Journal of Frontiers in Multidisciplinary Research

Glutamine Metabolism in Cancer: Identifying and Overcoming Therapeutic Resistance

Sarah Oparah [1*], Opeoluwa Oluwanifemi Akomolafe [2], Irene Sagay [3], Tolulope Bolarinwa [4], Ajao Ebenezer Taiwo [5]
[1] Independent Researcher, Maryland, USA
[2] Independent Researcher, UK
[3] Marley Neck Health and Rehabilitation, Maryland, USA
[4] Indepenent Researcher, Indiana, USA
[5] Independent Researcher, Indiana, USA

* Corresponding Author: **Sarah Oparah**

Article Info

E-ISSN: 3050-9726
P-ISSN: 3050-9718
Volume: 05
Issue: 01
January-June 2024
Received: 03-04-2024
Accepted: 04-05-2024
Published: 03-06-2024
Page No: 283-288

Abstract
Cancer cells exhibit a heightened dependency on glutamine metabolism to sustain their rapid proliferation and survival. Targeting this metabolic vulnerability has emerged as a promising therapeutic strategy. This paper explores the role of glutamine metabolism in cancer, the mechanisms of therapeutic resistance, and strategies to overcome these challenge. Advances in research, including metabolomics and tumor microenvironment studies, enhance our understanding of cancer metabolism. Clinical trials are evaluating various glutamine-targeted therapies, showing promising results. Translational potential is high, with efforts focused on personalized treatment approaches. Despite challenges, the future of targeting glutamine metabolism in cancer treatment is promising, with significant opportunities for developing effective therapies.

DOI: https://doi.org/10.54660/.JFMR.2024.5.1.283-288

Keywords: Glutamine metabolism, Cancer therapy, Therapeutic resistance, Metabolic pathways, Clinical trials

Introduction

Cancer remains one of the most formidable challenges in modern medicine, characterized by its ability to evade traditional therapeutic interventions through complex and adaptive mechanisms. Central to this adaptability is the unique metabolic reprogramming that cancer cells undergo to sustain rapid proliferation and survival under hostile conditions (Johariya, Joshi, Malviya, & Malviya, 2024). Unlike normal cells, which rely primarily on glucose for energy, cancer cells exhibit a pronounced dependency on glutamine, an amino acid that serves multiple critical functions beyond mere energy provision. Understanding the intricacies of cancer metabolism, particularly the role of glutamine, is pivotal in devising effective therapeutic strategies (Quek *et al*., 2022; Tu *et al*., 2024).

Glutamine metabolism in cancer cells is multifaceted, involving its conversion into glutamate through glutaminase, which then enters the tricarboxylic acid (TCA) cycle (Yoo, Yu, Sung, & Han, 2020). This process provides energy, carbon, and nitrogen for synthesizing nucleotides, amino acids, and other macromolecules necessary for cell proliferation. Additionally, glutamine contributes to the maintenance of redox balance by producing glutathione, a vital antioxidant that protects cancer cells from oxidative stress. These functions underscore glutamine's critical role in supporting cancer cells' aggressive growth and survival (Basak, Uddin, & Hancock, 2020).The significance of studying glutamine metabolism in cancer is manifold. Firstly, it offers insights into the fundamental biological processes that distinguish cancer cells from their normal counterparts. This understanding is essential for identifying metabolic vulnerabilities that can be targeted therapeutically. Secondly, as cancer cells often exhibit glutamine addiction, targeting glutamine metabolism presents a promising strategy to selectively impair cancer cell viability while sparing normal cells.

Thirdly, exploring the metabolic adaptations that cancer cells employ in response to glutamine-targeted therapies can reveal mechanisms of therapeutic resistance, thereby guiding the development of more effective and durable treatment regimens.

Therapeutic resistance remains a major hurdle in the successful treatment of cancer. Despite initial responses, many cancers eventually develop resistance to conventional therapies, leading to disease recurrence and progression (Marine, Dawson, & Dawson, 2020). This resistance is often driven by the ability of cancer cells to rewire their metabolic pathways, enabling them to withstand and evade the cytotoxic effects of treatment. In glutamine metabolism, cancer cells can activate compensatory pathways, alter glutamine uptake, or modify metabolic fluxes to circumvent the inhibitory effects of glutamine-targeted therapies. Therefore, a comprehensive understanding of these resistance mechanisms is crucial for developing strategies that can effectively overcome them.

