Altered Glutamine Metabolism and Therapeutic Opportunities for Lung Cancer

Amr Mohamed,[1] Xingming Deng,[2] Fadlo R. Khuri,[3] Taofeek K. Owonikoko[3]

Abstract

Disordered cancer metabolism was described almost a century ago as an abnormal adaptation of cancer cells to glucose utilization especially in hypoxic conditions; the so-called Warburg effect. Greater research interest in this area in the past two decades has led to the recognition of the critical coupling of specific malignant phenotypes such as increased proliferation and resistance to programmed cell death (apoptosis) with altered metabolic handling of key molecules that are essential for normal cellular metabolism. The altered glucose metabolism frequently encountered in cancer cells has already been exploited for cancer diagnosis and treatment. The role of other glycolytic pathway intermediates and alternative pathways for energy generation and macromolecular synthesis in cancer cells has only become recognized more recently. Especially, the important role of altered glutamine metabolism in the malignant behavior of cancer cells and the potential exploitation of this cellular adaptation for therapeutic targeting has now emerged as an important area of cancer research. Expectedly, attempts to exploit this understanding for diagnostic and therapeutic ends are running apace with the elucidation of the complex metabolic alterations that accompany neoplastic transformation. Because lung cancer is a leading cause of cancer death with limited curative therapy options, careful elucidation of the mechanism and consequences of disordered cancer metabolism in lung cancer is warranted. This review provides a concise, systematic overview of the current understanding of the role of altered glutamine metabolism in cancer, and how these findings intersect with current and future approaches to lung cancer management.

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Introduction

Lung cancer is the most common cancer worldwide, and the leading cause of cancer-associated deaths in the United States.[1] Similar to other cancer types, altered glucose metabolism by cancer cells has been exploited in the diagnosis and staging of lung cancer mainly through the use of ^{18}fluorodeoxyglucose (FDG)-positron emission tomography (PET) imaging of patients with various stages of lung cancer.[2] However, major new advances in exploiting abnormal cancer cell metabolism for the management of lung cancer are unlikely to arise from the already established utility of FDG-PET. Indeed, an increasing body of evidence suggests that the dysregulated metabolism of other enzymes and substrates beyond glucose are common accompaniments of neoplastic transformation, progression, and resistance to therapy of cancer cells. Furthermore, recent findings highlighting the frequent mutations of genes encoding for metabolizing enzymes such as isocitrate dehydrogenase (IDH) 1 and 2, pyruvate kinase M2 (PKM2), fumarate hydratase, and succinate dehydrogenase have further encouraged the research interest in cancer metabolism and how such findings can be translated into therapeutic interventions.[3] Importantly, the activation of alternative glycolytic pathway intermediate enzymes such as PKM2 and phosphoglycerate mutase 1 has been directly linked to tumor growth.[4,5] However, recognition of the role of glutamine metabolic pathway as an alternative source of energy and anabolic building block offers one of the most promising targets for anticancer strategies.[6] The recognition of the important role of altered glutamine metabolism in cancer has led to the focus on this pathway as an actionable therapeutic target and the development of pharmacological agents that inhibit key enzymes involved in glutamine metabolism.[7] Considering the overall poor prognosis of lung cancer

[1]Department of Medicine, Emory University School of Medicine, Atlanta, GA
[2]Department of Radiation Oncology, Emory University School of Medicine and Winship Cancer Institute, Atlanta, GA
[3]Department of Hematology and Medical Oncology, Emory University School of Medicine and Winship Cancer Institute, Atlanta, GA

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Address for correspondence: Taofeek K. Owonikoko, MD, PhD, Associate Professor, Department of Hematology and Medical Oncology, Emory University School of Medicine, 1365C Clifton Rd NE, Building C, Room C3080, Atlanta, GA 30322
Fax: 404-778-5520; e-mail contact: towonik@emory.edu

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and the need for unconventional therapeutic strategies, it is reasonable to anticipate that translational and eventual clinical evaluation of this therapeutic approach will soon be extended to lung cancer patients. In this review, the current state of the literature regarding the altered metabolism of glutamine in cancers is summarized, and a contextual discussion is provided, regarding the relevance and potential application of such findings to the comprehensive management of lung cancer.

