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A review of metabolic reprogramming in cancer cells: Mechanisms and therapeutic targets

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Abstract

Metabolic reprogramming is a hallmark of cancer, enabling tumor cells to sustain rapid proliferation, resist cell death, and adapt to varying microenvironmental conditions. This review elucidates the key mechanisms underlying metabolic reprogramming in cancer cells, including alterations in glucose metabolism, glutamine addiction, and lipid biosynthesis. A central feature of cancer metabolism is the Warburg effect, where cancer cells preferentially utilize aerobic glycolysis over oxidative phosphorylation, even in the presence of oxygen. This metabolic shift is driven by oncogenes and tumor suppressor genes, such as MYC and TP53, which modulate the expression and activity of enzymes involved in glycolysis and mitochondrial function. Additionally, cancer cells exhibit increased glutaminolysis, relying on glutamine as a carbon and nitrogen source to support anabolic processes and redox balance. Lipid metabolism is also reprogrammed, with enhanced de novo lipogenesis supplying membrane components and signaling molecules critical for tumor growth and survival. Understanding these metabolic alterations provides a basis for developing targeted therapies. Several therapeutic strategies have emerged, including inhibitors of key metabolic enzymes, such as hexokinase 2 (HK2), pyruvate kinase M2 (PKM2), and glutaminase. Metabolic interventions can disrupt the metabolic flexibility of cancer cells, sensitizing them to conventional therapies and overcoming resistance mechanisms. This review highlights the potential of metabolic targets in cancer treatment and emphasizes the need for personalized approaches considering tumor-specific metabolic profiles. Future research should focus on identifying biomarkers of metabolic vulnerabilities and developing combination therapies that exploit the intricate metabolic dependencies of cancer cells. Ultimately, targeting metabolic reprogramming holds promise for improving cancer prognosis and achieving more effective and durable therapeutic outcomes.

Keywords: Metabolic Reprogramming; Cancer cells; Therapeutic target

1. Introduction

Cancer remains a significant global health challenge, accounting for millions of deaths annually worldwide (Bray *et al.*, 2018). Characterized by uncontrolled cell growth and proliferation, cancer arises from genetic mutations that disrupt normal cellular processes, leading to the development of malignant tumors (Nenclares and Harrington, 2020). The complexity and heterogeneity of cancer make it a multifaceted disease requiring diverse treatment approaches (Compton, 2020). Central to cancer biology is the concept of metabolic reprogramming, which refers to the profound alterations in cellular metabolism that enable cancer cells to meet the increased demands of rapid proliferation and survival in hostile microenvironments. Normal cells typically rely on oxidative phosphorylation (OXPHOS) for energy production, a process that efficiently generates adenosine triphosphate (ATP) using oxygen (Schirrmacher, 2020). In contrast, cancer cells often exhibit a metabolic preference known as the Warburg effect, where they preferentially utilize aerobic glycolysis even in the presence of adequate oxygen. This metabolic shift not only facilitates the generation of

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ATP but also provides metabolic intermediates necessary for biosynthesis, such as nucleotides, amino acids, and lipids (Schiliro and Firestein, 2022). Studying metabolic reprogramming in cancer cells is crucial for several reasons. First, it offers insights into the fundamental differences between normal and malignant cells, shedding light on the mechanisms driving tumor growth and progression. Second, understanding these metabolic adaptations can uncover vulnerabilities that may be exploited for therapeutic purposes. Third, metabolic reprogramming contributes to treatment resistance, making it essential to develop strategies that target metabolic dependencies alongside conventional therapies.

