International Journal of Multidisciplinary Research and Growth Evaluation.

Exploiting Oncogenes and Tumor Suppressors for Metabolic Reprogramming in Cancer Treatment

Tolulope Bolarinwa [1*], Opeoluwa Oluwanifemi Akomolafe [2], Irene Sagay-Omonogor [3]
[1] Indepenent Researcher, Indiana, USA
[2] Independent Researcher, UK
[3] Independent Researcher, Maryland, MD, USA

* Corresponding Author: **Tolulope Bolarinwa**

Article Info

ISSN (online): 2582-7138
Volume: 04
Issue: 02
March - April 2023
Received: 17-03-2023
Accepted: 18-04-2023
Page No: 877-882

Abstract
Metabolic reprogramming in cancer, driven by oncogenes and tumor suppressors, has become a pivotal focus in oncology research. This review explores the intricate roles of oncogenes like MYC and RAS in promoting glycolysis and glutaminolysis, while tumor suppressors such as p53 and PTEN counterbalance these effects by regulating oxidative phosphorylation and lipid metabolism. Integrative therapeutic approaches targeting these metabolic pathways promise to overcome treatment resistance and enhance patient outcomes. Challenges include tumor heterogeneity and the translation of preclinical findings into clinical applications. Future research directions include leveraging emerging technologies like CRISPR and metabolic inhibitors to develop personalized therapies that exploit metabolic vulnerabilities in individual tumors. By understanding and manipulating oncogene and tumor suppressor-driven metabolic pathways, this review underscores their potential to revolutionize cancer treatment.

DOI: https://doi.org/10.54660/.IJMRGE.2023.4.2.877-882

Keywords: Cancer Metabolism, Oncogenes, Tumor Suppressors, Metabolic Reprogramming, Personalized Medicine, Combination Therapy

1. Introduction

Cancer metabolism has emerged as a pivotal area of research, revealing that cancer cells reprogram their metabolic pathways to support rapid growth and survival. Unlike normal cells, which primarily rely on oxidative phosphorylation to generate energy, cancer cells often depend on aerobic glycolysis, known as the Warburg effect(Kocianova, Piatrikova, & Golias, 2022; Urbano, 2021; Vaupel & Multhoff, 2021). This metabolic reprogramming provides energy and supports proliferating tumour cells' biosynthetic and redox needs. Understanding these unique metabolic traits is crucial, as they offer potential targets for novel therapeutic strategies to disrupt the metabolic dependencies of cancer cells.

The roles of oncogenes and tumor suppressors are central to the regulation of cellular metabolism. Oncogenes, which promote cell growth and proliferation when mutated or overexpressed, often drive the metabolic shifts observed in cancer cells(Martínez-Reyes & Chandel, 2021). For instance, the MYC oncogene enhances glycolysis and glutaminolysis, supplying cancer cells with the necessary precursors for nucleotides, amino acids, and lipids. Similarly, the RAS oncogene activates pathways that increase glucose uptake and glycolytic flux, supporting the anabolic needs of rapidly dividing cells. These metabolic adaptations fuel tumour growth and contribute to resistance against various treatments, highlighting the need to target these pathways therapeutically(Kontomanolis *et al*., 2020).

Conversely, tumor suppressors brake cell proliferation and survival by regulating metabolic processes. The p53 tumor suppressor, known as the guardian of the genome, also plays a crucial role in metabolic regulation. It can induce the expression of genes involved in oxidative phosphorylation, promoting a metabolic state that is less favorable for cancer cell proliferation(Capuozzo *et al*., 2022). Additionally, p53 can inhibit glycolysis and promote apoptosis in response to cellular stress, acting as a metabolic checkpoint.

Another key tumor suppressor, PTEN, negatively regulates the PI3K/AKT pathway, a major driver of glucose metabolism and cell survival in cancer cells. Loss of PTEN function results in unchecked activation of this pathway, enhancing glycolytic activity and contributing to tumorigenesis(Aquila *et al*., 2020; Cao *et al*., 2020).

The interplay between oncogenes and tumor suppressors in regulating cellular metabolism presents a complex but promising landscape for therapeutic intervention. By understanding how these genetic alterations drive metabolic reprogramming, researchers can identify novel targets for cancer therapy. The main objective of this paper is to explore the potential of targeting oncogenes and tumor suppressors for metabolic reprogramming in cancer treatment. This approach aims to disrupt the metabolic dependencies of cancer cells, thereby inhibiting their growth and survival. Through a comprehensive analysis of how oncogenes and tumor suppressors influence metabolism, we seek to highlight innovative strategies that could lead to more effective and personalized cancer therapies.

The concept of targeting cancer metabolism is grounded in the idea that cancer cells exhibit unique metabolic requirements that distinguish them from normal cells(Li *et al*., 2020; Ngoi *et al*., 2020). These requirements are driven by the need to sustain rapid proliferation, manage oxidative stress, and adapt to fluctuating nutrient availability within the tumor microenvironment. Oncogenes and tumor suppressors orchestrate these metabolic adaptations, making them attractive targets for therapeutic intervention. By specifically targeting the metabolic pathways regulated by these genes, it is possible to selectively impact cancer cells while sparing normal tissues, thereby reducing the side effects commonly associated with conventional chemotherapy and radiation therapy(Ngoi *et al*., 2020).