Discussion

Glutamine Structure and Function

Glutamine is the most abundant, naturally occurring, nonessential amino acid in the human body.[8] It is synthesized through enzymatic action of glutamine synthetase (GS) that combines glutamate and ammonia.[9,10] Glutamine has 2 nitrogen-containing side chains, an amino, and an amide group. This property makes it one of the most important circulating nitrogen shuttles, accounting for 30% to 35% of all amino acid nitrogen transported in the blood.[11] It serves as a vehicle for transporting ammonia in a nontoxic form from the peripheral tissues to visceral organs where it is cleared and excreted either as ammonium in urine or as urea through the liver. Glutamine is also central to a variety of biochemical functions such as protein synthesis, cellular energy homeostasis, purine synthesis and the citric or tricarboxylic acid (TCA) cycle through its capacity to serve as a nitrogen or carbon donor. Glutamine exists in a free circulating form in the blood and in storage forms mainly in skeletal muscles and in smaller amounts in other organs such as the lung and brain.[12] Physiologically, glutamine is used by the small intestine and the renal epithelial cells for acid base balance.[13] However, other metabolically active cells including activated immune cells and cancer cells can become major glutamine users.[14] Hepatocytes serve as a glutamine producer and consumer depending on the overall metabolic needs of the body. As such, hepatocytes play a regulatory role in glutamine metabolism by taking up large amounts of glutamine derived from the gut.[13]

Glutamine Metabolism in Normal and Neoplastic Cells

Glutamine is one of the most abundant amino acids in the body and is especially abundant in the liver, kidney, skeletal muscle, and brain.[8,12] It is the precursor for the synthesis of many amino acids, proteins, nucleotides, and other biologically important molecules.[13] It is also required for the removal of alpha amino nitrogen from other amino acids through transdeamination and is considered the main precursor for ammoniagenesis and urea formation in the kidney.[13,15] Hepatic glutamine metabolism has a vital role in the stimulation of glycogen synthesis and is one of the major end products of ammonia-trapping pathways.[16,17] Moreover, glutamine metabolism plays a critical role in gluconeogenesis and is an oxidative fuel in rapidly proliferating cells and tissues.[12] It is required for synthesis of glutathione, a key component in the body's scavenging defense mechanism against oxidative stress.[18,19] Because of the varied roles of glutamine in normal cell physiology and metabolism, it is expected that altered handling of glutamine metabolism will contribute to neoplastic transformation and cancer progression. Careful study and elucidation of potential alteration in glutamine metabolism in cancer cells is currently one of the most active areas of cancer metabolism research. Recent findings have shown that aberrant energy metabolism and the associated alterations in intracellular handling of glutamine by cancer cells form an adaptive mechanism that contributes directly to the malignant phenotype. Thus, proliferating cancer cells compete with normal cells for circulating glutamine.[10] As a consequence, marked changes in glutamine metabolism might occur with progressive tumor growth. A careful elucidation of glutamine metabolism in cancer patients and its effect on cancer prognosis might inform optimal patient management.

The stiff competition between neoplastic and normal cells for glutamine and the requirement for glutamine supplementation for optimal growth of cancer cells in in vitro culture constitute empiric evidence in support of the role of glutamine as a major energy source for cancer cell proliferation.[20-23] In vivo studies in hepatomas and fibrosarcomas[24,25] showed a 5- to 10-fold higher rate of glutamine consumption by cancer cells compared with normal hepatocytes.[26] Also, the dependence of lung cancer cells on sufficient availability of glutamine for short-term proliferation and long-term survival was previously demonstrated in studies of human-derived lung cancer cell lines and tissue grafts.[27-29] Metabolic reprogramming in cancer cells facilitates glutamine uptake and utilization for anabolism.[21] One of the earliest steps in the generation of metabolic intermediates required for cell growth and replication is the oxidative action of mitochondrial phosphate-dependent glutaminase (GLS) which converts glutamine to glutamate and ammonia.[22] Glutaminolysis mediated by GLS promotes the generation of metabolic intermediates required for macromolecular biosynthesis in proliferating cancer cells. A series of cellular adaptations ensures the availability of glutamine to cancer cells. This includes the development of efficient sodium ion-dependent membrane transporter systems, System A and System alanine, serine, and cysteine (ASC), leading to enhanced transmembrane transfer of glutamine from the circulation to overcome the stiff competition with normal cells.[10,30,31] The normal repression of the System A glutamine transporter in normal cells is derepressed after neoplastic transformation, leading to augmented glutamine membrane transport into the cell.[32] In addition, a carrier-mediated process determines the intracellular trafficking of glutamine into the mitochondria.[33] However, this intracellular flow of glutamine is bidirectional depending on the dynamic balance between the need for optimal blood levels of glutamine and the intracellular metabolic requirements.

In animal experiments, an inverse relationship exists between rapid tumor cell growth and proliferation and a fall in blood glutamine concentration.[34-36] Furthermore, a series of interrelated adaptive changes occurs in different organs in response to the disproportionate use of glutamine by the proliferating cancer cells. For instance, low blood glutamine levels induce reciprocal adaptive changes in organs involved in body glutamine balance such as skeletal muscles, intestine, liver, and lung. As such, low blood glutamine levels resulting from increased tumor burden induces an increase in the activity of GS enzyme and a consequent increase in intracellular glutamine stores in muscle cells.[37] Failure of this compensatory mechanism results in significant depletion of glutamine in skeletal muscle and might contribute to the commonly observed tumor-associated cachexia of advanced cancer.[38,39] Similarly, in response to the diminished extractable fraction of