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#### Review

# Metabolic reprogramming in cancer: Unraveling the role of glutamine in tumorigenesis

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#### ABSTRACT

Increased glutaminolysis is now recognized as a key feature of the metabolic profile of cancer cells, along with increased aerobic glycolysis (the Warburg effect). In this review, we discuss the roles of glutamine in contributing to the core metabolism of proliferating cells by supporting energy production and biosynthesis. We address how oncogenes and tumor suppressors regulate glutamine metabolism and how cells coordinate glucose and glutamine as nutrient sources. Finally, we highlight the novel therapeutic and imaging applications that are emerging as a result of our improved understanding of the role of glutamine metabolism in cancer.

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Abbreviations: Gls, glutaminase; GDH, glutamate dehydrogenase; PC, pyruvate carboxylase; GFAT, fructose-6-phosphate amido-transferase; GSH, glutathione; GlcNAc, N-acetyl-D-glucosamine; PRPP, 5-phospho- $\alpha$ -D-ribosyl 1-pyrophosphate; AOA, aminooxyacetate; EAA, essential amino acids; DON, 6-diazo-5-oxo-L-norleucine; IDH, isocitrate dehydrogenase; 2-HG, 2-hydroxyglutarate; SDH, succinate dehydrogenase; FH, fumarate hydratase; PHD, prolyl hydroxylase; HIF-1 $\alpha$ , hypoxia inducible factor-1 $\alpha$ ; MRS, magnetic resonance spectroscopy; DNP, dynamic nuclear polarization; Got, glutamate: oxaloacetate transaminase; Gpt, glutamate: pyruvate transaminase.

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#### 1. Introduction

Glutamine has long been recognized to play a unique role in the metabolism of proliferating cells, as compared to other amino acids [1,2]. It is the most abundant amino acid in plasma, and most tumors consume and utilize glutamine at much higher rates than other amino acids [1]. Although glutamine is a non-essential amino acid in normal, non-dividing tissue, it is essential for the proliferation of most cells and the viability of some cancer cells that have become addicted to glutamine [3]. Glutamine metabolism contributes to the ability cancer cells to continuously grow and proliferate by supporting ATP production and biosynthesis of proteins, lipids, and nucleic acids. Glutamine also modulates redox homeostasis and can impact the activity of signal transduction pathways [4,5].

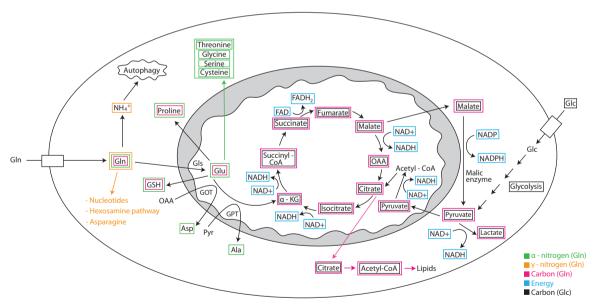
Glutamine's involvement in oxidative mitochondrial metabolism in cancer cells was reported as early as the 1970s [6], and recent investigation has greatly expanded our understanding of the role and regulation of glutamine metabolism in cancer. In this article, we discuss the role of glutamine in supporting cellular proliferation and review current knowledge of how oncogenes and tumor suppressors regulate glutamine metabolism. We also discuss mechanisms through which metabolism of glutamine and glucose may be coordinated. Finally, we address the therapeutic and imaging applications that are emerging as a result of increasing recognition of the importance of glutamine metabolism in cancer.

#### 2. Glutamine metabolism supports cell proliferation

Glutamine plays several important metabolic roles in the cell. It serves as a carbon source for energy production, contributes carbon and nitrogen to biosynthetic reactions, and regulates redox homeostasis (Fig. 1). Glutamine availability and metabolism can also modulate activity of signal transduction pathways. As we discuss below, each of these functions of glutamine contributes to its ability to support cell growth and proliferation.

### 2.1. Glutamine: a primary carbon source for energy production and biosynthesis

Each of glutamine's fates in the cell serve important functions, although it is glutamine's role in supporting mitochondrial metabolism that is the primary reason that it is required in such large quantities. While non-proliferating cells can completely oxidize glucose-derived carbon in the TCA cycle to support their energy needs, proliferating cells use nutrients to support biosynthesis in addition to ATP production [7]. In proliferating cells, the TCA cycle metabolite citrate is exported out of the mitochondria to be used for generation of acetyl-CoA in the cytoplasm, which serves as a precursor for lipid biosynthesis. Because of the continual loss of citrate from the TCA cycle, replenishment of TCA intermediates (anaplerosis) is necessary, and glutamine serves as an important anaplerotic substrate in most proliferating cells. Citrate is generated from the condensation of acetyl-CoA and oxaloacetate, and <sup>13</sup>C labeling of glucose and glutamine in proliferating glioblastoma cells demonstrated that in these cells glutamine is a major source of oxaloacetate, whereas glucose carbon is the predominant source of acetyl-CoA [8]. Glutamine's role as a carbon source supporting TCA cycle function is critical for glutamine-addicted cancer cells. Cells expressing oncogenic levels of c-Myc die upon glutamine withdrawal, and viability can be restored by supplementing cells



**Fig. 1.** Glutamine metabolism in cancer cells. Glutamine contributes to bioenergetics and biosynthesis through reactions that use its α-nitrogen (green),  $\gamma$ -nitrogen (yellow) or carbon skeleton (pink). The  $\gamma$ -nitrogen from glutamine's amide group is a required nitrogen source for synthesis of nucleotides, hexosamines, and asparagine. During nucleotide synthesis, the  $\gamma$  nitrogen is contributed in three independent enzymatic steps in purine synthesis and two reactions in pyrimidine synthesis. The  $\gamma$  nitrogen can also be removed by glutaminase, which generates glutamate and ammonia. Ammonia has been previously shown to play a role in inducing autophagy. Glutamate carries most of glutamine's α-nitrogen and is a major nitrogen source for nonessential amino acid production in cells. Alanine aminotransferase (also known as glutamate: oxaloacetate transaminase; Gpt) and aspartate aminotransferase (also known as glutamate: oxaloacetate transaminase; Gpt) catalyze the transfer of glutamate's amino group directly into pyruvate and oxaloacetate to produce alanine and aspartate, respectively. Synthesis of other non-essential amino acids, including serine and the amino acids synthesized from serine, glycine and cysteine, requires contribution of the amino group from glutamate. Glutamate is also a precursor for synthesis of arginine and proline. In addition to its role in amino acid synthesis, glutamate is an important component of the synthesis of glutathione, an endogenous antioxidant that protects cells against various forms of oxidative stress. The final major fate of glutamine, following its conversion to glutamate and then glutamate's conversion to  $\alpha$ -ketoglutarate, is the oxidation of its carbon backbone in the mitochondria leading to energy production. Glutaminolysis contributes to production of mitochondrial NADH, which is used to support ATP production by oxidative phosphorylation. Glutamine metabolism also contributes to production of NADPH and lipid and amino acid biosynthesis. The TCA cycle metabolite cit

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