The primary objective of this review is to comprehensively summarize the current understanding of metabolic reprogramming mechanisms in cancer cells. This includes exploring the key metabolic pathways involved, such as glycolysis, glutaminolysis, and lipid metabolism, and elucidating how these pathways are dysregulated in cancer. By synthesizing existing research findings, we aim to provide a cohesive overview of the molecular and biochemical processes underlying metabolic reprogramming. Furthermore, this review aims to discuss potential therapeutic targets within these metabolic pathways. Given the pivotal role of metabolic alterations in cancer progression, targeting specific enzymes and metabolic pathways represents a promising approach for developing novel anticancer therapies (Qin *et al*., 2020). The efficacy of targeting key enzymes involved in glycolysis, such as hexokinase 2 (HK2) and pyruvate kinase M2 (PKM2), as well as inhibitors of glutaminolysis and lipid biosynthesis. Additionally, we will explore the concept of metabolic vulnerabilities and the potential of combination therapies that exploit these vulnerabilities to enhance treatment outcomes. This review aims to advance our understanding of metabolic reprogramming in cancer cells and its implications for therapeutic intervention. By elucidating the intricate metabolic networks that sustain tumor growth and survival, hope to contribute to the development of more effective and personalized treatment strategies for cancer patients.

2. Metabolic Reprogramming in Cancer Cells

Glycolysis is the metabolic pathway that converts glucose into pyruvate, generating ATP and NADH in the process (Chandel *et al*., 2021). This ten-step process occurs in the cytoplasm and does not require oxygen. In normal cells, glycolysis is a preparatory step for further oxidation of pyruvate in the mitochondria, under aerobic conditions.

Oxidative phosphorylation is a crucial process occurring in the mitochondria, where ATP is produced through the electron transport chain and chemiosmosis (Tabassum *et al*., 2020). Electrons from NADH and FADH2 are transferred through a series of complexes, ultimately reducing oxygen to water (Banerjee and Sadler, 2021). This process generates a proton gradient across the inner mitochondrial membrane, driving ATP synthesis. Oxidative phosphorylation is highly efficient, producing up to 36 molecules of ATP per glucose molecule (Nesci *et al*., 2021). Lipid metabolism encompasses the synthesis and degradation of lipids in cells, primarily involving fatty acids and triglycerides. Fatty acids are broken down via beta-oxidation in the mitochondria, producing acetyl-CoA, which enters the Krebs cycle for energy production (Zhelev *et al*., 2022). Lipids also serve as key structural components of cell membranes and signaling molecules. Amino acid metabolism involves the synthesis and degradation of amino acids. In normal cells, amino acids are primarily used for protein synthesis, but they can also be deaminated to produce intermediates for the Krebs cycle, providing an additional energy source. Certain amino acids, such as glutamine, play pivotal roles in cellular metabolism, contributing to nucleotide and lipid synthesis (Kelly and Pearce, 2020).

One of the hallmarks of cancer metabolism is the Warburg effect, where cancer cells preferentially utilize glycolysis over oxidative phosphorylation for ATP production, even in the presence of oxygen. This aerobic glycolysis results in the production of lactate from pyruvate, yielding less ATP compared to oxidative phosphorylation (Schurr and Passarella, 2022). However, this metabolic reprogramming supports rapid cell proliferation by providing intermediates for biosynthetic pathways. Cancer cells exhibit altered mitochondrial function, contributing to metabolic reprogramming (Li *et al*., 2021). These alterations include changes in mitochondrial dynamics, such as fission and fusion, and mutations in mitochondrial DNA. The mitochondria in cancer cells often have impaired oxidative phosphorylation, forcing cells to rely more on glycolysis. This shift helps cancer cells survive in hypoxic tumor microenvironments and supports anabolic processes necessary for growth and division. Cancer cells also reprogram lipid metabolism to support their rapid proliferation (Koundouros and Poulogiannis, 2020). They increase de novo lipid synthesis, enhancing the production of fatty acids and cholesterol required for membrane biosynthesis. Additionally, cancer cells often exhibit upregulated fatty acid uptake and beta-oxidation. These changes provide energy and biosynthetic precursors for membrane formation and signaling molecules, facilitating tumor growth and metastasis. Altered amino acid metabolism is another hallmark of cancer cells. Cancer cells often show increased uptake and utilization of amino acids, particularly glutamine. Glutamine is converted to glutamate and then to alpha-ketoglutarate, fueling the Krebs cycle and supporting biosynthesis of nucleotides, amino acids, and lipids (Li and Le, 2018; Abdul *et al*., 2024). Some cancer cells are also capable of synthesizing non-essential amino acids to sustain their proliferative demands. This reprogramming ensures a continuous supply of building blocks and energy for rapid cell division.