The primary objective of this paper is to delve into the complex interplay between glutamine metabolism and therapeutic resistance in cancer. By examining the biochemical pathways of glutamine metabolism, the mechanisms by which cancer cells develop resistance to glutamine-targeted therapies, and potential strategies to counteract this resistance, this paper aims to contribute to the growing body of knowledge in this field. Such insights are expected to pave the way for developing innovative therapeutic approaches that can enhance the efficacy of cancer treatments and improve patient outcomes.

1. Glutamine Metabolism in Cancer Cells

Glutamine metabolism plays a critical role in the sustenance and proliferation of cancer cells, serving as a cornerstone of their metabolic reprogramming (Safrhansova, Hlozkova, & Starkova, 2022). Unlike normal cells, which primarily rely on glucose for their metabolic needs, many cancer cells highly depend on glutamine. This phenomenon, often referred to as "glutamine addiction," underscores the significance of this amino acid in supporting the aggressive growth and survival of malignant cells. Understanding the biochemical pathways of glutamine metabolism, its role in cell proliferation, and the differences between cancerous and normal cells is essential for developing targeted cancer therapies (Halama & Suhre, 2022).

1.1. Biochemical Pathways

The metabolic processing of glutamine in cancer cells involves several intricate biochemical pathways. Glutamine is first taken up by cells through specific transporters such as ASCT2 and SN2. Once inside the cell, glutamine can be converted into glutamate by the enzyme glutaminase (GLS). This conversion is critical, as glutamate is a key intermediate in several metabolic processes.

Glutamate can enter the tricarboxylic acid (TCA) cycle after being converted to α-ketoglutarate (α-KG) by either glutamate dehydrogenase (GDH) or through transamination reactions involving aminotransferases (Dorai, Pinto, Denton, Krasnikov, & Cooper, 2022). The entry of α-KG into the TCA cycle is crucial for maintaining the cycle's function, providing both energy and biosynthetic precursors. The TCA cycle generates ATP, reducing equivalents like NADH and FADH2 and intermediate metabolites essential for synthesizing nucleotides, amino acids, and lipids. This process is vital for rapidly proliferating cancer cells with increased biosynthesis and energy demands (Hinca *et al*., 2021).

Another significant pathway involving glutamine is the synthesis of glutathione, a major cellular antioxidant. Glutamate, cysteine, and glycine form glutathione, which helps maintain the redox balance within the cell. This is particularly important for cancer cells, as they are often subjected to high levels of oxidative stress due to their rapid growth and metabolic activity. Glutamine also plays a role in synthesizing other amino acids through transamination reactions, further contributing to the cellular pool of building blocks required for protein synthesis (Lieu, Nguyen, Rhyne, & Kim, 2020).

1.2. Role in Cell Proliferation

Glutamine's role in cancer cell proliferation is multifaceted. It provides carbon and nitrogen, which are essential for synthesizing nucleotides and amino acids. These building blocks are crucial for DNA replication and protein synthesis, processes that are highly upregulated in proliferating cancer cells. The conversion of glutamine to α-KG and its subsequent entry into the TCA cycle not only supplies energy but also generates precursors for the biosynthesis of fatty acids and cholesterol, vital components of cell membranes (Peng *et al*., 2021; Yoo *et al*., 2020).

Moreover, glutamine metabolism supports the production of ATP through the TCA cycle and oxidative phosphorylation. This is particularly important for cancer cells that require large amounts of energy to sustain their rapid growth and division. The generation of NADPH through the TCA cycle and the pentose phosphate pathway is another critical aspect of glutamine metabolism. NADPH is essential for reductive biosynthesis and for maintaining the cellular redox state, protecting cells from oxidative damage (Chandel, 2021).Glutamine also regulates cell signaling pathways involved in cell growth and survival. For instance, the activation of the mTOR pathway, which is crucial for protein synthesis and cell growth, can be influenced by glutamine availability. Additionally, glutamine metabolism can impact the activity of oncogenes and tumor suppressor genes, further highlighting its role in cancer cell biology (Delgir *et al*., 2021).

1.3. Comparison with Normal Cells

The differences in glutamine metabolism between cancerous and normal cells are profound and have significant implications for therapeutic strategies. While normal cells can utilize glutamine, they do not exhibit the same level of dependency as cancer cells. Normal cells typically rely more heavily on glucose metabolism through glycolysis and the TCA cycle for their energy and biosynthetic needs. They possess a greater metabolic flexibility and can switch between different nutrient sources based on availability and demand.

