Harnessing Glutamine: Strategies and Perspectives in Cancer Therapy

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Glutamine, a multifaceted nonessential/conditionally essential amino acid integral to cellular metabolism and immune function, holds pivotal importance in the landscape of cancer therapy.

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Glutamine, a conditionally essential amino acid, has garnered significant attention in cancer research and therapy due to its diverse roles in cellular physiology. It plays crucial roles in nucleotide/protein biosynthesis, redox balance management, epigenetic regulation, and immune response [1]. Glutamine's implication in various cellular processes has made it a focal point in cancer biology research, where it has been shown to support the aberrant growth and survival mechanisms of cancer cells [7–9]. As a result, targeting glutamine metabolism has become an attractive strategy for cancer therapy. Glutamine deprivation strategies involve various approaches, including glutamine-mimicking compounds, glutamine transporter blockers, glutamine depletion, and targeting glutamine-metabolism enzymes [12,14,53].

One of the recent strategies in targeting glutamine metabolism involves the inhibition of glutaminase, an enzyme crucial for converting glutamine to glutamate, a vital step in glutamine metabolism [54,55]. Glutaminase inhibitors, such as CB-839, have shown promise in preclinical studies and early-phase clinical trials by impeding glutamine catabolism and disrupting the supply of glutamate, a precursor for numerous biosynthetic pathways critical for cancer cell survival and proliferation [12,56]. In addition to glutaminase inhibition, modulating the transport systems responsible for glutamine uptake by cancer cells has emerged as another avenue for targeted interventions [59]. Inhibitors targeting glutamine transporters have shown the potential to disrupt the influx of extracellular glutamine, thereby impairing its supply to intracellular metabolic pathways [62,63]. However, despite the promise of these glutamine deprivation strategies, several challenges and limitations exist.

One concern with glutamine deprivation strategies is cancer cells' metabolic plasticity, which allows them to reroute metabolic flux through alternative pathways in response to therapeutic interventions. This phenomenon undermines the efficacy of glutamine-targeted strategies and necessitates a comprehensive understanding of cancer cells' reprogramming mechanisms [41–43]. Additionally, the intricate metabolic microenvironment within the tumor, characterized by nutrient gradients, hypoxia, and interactions with stromal cells, adds another layer of complexity to the design and implementation of glutamine-targeted therapies [41,44–47].

Some attempts at blocking glutamine metabolism in cancer patients have resulted in unacceptable toxicity, particularly in the gastrointestinal tract [72]. The design of prodrug forms of glutamine antagonists, such as JHU083, has aimed to mitigate toxicity while still effectively targeting glutamine metabolism in tumors [73]. Nevertheless, the potential for adverse effects remains a concern, highlighting the importance of careful consideration and individualized approaches in the clinical application of glutamine deprivation strategies.

In contrast to glutamine deprivation strategies, glutamine supplementation has emerged as a potential adjunct therapy in the comprehensive management of cancer. Glutamine supplementation offers diverse benefits, including supporting immune function, preserving gut integrity, alleviating treatment-related toxicities, and potentially modulating epigenetic regulation in cancer cells [5,18,74]. The immune system plays a vital role in surveilling and eliminating cancer cells. Glutamine supplementation has been shown to enhance anti-cancer immune responses, presenting a compelling avenue for improving the efficacy of immunotherapeutic approaches in cancer treatment [74]. Glutamine supplementation has significantly improved gut integrity, particularly in mitigating gastrointestinal toxicities associated with cancer therapy [77]. By promoting the proliferation of intestinal epithelial cells and enhancing mucin synthesis, glutamine supplementation has shown promise in alleviating gastrointestinal toxicities and reducing the severity of treatment-induced side effects [79].

Furthermore, glutamine supplementation has shown potential in modulating epigenetic regulation in cancer cells by serving as a critical substrate for α-ketoglutarate production, essential for several enzymes involved in epigenetic modifications [44,90]. By influencing the epigenetic landscape of cancer cells, glutamine supplementation holds promise in regulating gene expression patterns and modulating critical signaling pathways implicated in tumorigenesis and cancer progression [44,90].

Despite the promising roles of glutamine supplementation in cancer therapy, several challenges persist, including the need for a comprehensive understanding of the metabolic adaptation of cancer cells, personalized delivery methods, and identifying patient subgroups likely to benefit the most. The fine-tuning between glutamine supplementation and deprivation still needs to be better understood and depends on specific personalized patient profiles and timing [39]. Moreover, concerns regarding potential interactions with particular cancer types and treatments persist, as some studies have suggested that glutamine may not promote tumor growth and may not adversely affect outcomes of diverse cancer treatments [107,122,123].

The safety profile of glutamine supplementation is critical to its clinical evaluation, as adverse effects such as toxicity in the liver and kidneys have been reported in limited/rare instances [119–121]. Determining the optimal dosage, duration, and delivery method of glutamine supplementation remains an area of ongoing exploration. Glutamine's solubility challenges and variability in bioavailability and effectiveness based on the route of administration underscore the importance of considering patient-specific factors in deciding the approach to glutamine supplementation [125,126].

Clinical evidence for the optimal delivery methods, concentration, and chemical stability of glutamine supplementation remains an area of ongoing exploration; the efficacy of the treatment can be influenced by factors such as solubility and absorption. Glutamine solubility is low (25 g/L); thus, suspensions are needed for topical, oral, and enteral supplementation; therefore, adding disaccharides can facilitate mucosal uptake. Manipulating glutamine levels is challenging because glutamine is abundant in the body, as studies show minimal changes in plasma glutamine levels even after repeated high-dose supplementations [125]. Additionally, monitoring local glutamine concentrations might be difficult since, in general, there is a poor correlation between plasma concentration and tissue concentrations [126]. Moreover, whether administered orally, intravenously, or even locally, the bioavailability and effectiveness of glutamine supplementation may vary. Determining the optimal dosage and duration of supplementation and identifying patient populations that derive the most benefit are crucial considerations for refining the clinical application of glutamine supplementation in cancer therapy. In addition, glutamine delivery through free and dipeptide forms has been explored, focusing on the efficacy of glutamine dipeptides [127]. Glutamine dipeptides, particularly l-alanyl-l-glutamine (Ala-Gln), have shown efficacy in reducing infectious complications, hospital stay length, and mortality in critically ill patients, as supported by clinical and experimental studies [127–134]. The choice between free glutamine and glutamine dipeptides depends on the patient’s catabolic circumstance and route of administration. Therefore, it is crucial to consider patient-specific factors when deciding the route, dose, and form of glutamine supplementation.

In summary, while both glutamine deprivation strategies and supplementation offer promising avenues in cancer therapy, each approach has advantages, disadvantages, and challenges. Glutamine deprivation strategies target the metabolic vulnerabilities of cancer cells but may face issues such as metabolic plasticity and toxicity. On the other hand, glutamine supplementation offers diverse benefits in supporting immune function, preserving gut integrity, and mitigating treatment-related toxicities, but the optimal dosage, delivery method, and safety profile need further exploration. Continued research is warranted to optimize the clinical application of both approaches and enhance patient outcomes in cancer therapy.