Metabolic reprogramming is a fundamental aspect of cancer cell biology, enabling tumors to sustain uncontrolled growth and proliferation (Schiliro and Firestein, 2021). By understanding these metabolic alterations, new therapeutic strategies can be developed to target the metabolic vulnerabilities of cancer cells, potentially improving treatment outcomes.

2.1. Mechanisms Underlying Metabolic Reprogramming

Metabolic reprogramming is a hallmark of cancer, allowing tumor cells to meet the increased energy demands and biosynthetic needs required for rapid proliferation (Navarro *et al*., 2022). This reprogramming is driven by a combination of genetic alterations, epigenetic modifications, signal transduction pathways, and microenvironmental influences.

Oncogenes are genes that, when mutated or overexpressed, drive the transformation of normal cells into cancerous ones (Martínez-Jiménez *et al*., 2020). The MYC oncogene, for example, plays a crucial role in metabolic reprogramming by upregulating glycolysis and glutaminolysis, pathways essential for the rapid growth of cancer cells. MYC increases the expression of glucose transporters and glycolytic enzymes, thereby enhancing glucose uptake and metabolism. Similarly, RAS oncogenes, when mutated, activate pathways that promote anabolic processes, such as lipid synthesis and nucleotide production, further supporting tumor growth and survival. Tumor suppressor genes typically function to inhibit cell proliferation and promote apoptosis. Mutations in these genes can lead to unchecked cell growth and metabolic reprogramming. The tumor suppressor p53, for instance, regulates cellular metabolism by modulating oxidative phosphorylation and glycolysis. Loss of p53 function often results in a shift towards glycolysis, known as the Warburg effect. PTEN, another tumor suppressor, negatively regulates the PI3K/AKT pathway, and its loss leads to enhanced glycolysis and lipid synthesis, promoting cancer cell survival and growth (Pascale *et al*, 2020; Abdul *et al*., 2024).

Epigenetic modifications, such as DNA methylation, play a significant role in regulating gene expression and, consequently, cellular metabolism (Huo *et al*., 2021). Aberrant DNA methylation patterns in cancer can lead to the silencing of tumor suppressor genes and activation of oncogenes. For example, hypermethylation of the promoter regions of genes involved in oxidative phosphorylation can result in reduced mitochondrial function and a shift towards glycolysis. This alteration supports the rapid proliferation and survival of cancer cells under hypoxic conditions (Abdul *et al*., 2024). Histone modifications, including acetylation, methylation, and phosphorylation, also influence gene expression and metabolic reprogramming in cancer. Histone acetylation generally leads to an open chromatin structure and increased gene expression. In cancer, histone acetylation of genes involved in glycolysis and lipid metabolism can enhance their expression, promoting anabolic processes necessary for tumor growth (Morrison, 2022). Conversely, histone methylation can either activate or repress gene expression, depending on the specific histone residue and context.

The PI3K/AKT/mTOR pathway is a central regulator of cellular metabolism, growth, and survival (Cirone *et al*., 2021). Activation of this pathway, often through mutations in upstream components like PI3K or loss of PTEN, leads to increased glucose uptake and glycolysis, lipid synthesis, and protein translation. mTOR, in particular, promotes anabolic processes by enhancing the expression of genes involved in glycolysis, lipid synthesis, and nucleotide biosynthesis, thereby supporting cancer cell proliferation. Hypoxia-inducible factor 1 (HIF-1) is a transcription factor activated under low oxygen conditions (hypoxia) (Mukherjee and Ray, 2022). HIF-1 upregulates the expression of glycolytic enzymes and glucose transporters, facilitating the Warburg effect. It also promotes angiogenesis and adaptation to hypoxic environments by inducing the expression of vascular endothelial growth factor (VEGF) (Du *et al*., 2021; Abdul *et al*., 2024). This adaptation is crucial for tumor survival and growth in poorly oxygenated regions of the tumor microenvironment. The AMP-activated protein kinase (AMPK) pathway acts as a cellular energy sensor, responding to low energy levels by inhibiting anabolic processes and promoting catabolic pathways to restore energy balance. In cancer, the AMPK pathway is often downregulated, allowing cancer cells to bypass energy stress and continue proliferating (Chomanicova *et al*., 2021). However, in some contexts, AMPK activation can inhibit tumor growth by blocking mTOR signaling and inducing autophagy.