In contrast, many cancer cells have reprogrammed their metabolism to rely heavily on glutamine. This is partly due to the activation of oncogenes and loss of tumor suppressor genes, which drive the metabolic shift towards glutamine dependency. For example, the oncogene MYC is known to upregulate glutamine transporters and enzymes involved in glutamine metabolism, enhancing the cell's ability to utilize glutamine. Additionally, mutations in genes such as IDH1 and IDH2, which are involved in the TCA cycle, can alter the

metabolic fluxes in cancer cells, making them more reliant on glutamine (Eniafe & Jiang, 2021; Han *et al*., 2020).

Cancer cells' heavy reliance on glutamine presents a therapeutic opportunity. Targeting glutamine metabolism can selectively impair cancer cell viability while sparing normal cells, which have a greater ability to adapt to metabolic changes. Inhibitors of glutaminase, which converts glutamine to glutamate, have shown promise in preclinical studies by effectively reducing cancer cell growth and inducing cell death. Additionally, targeting glutamine transporters or key enzymes in the TCA cycle can further disrupt the metabolic pathways that cancer cells depend on.However, the metabolic plasticity of cancer cells also poses a challenge. Cancer cells can adapt to metabolic stress by activating alternative pathways or increasing the uptake of other nutrients. Therefore, understanding the metabolic network and the potential compensatory mechanisms is crucial for developing effective and durable therapeutic strategies (Ngoi *et al*., 2020; Sainero-Alcolado, Liaño-Pons, Ruiz-Pérez, & Arsenian-Henriksson, 2022).

In summary, glutamine metabolism in cancer cells involves a complex network of biochemical pathways that support their growth and survival. The conversion of glutamine to glutamate and its entry into the TCA cycle provides energy, biosynthetic precursors, and redox balance, all essential for rapidly proliferating cancer cells. The significant differences in glutamine metabolism between cancerous and normal cells highlight the potential for targeting this metabolic pathway in cancer therapy. However, the adaptive capacity of cancer cells necessitates a comprehensive understanding of their metabolic reprogramming to overcome therapeutic resistance effectively.

2. Mechanisms of Therapeutic Resistance

The challenge of therapeutic resistance in cancer treatment is a significant obstacle to achieving long-term remission and cure. Resistance to therapies targeting glutamine metabolism, in particular, is multifaceted, involving both intrinsic and adaptive mechanisms. These mechanisms allow cancer cells to survive and proliferate despite the metabolic stress imposed by therapeutic interventions. Furthermore, the intricate cross-talk between glutamine metabolism and other metabolic pathways enhances the resilience of cancer cells, complicating treatment efforts. This section explores the genetic and molecular factors contributing to intrinsic resistance, the adaptive strategies employed by cancer cells, and the interaction between glutamine metabolism and other metabolic pathways.

2.1. Intrinsic Resistance

Intrinsic resistance refers to the pre-existing genetic and molecular characteristics within cancer cells that confer an inherent ability to withstand therapeutic interventions. Several genetic mutations and alterations in signaling pathways contribute to intrinsic resistance to therapies targeting glutamine metabolism. For instance, mutations in oncogenes such as MYC and KRAS are known to enhance glutamine uptake and utilization, promoting cell survival and proliferation even in the presence of metabolic inhibitors (Kerk, Papagiannakopoulos, Shah, & Lyssiotis, 2021; Ni *et al*., 2023).

The MYC oncogene, in particular, plays a pivotal role in regulating glutamine metabolism. MYC upregulates the expression of glutamine transporters and enzymes involved in glutamine catabolism, such as ASCT2 and glutaminase (GLS). This upregulation ensures a steady supply of glutamine for energy production and biosynthesis. As a result, cancer cells with elevated MYC activity can maintain their metabolic demands even when glutamine availability is compromised. Similarly, mutations in KRAS can activate multiple signaling pathways that enhance glutamine metabolism, including the PI3K-AKT-mTOR pathway, further contributing to intrinsic resistance (Glaviano *et al*., 2023; Zhu *et al*., 2022).

