glucose. The high rate of glutamine uptake exhibited by glutamine-dependent cells does not appear to result solely from its role as a nitrogen donor in nucleotide and amino acid biosynthesis. Instead, glutamine plays a required role in the uptake of essential amino acids and in maintaining activation of TOR (target of rapamycin) kinase. Moreover, in many cancer cells, glutamine is the primary mitochondrial substrate and is required for maintenance of mitochondrial membrane potential and integrity and for support of the NADPH production needed for redox control and macromolecular synthesis (David and Craig ,2010).

Many types of cancers are characterized by elevated glutamine consumption. Dysregulation of glutaminase and glutamine synthetase are key events that allow anabolic adaptation of tumors. Several specific drugs that inhibit metabolic enzymes dealing with glutamine metabolism have been able to eliminate some neoplasms (José E et al.,2019).

Explanation of "Warburg effect" in a way to demonstrate the importance of glucose as a supplier of building block, beyond to be an energetic molecule, partially solves the puzzle. However, some recent studies suggest glutamine, the most abundant amino acids in plasma, may contribute to cancer cell proliferation through the glutaminolysis pathway, which is eventually integrated into the TCA cycle (Li et al.,2018).

Among them are the transporters for amino acids. Fourteen of them, capable of transporting glutamine across the plasma membrane, are found in four families: SLC1, SLC6, SLC7, and SLC38. However, it is generally thought that the members of the SLC38 family are the principal transporters for glutamine. Some of the glutamine transporters are obligatory exchangers whereas some function as active transporters in one direction. While most glutamine transporters mediate the influx of the amino acid into cells, some actually mediate the efflux of the amino acid out of the cells. Glutamine transporters play important roles in a variety of tissues, including the liver, brain, kidney, and placenta. Owing to the obligatory role of glutamine in growth and proliferation of tumor cells, there is increasing attention on glutamine transporters in cancer biology as potential drug targets for cancer treatment (Yangzom D Bhutia, Vadivel Ganapathy (2016).

Glutamine addiction in gliomas

Glutamine addiction becomes a solution. Increased transport provides glutamine as a source of carbon for the TCA cycle, and then it may be redirected via the malate shuttle to become a source of additional energy and to add up lactate. Further, glutamine becomes essential for nucleotide synthesis and augments the GSH redox system capability, enabling gliomas to resist radio- and chemotherapy Marta Obara-Michlewska and Monika Szeliga (2020).

oncogene c-Myc is one of the major players responsible for this metabolic alteration. p32, a mitochondrial protein known to play a role in the expression of mitochondrial respiratory chain complexes, as a critical player in Myc-induced glutamine addiction. p32 is a direct transcriptional target of Myc (Fogal et al.,2015). Thus, the mitochondrial protein p32 is a validated therapeutic target of cancer overexpressed in glioma.

Glutamine addiction in Kidney cancer

Metabolic reprogramming of the glutamine and NADH pathways are responsible for this state of affairs at least in kidney cancer (Omran Abu Aboud et al.,2017). Cancer cells in which HIF is activated, by contrast, lose the ability to use glucose as major TCA cycle 'fuel', thus developing a particular dependence on glutamine. This may explain why interfering with glutamine utilization via glutaminase inhibition negatively impacts cancer cells preferentially compared to normal cells (Hoerner et al.,22019).

Glutamine addiction in Hepatocellular carcinoma

human liver cancer was dependent on extracellular glutamine. However, cancer cells often suffer from glutamine starvation, which largely results from the fast growth of cancer cells and the insufficient vascularization in the interior of cancer tissues (Zhang et la.,2022).

Targeting glutamine addiction using the glutaminase inhibitor CB-839 as monotherapy had a very limited anticancer effect, even against the most glutamine addicted human liver cancer cells (Jin et al.,2020).

Glutamine addiction in Breast cancer

Glutamine-indispensable triple-negative breast cancer (TNBC) cells rely on a non-canonical glutamine-to-glutamate overflow, with glutamine carbon routed once through the TCA cycle. Importantly, this single-pass glutaminolysis increases TCA cycle fluxes and replenishes TCA cycle intermediates in TNBC cells, a process that achieves net oxidation of glucose but not glutamine. The coupling of glucose and glutamine catabolism appears hard-wired via a distinct TNBC gene expression profile biased to strip and then sequester glutamine nitrogen, but hampers the ability of TNBC cells to oxidise glucose when glutamine is limiting (Lake et al.,2022).

Glutamine addiction in ovarian cancer

Potential therapeutic approaches for ovarian cancer including blocking the entry of glutamine into the tricarboxylic acid cycle in highly aggressive ovarian cancer cells or inhibiting glutamine synthesis in less aggressive ovarian cancer cells. Glutamine metabolism is associated with poor prognosis of ovarian cancer. Combining platinum-based chemotherapy with inhibition of glutamine metabolic pathways may be a new strategy for treating ovarian cancer, especially drug-resistant ovarian cancer (Yang et al.,2022).

Glutamine addiction in colorectal cancer

Glutamine represents an important metabolite for cell growth and that its deprivation reduces the proliferation of colorectal cancer cells. Glutamine depletion induces cell death and cell cycle arrest in the GO/G1 phase by modulating energy metabolism, the amino acid content and antioxidant defenses (Spadaet al.,2023).

Glutamine addiction in multiple melanoma

Glutamine (Gln) metabolism in multiple myeloma (MM) cells and its potential role as a therapeutic target are still unknown, However, MM cells strictly depend on extracellular Gln and show features of Gln addiction. Therefore, the inhibition of Gln uptake is a new attractive therapeutic strategy for MM (Marina et al.,2016).

Melanoma cells, irrespective of their oncogenic background, depend on glutamine for growth. A quantitative audit of how carbon from glutamine is used showed that TCA-cycle-derived glutamate is, in most melanoma cells, the major glutamine-derived cataplerotic output and product of glutaminolysis. In contrast to melanoma cells, melanocytes could grow in the absence of glutamine. Melanocytes use more glutamine for protein synthesis rather than secreting it as glutamate and are less prone to loss of glutamate and TCA cycle metabolites when starved of glutamine (Ratnikov et al.,2015).

Glutamine addiction in Lung cancer

Over the past years, increasing evidence has shown that lung cancer cells require glutamine to fulfill their metabolic needs. As a nitrogen source, glutamine contributes directly (or indirectly upon conversion to glutamate) to many anabolic processes in cancer, such as the biosynthesis of amino acids, nucleobases, and hexosamines. It plays also an important role in the redox homeostasis, and last but not least, upon conversion to α-ketoglutarate, glutamine is an energy and anaplerotic carbon source that replenishes tricarboxylic acid cycle intermediates. The latter is generally indicated as glutaminolysis(Vanhove et al.,2019).

Conclusion

The present review aims at presenting the research and clinical attempts targeting the different metabolic pathways involved in glucose and glutamine metabolism in different types of cancer. That will forego a detailed comparison of the therapeutic strategies undertaken to inhibit glucose and glutamine addiction by cancer cells.

Acknowledgements:

The unit of clinical research thanks Prof. Dr. Menan Rabie secretary general of mental health and addiction treatment. Ministry of Egyptian health for her kind support. Also, Clinical Pharmacy department appreciate the great efforts and encouragement of Dr Monsef Mahfouz, clinical research unit, El Minia hospital for mental health and addiction treatment.

Conflict of interest:

The Author has declared that there are no conflicts of interest in relation to the subject of this work.

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DOI:10.31579/2690-4861/325