The tumor microenvironment is characterized by regions of hypoxia due to inadequate blood supply (Roy *et al*., 2020). Hypoxia stabilizes HIF-1, leading to metabolic reprogramming that favors glycolysis over oxidative phosphorylation. This adaptation enables cancer cells to thrive in low oxygen conditions and contributes to their aggressive behavior. Fluctuations in nutrient availability within the tumor microenvironment also drive metabolic reprogramming. Cancer cells adapt by upregulating nutrient transporters and altering metabolic pathways to efficiently utilize available resources (Yadav *et al*., 2020). For example, increased glucose and glutamine uptake supports glycolysis and glutaminolysis, providing energy and biosynthetic precursors. Interactions between cancer cells and stromal cells in the

tumor microenvironment further influence metabolic reprogramming. Stromal cells, such as fibroblasts and immune cells, secrete cytokines and growth factors that modulate cancer cell metabolism. For instance, cancer-associated fibroblasts can provide lactate and other metabolites to cancer cells, supporting their metabolic needs and promoting tumor growth. Metabolic reprogramming in cancer is a complex process driven by genetic alterations, epigenetic modifications, signal transduction pathways, and microenvironmental influences (Abdul *et al*., 2024). Understanding these mechanisms is crucial for developing targeted therapies that can disrupt the metabolic dependencies of cancer cells and improve treatment outcomes.

2.2. Metabolic Pathways in Cancer Cells

Cancer cells exhibit distinct metabolic alterations that enable them to sustain rapid proliferation, survive in harsh environments, and resist cell death (Kreuzaler *et al*., 2020). These metabolic changes, collectively known as metabolic reprogramming, involve shifts in glycolysis and glucose metabolism, mitochondrial metabolism, lipid metabolism, and amino acid metabolism.

Cancer cells often rely on glycolysis for energy production, even in the presence of oxygen, a phenomenon known as the Warburg effect. This metabolic shift is driven by key enzymes such as hexokinase 2 (HK2) and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) (Gold, 2020). HK2 catalyzes the first step of glycolysis, converting glucose to glucose-6-phosphate, which is critical for trapping glucose within the cell and initiating glycolytic flux. PFKFB3 increases levels of fructose-2,6-bisphosphate, a potent activator of phosphofructokinase-1 (PFK1), thus enhancing the glycolytic pathway. The end product of glycolysis, pyruvate, is often converted to lactate by lactate dehydrogenase A (LDHA) in cancer cells. This conversion regenerates NAD+, necessary for continued glycolysis under anaerobic conditions. Lactate production and export, facilitated by monocarboxylate transporters (MCTs), prevent intracellular acidification and promote an acidic tumor microenvironment, which can aid in immune evasion and invasion (Pérez-Tomás and Pérez-Guillén, 2020; Abdul *et al*., 2024).

Despite the reliance on glycolysis, mitochondrial metabolism remains essential in cancer cells. Alterations in the tricarboxylic acid (TCA) cycle are common, including increased uptake of intermediates like citrate and succinate. These changes support biosynthetic processes and redox balance (Scagliola *et al*., 2020; Maha *et al*., 2024). Mutations in TCA cycle enzymes, such as isocitrate dehydrogenase (IDH1/2), can lead to the production of oncometabolites like 2-hydroxyglutarate, which contribute to oncogenesis by altering epigenetic regulation. Mitochondrial dynamics, including fission and fusion processes, also play a critical role in cancer cell metabolism. Enhanced mitochondrial fission, regulated by dynamin-related protein 1 (DRP1), facilitates rapid adaptation to metabolic stress and supports cell proliferation. Conversely, mitochondrial fusion helps maintain mitochondrial function and integrity, critical for cancer cell survival (Adebayo *et al*., 2021).