Another key player in intrinsic resistance is the tumor suppressor gene TP53. Mutations or loss of TP53 function can lead to altered cellular metabolism and increased dependency on glutamine. TP53 is involved in regulating cellular stress responses, including metabolic stress. When TP53 is mutated, cancer cells can evade apoptosis and continue to thrive under conditions of metabolic stress, thereby resisting therapies targeting glutamine metabolism (Lacroix, Riscal, Arena, Linares, & Le Cam, 2020).

2.2. Adaptive Resistance

Adaptive resistance, on the other hand, develops as a result of cancer cells' ability to dynamically respond to and survive the selective pressures imposed by therapeutic interventions. This type of resistance involves metabolic reprogramming and the activation of alternative pathways that compensate for the inhibited glutamine metabolism. Adaptive resistance is characterized by the plasticity of cancer cells, allowing them to rapidly adapt to changing environmental conditions.

One common adaptive mechanism is the upregulation of compensatory metabolic pathways. For example, when glutaminase inhibitors are used to block glutamine conversion to glutamate, cancer cells can increase the uptake and utilization of other nutrients such as glucose and fatty acids. This metabolic flexibility allows cancer cells to maintain their energy production and biosynthetic needs despite inhibiting glutamine metabolism. Additionally, cancer cells can enhance the activity of enzymes involved in alternative pathways, such as pyruvate carboxylase, which provides an alternative source of α-ketoglutarate for the TCA cycle (Kumar, Ashraf, & CK, 2022).

Cancer cells can also adapt by altering their microenvironment to support survival. For instance, they can induce autophagy, where cells degrade and recycle their components to generate essential nutrients and maintain cellular homeostasis. Autophagy allows cancer cells to survive nutrient deprivation and therapeutic stress by providing an internal source of glutamine and other metabolites (Fares *et al*., 2022). This adaptive mechanism is particularly relevant in tumors with poor vascularization, with limited nutrient supply.Epigenetic modifications also play a role in adaptive resistance. Changes in DNA methylation and histone modifications can alter the expression of genes involved in glutamine metabolism and related pathways. These epigenetic alterations enable cancer cells to rapidly adapt to metabolic stress by reprogramming gene expression profiles. For example, increased histone deacetylases (HDACs) expression can lead to the repression of genes that inhibit glutamine metabolism, thereby promoting cell survival under therapeutic pressure (G. Li, Tian, & Zhu, 2020).

2.3. Cross-talk with Other Pathways

The extensive cross-talk between glutamine metabolism and

other metabolic pathways further compounds the complexity of therapeutic resistance. Cancer cells can exploit these interactions to enhance their survival and resistance to therapy. One such interaction involves the interplay between glutamine metabolism and glycolysis, often called the Warburg effect. Many cancer cells exhibit high rates of glycolysis even in the presence of oxygen, leading to increased lactate production and reliance on glucose for energy. This metabolic reprogramming can compensate for the inhibition of glutamine metabolism by providing alternative sources of ATP and biosynthetic precursors.

The pentose phosphate pathway (PPP) is another critical pathway that interacts with glutamine metabolism. The PPP generates NADPH, essential for maintaining redox balance and supporting anabolic reactions. Glutamine metabolism can contribute to the PPP by providing intermediates such as ribose-5-phosphate for nucleotide synthesis. Inhibition of glutamine metabolism can impact the PPP and disrupt the production of NADPH and nucleotides. However, cancer cells can adapt by upregulating glucose metabolism to support the PPP, thereby maintaining their redox balance and biosynthetic capacity (Ge *et al*., 2020; TeSlaa, Ralser, Fan, & Rabinowitz, 2023).

Furthermore, lipid metabolism is closely linked to glutamine metabolism. Glutamine-derived carbon can contribute to the synthesis of fatty acids and cholesterol, which are essential for membrane biogenesis and signaling. Inhibition of glutamine metabolism can disrupt lipid synthesis, leading to impaired cell growth and survival. However, cancer cells can activate alternative lipid synthesis pathways, such as those involving acetate or other amino acids, to compensate for the reduced availability of glutamine-derived carbon.

Additionally, the interaction between glutamine metabolism and amino acid sensing pathways, such as the mTOR pathway, plays a significant role in therapeutic resistance. The mTOR pathway regulates cell growth and metabolism in response to nutrient availability. Glutamine can activate the mTOR pathway directly or indirectly by influencing other amino acids such as leucine levels. Inhibition of glutamine metabolism can activate compensatory signaling pathways that maintain mTOR activity and support cell survival (C. Liu *et al*., 2021; Liu & Sabatini, 2020).

3. Strategies to Overcome Therapeutic Resistance

The development of therapeutic resistance is a significant challenge in cancer treatment, particularly concerning targeting glutamine metabolism. Several innovative strategies have been proposed and are under investigation to overcome this resistance. These strategies include targeting metabolic flexibility, utilizing combination therapies, and identifying emerging therapeutic targets. Each of these approaches aims to exploit the unique metabolic dependencies of cancer cells and enhance the efficacy of treatments.

3.1. Targeting Metabolic Flexibility

Cancer cells exhibit remarkable metabolic flexibility, allowing them to adapt to various metabolic stresses, including those imposed by therapeutic interventions. This adaptability is a major factor in therapeutic resistance, as cancer cells can switch to alternative metabolic pathways when their primary pathways are inhibited. Therefore, one promising strategy to overcome resistance is to inhibit these alternative metabolic pathways, effectively trapping cancer cells without viable metabolic escape routes.

One approach is to target the glycolytic pathway, which many cancer cells rely on for energy production even in the presence of oxygen, a phenomenon known as the Warburg effect. Inhibitors of key glycolytic enzymes, such as hexokinase 2 (HK2) and lactate dehydrogenase A (LDHA), can be used to disrupt glycolysis. By blocking glycolysis, cancer cells are deprived of a critical energy source and biosynthetic intermediates, which can potentiate the effects of glutamine metabolism inhibitors (Urbano, 2021; Vaupel & Multhoff, 2021).

Another target is the pentose phosphate pathway (PPP), which is crucial for generating NADPH and ribose-5-phosphate for nucleotide synthesis. Inhibitors of glucose-6-phosphate dehydrogenase (G6PD), the rate-limiting enzyme of the PPP, can reduce the availability of NADPH and nucleotides, exacerbating the metabolic stress on cancer cells already compromised by glutamine metabolism inhibition. This dual blockade can significantly impair cancer cell growth and survival.Additionally, targeting lipid metabolism can be effective. Cancer cells often rely on glutamine-derived carbon for lipid biosynthesis. Inhibitors of acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN), key enzymes in fatty acid synthesis, can disrupt lipid production and induce lipotoxicity in cancer cells. This approach can be particularly potent when combined with glutamine metabolism inhibitors, as it targets another critical aspect of cancer cell metabolism (Jin, Chai, & Hu, 2021; C. Li, Zhang, Qiu, Deng, & Wang, 2022).

3.2. Combination Therapies

Combination therapies represent another promising strategy to overcome therapeutic resistance in cancer treatment. By simultaneously targeting multiple pathways, combination therapies can reduce the likelihood of cancer cells developing resistance through metabolic adaptation. The rationale is to create a more hostile environment for cancer cells, making it more difficult for them to survive and proliferate.

One effective combination involves the use of glutamine metabolism inhibitors with traditional chemotherapies. For example, combining glutaminase inhibitors with cisplatin, a commonly used chemotherapy agent, has shown synergistic effects in preclinical studies. Cisplatin induces DNA damage, while glutaminase inhibitors exacerbate metabolic stress by depriving cancer cells of glutamine. This dual assault can enhance cancer cell death and reducetumor growth (Bera, Verma, Bhatt, & Dwarakanath, 2022).

Another combination approach is to use glutamine metabolism inhibitors with targeted therapies, such as inhibitors of the PI3K-AKT-mTOR pathway. This pathway is often upregulated in cancer cells and contributes to their growth and survival. By inhibiting both glutamine metabolism and the PI3K-AKT-mTOR pathway, cancer cells are deprived of essential nutrients and signaling cues, leading to a more comprehensive disruption of their metabolic and proliferative capabilities (Glaviano *et al*., 2023).

Immune checkpoint inhibitors, such as those targeting PD-1/PD-L1, represent another promising partner for combination therapies. These inhibitors enhance the immune system's ability to recognize and destroy cancer cells. Combining immune checkpoint inhibitors with glutamine metabolism inhibitors can create a hostile metabolic environment for cancer cells while simultaneously boosting the immune response. This approach can potentially improve

treatment outcomes, particularly in tumors that are otherwise resistant to immune checkpoint blockade alone (J. Liu *et al*., 2021).