Lipid metabolism is markedly reprogrammed in cancer cells to support membrane biosynthesis, energy production, and signaling. Fatty acid synthesis is upregulated, with enzymes like fatty acid synthase (FASN) and acetyl-CoA carboxylase (ACC) playing pivotal roles (Wang *et al*., 2022). These enzymes drive the conversion of acetyl-CoA to malonyl-CoA and subsequently to long-chain fatty acids, which are essential for the formation of new cell membranes. Fatty acid oxidation (FAO) also contributes to the metabolic flexibility of cancer cells, providing ATP and reducing equivalents under nutrient-limited conditions. Lipid droplets, intracellular organelles storing neutral lipids, are abundant in many cancer cells. They serve as reservoirs of fatty acids and cholesterol, supporting membrane synthesis and energy production during metabolic stress.

Amino acid metabolism is crucial for cancer cell growth and survival. Many cancer cells exhibit "glutamine addiction," relying heavily on glutamine for anaplerosis, redox balance, and biosynthesis (Halama and Suhre, 2022; Maha *et al*., 2024). Glutamine is converted to glutamate by glutaminase (GLS), and then to alpha-ketoglutarate, which feeds into the TCA cycle. Serine and glycine metabolism also play vital roles in cancer cells, particularly in nucleotide and lipid biosynthesis. Serine is synthesized from 3-phosphoglycerate, a glycolytic intermediate, and is used in the production of glycine and one-carbon units essential for purine and pyrimidine synthesis. Glycine contributes to the synthesis of glutathione, a critical antioxidant that helps maintain redox balance in cancer cells. The metabolic pathways in cancer cells are intricately reprogrammed to support their high proliferative and survival demands. Understanding these pathways provides insights into potential therapeutic targets, as disrupting key metabolic processes can impair cancer cell growth and survival.

2.3. Therapeutic Targets in Metabolic Pathways

Targeting metabolic pathways in cancer cells offers a promising avenue for developing novel cancer therapies (Ngoi *et al*., 2020). By disrupting the metabolic processes essential for tumor growth and survival, researchers aim to create

effective treatments with potentially fewer side effects. This discusses the current strategies for targeting glycolysis, mitochondrial metabolism, lipid metabolism, and amino acid metabolism in cancer therapy.

Cancer cells often rely on glycolysis for ATP production and biosynthesis, even in the presence of oxygen. This phenomenon, known as the Warburg effect, makes glycolytic enzymes attractive therapeutic targets. Hexokinase 2 (HK2), which catalyzes the first step of glycolysis, is overexpressed in many tumors. Inhibitors such as 2-deoxy-D-glucose (2-DG) and lonidamine target HK2, reducing glycolytic flux and energy production (Zhang *et al*., 2022). Another key enzyme is pyruvate kinase M2 (PKM2), which regulates the final step of glycolysis. Small molecules like TEPP-46 and shikonin activate PKM2, promoting a metabolic shift that can hinder cancer cell proliferation. Glycolysis inhibitors have shown promise in preclinical studies and early-phase clinical trials. 2-DG, for example, has been tested in combination with chemotherapy and radiotherapy, demonstrating enhanced anti-tumor effects. However, the clinical efficacy of glycolysis inhibitors has been limited by toxicity and off-target effects, necessitating further optimization and combination strategies to improve therapeutic outcomes (Zhao *et al*., 2020).

Mitochondrial respiration is crucial for energy production and biosynthesis in cancer cells. Inhibitors of mitochondrial complexes, such as metformin (which targets complex I) and oligomycin (which targets complex V), disrupt ATP production and induce metabolic stress. These inhibitors can sensitize cancer cells to other treatments by impairing their energy supply and promoting apoptosis. Mitochondrial biogenesis and dynamics, including fission and fusion processes, are essential for maintaining mitochondrial function and adapting to metabolic demands. Drugs like Mdivi-1, which inhibits the fission protein Drp1, have shown potential in reducing tumor growth by inducing mitochondrial dysfunction (Deng *et al*., 2020). Targeting mitochondrial biogenesis through compounds like resveratrol, which activates PGC-1α, may also impair cancer cell survival by disrupting their metabolic flexibility.

Cancer cells often upregulate fatty acid synthesis to support membrane production and signaling. Fatty acid synthase (FASN) is a key enzyme in this pathway, and its inhibition by compounds like orlistat and TVB-2640 has demonstrated anti-tumor activity. By blocking fatty acid synthesis, these inhibitors reduce the availability of lipids needed for cell growth and division, leading to cancer cell death (Fhu and Ali, 2020). Lipid metabolism inhibitors are being explored in various cancer types, particularly those with high rates of lipid synthesis. TVB-2640, for instance, is currently undergoing clinical trials for breast cancer and other solid tumors. These inhibitors may also enhance the efficacy of existing therapies by disrupting the lipid-dependent signaling pathways that drive cancer progression.

Glutamine addiction is a hallmark of many cancers, as glutamine supports anabolic processes and redox balance. Inhibitors of glutaminase (GLS), the enzyme that converts glutamine to glutamate, such as CB-839, have shown promise in preclinical models (Nguyen *et al*., 2022). By blocking glutamine metabolism, these inhibitors induce metabolic stress and apoptosis in cancer cells dependent on glutamine. Serine and glycine are critical for nucleotide synthesis and one-carbon metabolism. Inhibitors targeting serine biosynthesis enzymes, such as PHGDH inhibitors, reduce the availability of serine for cancer cell growth. Additionally, targeting the enzyme SHMT, which converts serine to glycine, disrupts glycine metabolism and impairs nucleotide synthesis. These strategies are being investigated for their potential to selectively target cancer cells with high serine and glycine demands.

Targeting metabolic pathways in cancer cells represents a promising approach to cancer therapy. By inhibiting key enzymes and pathways involved in glycolysis, mitochondrial metabolism, lipid metabolism, and amino acid metabolism, researchers aim to develop effective treatments that can disrupt the metabolic dependencies of cancer cells and improve patient outcomes (Shen *et al*., 2021; Zhu *et al*., 2022).

2.4. Challenges and Future Directions in Targeting Cancer Metabolism

One of the major challenges in targeting cancer metabolism is the development of drug resistance. Cancer cells can adapt to metabolic inhibitors by activating alternative pathways or upregulating compensatory mechanisms (Park *et al*., 2020). For instance, when glycolysis is inhibited, cancer cells may increase their reliance on oxidative phosphorylation or fatty acid oxidation.

This metabolic plasticity allows tumors to survive and continue proliferating despite therapeutic interventions, necessitating the development of strategies to overcome or prevent resistance (Sebestyén *et al*., 2021). Cancer cells exhibit remarkable metabolic flexibility, allowing them to thrive under various environmental conditions. This adaptability complicates the design of effective metabolic therapies, as targeting a single pathway may not be sufficient to impair tumor growth. Cancer cells can switch between different energy sources and metabolic pathways based on nutrient availability, oxygen levels, and other microenvironmental factors. This flexibility poses a significant challenge in identifying and targeting metabolic vulnerabilities that are consistently exploitable across different tumor types and

conditions. Therapies targeting metabolic pathways often face issues related to toxicity and specificity (Farhadi *et al*., 2020). Many metabolic processes are shared between cancerous and normal cells, making it difficult to design inhibitors that selectively target tumor cells without affecting healthy tissues. For example, glycolytic inhibitors can impact rapidly proliferating normal cells, leading to adverse effects such as gastrointestinal toxicity and myelosuppression. Achieving the right balance between efficacy and safety remains a critical challenge in the development of metabolic therapies (Ratziu *et al*., 2022).

Advances in metabolomics and metabolic imaging technologies are providing new insights into cancer metabolism. Metabolomics, the comprehensive analysis of metabolites within a biological system, enables the identification of metabolic changes associated with cancer (Han *et al*., 2021). Coupled with metabolic imaging techniques such as positron emission tomography (PET) and magnetic resonance spectroscopy (MRS), these tools allow for real-time visualization of metabolic activity in tumors. These technologies can aid in the identification of metabolic biomarkers, monitoring treatment response, and tailoring therapies to individual patients. Combination therapies that target multiple metabolic pathways simultaneously or pair metabolic inhibitors with other treatment modalities are emerging as a promising strategy to overcome the challenges of drug resistance and metabolic flexibility. For instance, combining glycolytic inhibitors with inhibitors of oxidative phosphorylation or fatty acid synthesis can synergistically impair tumor metabolism and reduce the likelihood of resistance. Additionally, combining metabolic therapies with immunotherapy or targeted therapies may enhance their efficacy and provide a more comprehensive approach to cancer treatment. Personalized medicine approaches are increasingly being explored to tailor metabolic therapies to the specific metabolic profile of individual tumors (Di Federico *et al*., 2021). By integrating genomic, transcriptomic, and metabolomic data, researchers can identify unique metabolic dependencies and vulnerabilities in each patient's tumor. This precision medicine approach allows for the design of tailored treatment strategies that are more likely to be effective and less toxic compared to one-size-fits-all therapies (Behl *et al*., 2022).