3.3. Emerging Therapeutic Targets

As our understanding of cancer metabolism deepens, several novel targets within glutamine metabolism and related pathways have emerged. These targets offer new opportunities for developing therapies to overcome resistance and improve treatment efficacy.One emerging target is the enzyme glutamate dehydrogenase (GDH), which converts glutamate to α-ketoglutarate, feeding into the TCA cycle. Inhibiting GDH can disrupt this critical step, impairing the TCA cycle and energy production. GDH inhibitors have shown promise in preclinical studies, particularly in combination with other metabolic inhibitors (Kumar *et al*., 2022).

Another promising target is the amino acid transporter ASCT2 (also known as SLC1A5), which is responsible for glutamine uptake into cells. Inhibiting ASCT2 can reduce glutamine availability for cancer cells, effectively starving them of this essential nutrient. ASCT2 inhibitors are currently being explored in preclinical models, with encouraging results.Additionally, the enzyme glutaminase 2 (GLS2), which is involved in converting glutamine to glutamate, represents another potential target. GLS2 has a distinct expression pattern and regulatory mechanisms compared to GLS1, the primary glutaminase targeted by existing inhibitors. Targeting GLS2 could provide an alternative approach to disrupt glutamine metabolism, particularly in cancers where GLS1 inhibition is less effective (Conger, 2024; Yoshida, 2021).

Beyond glutamine metabolism, targeting the amino acid sensing pathways, such as the mTORC1 pathway, is another emerging strategy. mTORC1 integrates nutrient signals, including amino acids like glutamine, to regulate cell growth and metabolism. Inhibitors of mTORC1, or its upstream regulators such as the Rag GTPases, can disrupt this nutrient-sensing pathway, thereby inhibiting cancer cell growth and proliferation.Epigenetic regulators of metabolic genes also present novel therapeutic targets. Histone deacetylases and DNA methyltransferases (DNMTs) can modulate gene expression in glutamine metabolism and other metabolic pathways. Inhibitors of these epigenetic regulators can reprogram cancer cell metabolism and sensitize them to metabolic inhibitors (Saggese *et al*., 2020).

4. Future Perspectives and Clinical Implications

The landscape of cancer treatment is continuously evolving, driven by research and clinical practice advances. In the realm of targeting glutamine metabolism, several promising trends and developments hold the potential to significantly impact therapeutic strategies and patient outcomes.

4.1. Advances in Research

Current research trends focus on a deeper understanding of the metabolic dependencies of cancer cells, particularly their reliance on glutamine. Advanced metabolomics and genomics techniques enable researchers to map the intricate networks of metabolic pathways and identify key nodes that can be targeted therapeutically. Additionally, the integration of computational modeling with experimental data is providing new insights into the metabolic vulnerabilities of cancer cells, leading to the identification of novel therapeutic targets.

Emerging research is also exploring the role of the tumor microenvironment in modulating glutamine metabolism. The interaction between cancer cells and their surrounding stroma, immune cells, and vasculature can significantly influence metabolic pathways and therapeutic responses. Researchers aim to develop more effective and context-specific treatments by elucidating these interactions.

Numerous clinical trials are underway to evaluate the efficacy of targeting glutamine metabolism in cancer. These trials explore various strategies, including glutaminase inhibitors, glutamine transport inhibitors, and combination therapies. Early-phase trials have shown promising results, with some agents demonstrating significant anti-tumor activity and manageable safety profiles. Ongoing trials are focused on optimizing dosing regimens, identifying biomarkers for patient selection, and evaluating combination strategies to enhance efficacy.

4.2. Translational Potential

The potential for translating research findings into clinical practice is substantial. The identification of biomarkers that predict response to glutamine-targeted therapies can enable personalized treatment approaches, improving efficacy and reducing toxicity. Furthermore, developing robust diagnostic tools to monitor tumour metabolic changes can facilitate the real-time assessment of treatment responses and adjustments.Collaborative efforts between academic institutions, pharmaceutical companies, and clinicalresearchers are accelerating the translation of preclinical findings into clinical applications. These collaborations are essential for bridging the gap between bench and bedside, ensuring that promising therapies reach patients promptly.

Despite significant progress, several challenges remain in overcoming therapeutic resistance. The metabolic plasticity of cancer cells allows them to adapt to targeted therapies, necessitating the development of multi-targeted approaches. Additionally, the heterogeneity of tumors poses a challenge for the efficacy of metabolic inhibitors, as different tumor subtypes may exhibit distinct metabolic profiles.