Cancer metabolism is highly heterogeneous, with significant variations observed between different tumor types and even within different regions of the same tumor (Martínez-Reyes and Chandel, 2021). Understanding this metabolic heterogeneity is crucial for developing effective therapies. Future research should focus on characterizing the metabolic profiles of diverse cancer types and subtypes, as well as exploring the spatial and temporal heterogeneity of metabolic processes within tumors. The identification of novel metabolic vulnerabilities in cancer cells is a key area of future research. High-throughput screening technologies, coupled with advanced bioinformatics approaches, can help identify new metabolic targets and pathways that are critical for tumor survival and growth (Giri and Ianevski, 2022). Exploring the interplay between metabolic pathways and other cellular processes, such as signaling and epigenetics, may also reveal new therapeutic opportunities. Translational research and clinical trials are essential for translating basic scientific discoveries into effective cancer therapies. Continued investment in preclinical studies, including the use of patient-derived xenografts and organoid models, can help validate potential metabolic targets and refine therapeutic strategies. Rigorous clinical trials are necessary to evaluate the safety and efficacy of novel metabolic therapies, with a focus on developing biomarkers for patient selection and monitoring treatment response. While significant challenges exist in targeting cancer metabolism, emerging technologies and approaches offer promising avenues for overcoming these obstacles. Continued research into the metabolic heterogeneity of tumors, identification of novel metabolic vulnerabilities, and the integration of personalized medicine approaches are essential for advancing the field and improving outcomes for cancer patients (Tong *et al*., 2020).

3. Conclusion

This has explored the critical aspects of metabolic pathways in cancer cells, including glycolysis, mitochondrial metabolism, lipid metabolism, and amino acid metabolism. We discussed how cancer cells reprogram these pathways to meet their energy and biosynthetic demands, highlighting key enzymes like HK2 and PFKFB3 in glycolysis, as well as the alterations in the TCA cycle and mitochondrial dynamics. The role of lipid droplets and fatty acid synthesis in cancer cell survival and growth was also examined, alongside the significance of amino acid metabolism, particularly glutamine addiction and serine/glycine metabolism. Therapeutic targets within these pathways were identified, including inhibitors of glycolytic enzymes, mitochondrial respiration inhibitors, and blockers of fatty acid synthesis. The potential of targeting glutaminase and enzymes involved in serine and glycine metabolism was also discussed. Additionally, the challenges in targeting cancer metabolism, such as drug resistance, metabolic flexibility, and toxicity, were addressed, alongside emerging technologies and approaches like metabolomics, combination therapies, and personalized medicine.

The insights gained from understanding cancer metabolism have profound implications for cancer therapy. Targeting metabolic pathways offers a novel strategy to selectively impair cancer cell growth and survival, potentially leading to more effective treatments. By disrupting the metabolic dependencies of cancer cells, these therapies can complement

existing treatments, reduce the likelihood of resistance, and improve patient outcomes. Personalized approaches that tailor metabolic interventions to the specific metabolic profiles of individual tumors hold particular promise for enhancing treatment efficacy and minimizing adverse effects.

Continued research in cancer metabolism is crucial for advancing our understanding of tumor biology and developing innovative therapies. As we uncover more about the metabolic heterogeneity of tumors and identify novel metabolic vulnerabilities, new therapeutic opportunities will emerge. Investment in translational research and clinical trials will be essential for bringing these discoveries from the laboratory to the clinic. Ultimately, a deeper understanding of cancer metabolism will pave the way for more effective, targeted, and personalized cancer treatments, significantly improving the prognosis and quality of life for cancer patients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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