Future research opportunities lie in the exploration of combination therapies that target multiple metabolic pathways simultaneously. Leveraging insights from systems biology and high-throughput screening can aid in identifying synergistic drug combinations. Moreover, investigating the interplay between metabolic pathways and other cellular processes, such as epigenetics and immune responses, can provide a comprehensive understanding of therapeutic resistance mechanisms.

References

1. Basak D, Uddin MN, Hancock J. The role of oxidative stress and its counteractive utility in colorectal cancer (CRC). Cancers. 2020;12(11):3336.
2. Bera S, Verma A, Bhatt AN, Dwarakanath BS. Metabolic oxidative stress in initiation, progression, and therapy of cancer. In: Bera S, Verma A, Bhatt AN, Dwarakanath BS, editors. Handbook of Oxidative Stress in Cancer: Mechanistic Aspects. Springer; 2022. p. 1969-2003.
3. Chandel NS. NADPH—the forgotten reducing equivalent. Cold Spring Harb Perspect Biol. 2021;13(6):a040550.

4. Conger K. Identification of ASCT2 as the primary serine transporter in cancer [dissertation]. University of Illinois at Chicago; 2024.
5. Delgir S, Bastami M, Ilkhani K, Safi A, Seif F, Alivand MR. The pathways related to glutamine metabolism, glutamine inhibitors and their implication for improving the efficiency of chemotherapy in triple-negative breast cancer. Mutat Res Rev Mutat Res. 2021;787:108366.
6. Dorai T, Pinto JT, Denton TT, Krasnikov BF, Cooper AJ. The metabolic importance of the glutaminase II pathway in normal and cancerous cells. Anal Biochem. 2022;644:114083.
7. Eniafe J, Jiang S. The functional roles of TCA cycle metabolites in cancer. Oncogene. 2021;40(19):3351-63.
8. Fares HM, Lyu X, Xu X, Dong R, Ding M, Mi S, *et al*. Autophagy in cancer: The cornerstone during glutamine deprivation. Eur J Pharmacol. 2022;916:174723.
9. Ge T, Yang J, Zhou S, Wang Y, Li Y, Tong X. The role of the pentose phosphate pathway in diabetes and cancer. Front Endocrinol. 2020;11:365.
10. Glaviano A, Foo AS, Lam HY, Yap KC, Jacot W, Jones RH, *et al*. PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer. Mol Cancer. 2023;22(1):138.
11. Halama A, Suhre K. Advancing cancer treatment by targeting glutamine metabolism—A roadmap. Cancers. 2022;14(3):553.
12. Han S, Liu Y, Cai SJ, Qian M, Ding J, Larion M, *et al*. IDH mutation in glioma: molecular mechanisms and potential therapeutic targets. Br J Cancer. 2020;122(11):1580-9.
13. Hinca SB, Salcedo C, Wagner A, Goldeman C, Sadat E, Aibar MM, *et al*. Brain endothelial cells metabolize glutamate via glutamate dehydrogenase to replenish TCA-intermediates and produce ATP under hypoglycemic conditions. J Neurochem. 2021;157(6):1861-75.
14. Jin Z, Chai YD, Hu S. Fatty acid metabolism and cancer. In: Jin Z, Chai YD, Hu S, editors. Cancer Metabolomics: Methods and Applications. 2021. p. 231-41.
15. Johariya V, Joshi A, Malviya N, Malviya S. Introduction to cancer. In: Johariya V, Joshi A, Malviya N, Malviya S, editors. Medicinal Plants and Cancer Chemoprevention. CRC Press; 2024. p. 1-28.
16. Kerk SA, Papagiannakopoulos T, Shah YM, Lyssiotis CA. Metabolic networks in mutant KRAS-driven tumours: tissue specificities and the microenvironment. Nat Rev Cancer. 2021;21(8):510-25.
17. Kumar S, Ashraf R, CK A. Mitochondrial dynamics regulators: implications for therapeutic intervention in cancer. Cell Biol Toxicol. 2022;1-30.
18. Lacroix M, Riscal R, Arena G, Linares LK, Le Cam L. Metabolic functions of the tumor suppressor p53: Implications in normal physiology, metabolic disorders, and cancer. Mol Metab. 2020;33:2-22.
19. Li C, Zhang L, Qiu Z, Deng W, Wang W. Key molecules of fatty acid metabolism in gastric cancer. Biomolecules. 2022;12(5):706.
20. Li G, Tian Y, Zhu WG. The roles of histone deacetylases and their inhibitors in cancer therapy. Front Cell Dev Biol. 2020;8:576946.
21. Lieu EL, Nguyen T, Rhyne S, Kim J. Amino acids in cancer. Exp Mol Med. 2020;52(1):15-30.
22. Liu C, Ji L, Hu J, Zhao Y, Johnston LJ, Zhang X, *et al*. Functional amino acids and autophagy: diverse signal transduction and application. Int J Mol Sci. 2021;22(21):11427.
23. Liu GY, Sabatini DM. mTOR at the nexus of nutrition, growth, ageing and disease. Nat Rev Mol Cell Biol. 2020;21(4):183-203.
24. Liu J, Chen Z, Li Y, Zhao W, Wu J, Zhang Z. PD-1/PD-L1 checkpoint inhibitors in tumor immunotherapy. Front Pharmacol. 2021;12:731798.
25. Marine JC, Dawson SJ, Dawson MA. Non-genetic mechanisms of therapeutic resistance in cancer. Nat Rev Cancer. 2020;20(12):743-56.
26. Ngoi NY, Eu JQ, Hirpara J, Wang L, Lim JS, Lee SC, *et al*. Targeting cell metabolism as cancer therapy. Antioxid Redox Signal. 2020;32(5):285-308.
27. Ni R, Li Z, Li L, Peng D, Ming Y, Li L, *et al*. Rethinking glutamine metabolism and the regulation of glutamine addiction by oncogenes in cancer. Front Oncol. 2023;13:1143798.
28. Peng J, Cui Y, Xu S, Wu X, Huang Y, Zhou W, *et al*. Altered glycolysis results in drug-resistant in clinical tumor therapy. Oncol Lett. 2021;21(5):1-14.
29. Quek LE, van Geldermalsen M, Guan YF, Wahi K, Mayoh C, Balaban S, *et al*. Glutamine addiction promotes glucose oxidation in triple-negative breast cancer. Oncogene. 2022;41(34):4066-78.
30. Safrhansova L, Hlozkova K, Starkova J. Targeting amino acid metabolism in cancer. Int Rev Cell Mol Biol. 2022;373:37-79.
31. Saggese P, Sellitto A, Martinez CA, Giurato G, Nassa G, Rizzo F, *et al*. Metabolic regulation of epigenetic modifications and cell differentiation in cancer. Cancers. 2020;12(12):3788.
32. Bitragunta Sree Lakshmi Vineetha. A novel AI-blockchain-edge framework for fast and secure transient stability assessment in smart grids. Int J Multidiscip Res. 2024;6(6).
33. Sainero-Alcolado L, Liaño-Pons J, Ruiz-Pérez MV, Arsenian-Henriksson M. Targeting mitochondrial metabolism for precision medicine in cancer. Cell Death Differ. 2022;29(7):1304-17.
34. TeSlaa T, Ralser M, Fan J, Rabinowitz JD. The pentose phosphate pathway in health and disease. Nat Metab. 2023;5(8):1275-89.
35. Tu SM, Chen JZ, Singh SR, Maraboyina S, Gokden N, Hsu PC, *et al*. Stem cell theory of cancer: Clinical implications for cellular metabolism and anti-cancer metabolomics. Cancers. 2024;16(3):624.
36. Urbano AM. Otto Warburg: The journey towards the seminal discovery of tumor cell bioenergetic reprogramming. Biochim Biophys Acta Mol Basis Dis. 2021;1867(1):165965.
37. Vaupel P, Multhoff G. Revisiting the Warburg effect: historical dogma versus current understanding. J Physiol. 2021;599(6):1745-57.
38. Yoo HC, Yu YC, Sung Y, Han JM. Glutamine reliance in cell metabolism. Exp Mol Med. 2020;52(9):1496-516.
39. Yoshida GJ. The harmonious interplay of amino acid and monocarboxylate transporters induces the robustness of cancer cells. Metabolites. 2021;11(1):27.
40. Zhu C, Guan X, Zhang X, Luan X, Song Z, Cheng X, *et al*. Targeting KRAS mutant cancers: from druggable therapy to drug resistance. Mol Cancer. 2022;21(1):159.