One promising strategy involves using metabolic inhibitors that specifically target pathways upregulated by oncogenes. For example, glycolysis, glutaminolysis, and fatty acid synthesis inhibitors have shown potential in preclinical models by starving cancer cells of the essential nutrients required for their growth. Drugs that mimic the function of tumor suppressors or restore their activity can also be effective. For instance, reactivating p53 function in tumors where it is mutated can restore its ability to induce cell cycle arrest and apoptosis, leading to tumor regression.Moreover, the integration of metabolic therapies with existing treatment modalities holds significant promise. Combining metabolic inhibitors with targeted therapies, immunotherapies, or conventional treatments can enhance their efficacy and overcome resistance mechanisms. Personalized approaches, guided by the metabolic profile of individual tumors, can further optimize treatment outcomes(Sharma, Agnihotri, & Kumar, 2022; Wang *et al*., 2020). By tailoring therapy to the specific metabolic dependencies of a patient's tumor, it is possible to maximize therapeutic efficacy while minimizing toxicity.

2. Mechanisms of Oncogenes in Metabolic Reprogramming

2.1 Key Oncogenes and Their Functions

The field of cancer metabolism has revealed that oncogenes play a crucial role in reprogramming the metabolic pathways of cancer cells, enabling their rapid growth and survival. When mutated or overexpressed, oncogenes drive the metabolic alterations that support proliferating tumour cells' anabolic and energy demands, in this context, two of the most studied oncogenes are MYC and RAS, which profoundly affect cellular metabolism. Understanding their roles and the pathways they influence is essential for developing novel therapeutic strategies aimed at targeting cancer metabolism(Donati & Amati, 2022).

The MYC oncogene is a master regulator of cellular metabolism and growth. It encodes a transcription factor that controls the expression of numerous genes involved in various metabolic processes. MYC promotes glycolysis by upregulating the expression of key glycolytic enzymes, thereby increasing the flux of glucose through this pathway. This is crucial for generating the ATP and metabolic intermediates needed for biosynthetic processes. Additionally, MYC enhances glutaminolysis, the metabolic pathway that converts glutamine to glutamate and subsequently to alpha-ketoglutarate, feeding into the tricarboxylic acid (TCA) cycle. This process is vital for maintaining the TCA cycle's function in producing energy and biosynthetic precursors. By driving both glycolysis and glutaminolysis, MYC ensures that cancer cells have a continuous supply of power and the building blocks necessary for rapid cell division(Bhardwaj, He, & Jain, 2022; Jin, Byun, Choi, & Park, 2023).

The RAS oncogene is another key player in cancer metabolism. Mutations in RAS genes, such as KRAS, HRAS, and NRAS, are common in various cancers and lead to constitutive activation of the RAS protein, activating several downstream signaling pathways(Asl *et al*., 2021). One of the primary pathways influenced by RAS is the PI3K/AKT/mTOR pathway, which plays a significant role in regulating glucose metabolism. Activated RAS enhances glucose uptake by upregulating glucose transporter proteins, increasing glucose availability for glycolysis. Furthermore, RAS signaling promotes the conversion of pyruvate, a glycolytic end product, into lactate through lactate dehydrogenase (LDH), even in the presence of oxygen—a hallmark of the Warburg effect. This shift to aerobic glycolysis helps meet cancer cells' energy and anabolic demands. RAS also influences lipid metabolism by upregulating enzymes involved in fatty acid synthesis, providing lipids necessary for membrane biosynthesis and signaling molecules(Bartolacci, Andreani, El-Gammal, & Scaglioni, 2021).

2.2 Pathways Influenced by Oncogenes

Oncogenic activity influences several critical metabolic pathways, including glycolysis, glutaminolysis, and lipid metabolism. Glycolysis, the process of converting glucose into pyruvate, is significantly upregulated in cancer cells due to the activity of oncogenes like MYC and RAS. This upregulation provides ATP and generates intermediates for nucleotide, amino acid, and lipid biosynthesis(Cai *et al*., 2022). Glutaminolysis, driven by MYC, is another essential pathway, as it supplies the TCA cycle with alpha-ketoglutarate, supporting the production of ATP and biosynthetic precursors. Additionally, oncogenes can enhance lipid metabolism, with RAS promoting the synthesis of fatty acids, which are crucial for constructing cell membranes and generating signaling molecules(Bartolacci *et al*., 2021).

The reprogramming of these metabolic pathways by oncogenes has significant therapeutic implications. Understanding how oncogenes alter metabolism opens up

new avenues for targeted cancer therapies. One promising approach is the development of metabolic inhibitors that specifically target the pathways upregulated by oncogenic activity. For example, inhibitors of glycolytic enzymes such as hexokinase 2 (HK2) and pyruvate kinase M2 (PKM2) have shown potential in preclinical models by disrupting the glycolytic flux in cancer cells, thereby reducing their energy production and biosynthetic capacity. Similarly, targeting glutaminolysis with inhibitors of glutaminase, the enzyme that converts glutamine to glutamate, can starve cancer cells of essential TCA cycle intermediates, inhibiting their growth(Sharma *et al*., 2022).

Moreover, the interplay between oncogenic signaling and metabolism suggests that combining metabolic inhibitors with other targeted therapies could enhance therapeutic efficacy. For instance, combining glycolysis inhibitors with PI3K/AKT/mTOR pathway inhibitors, which are already in clinical use, could provide a more comprehensive blockade of the metabolic and proliferative signals driving cancer growth. This combinatorial approach could help overcome resistance mechanisms that often arise when targeting a single pathway(Chelakkot, Chelakkot, Shin, & Song, 2023).

Personalized medicine approaches, guided by individual tumours' specific oncogenic mutations and metabolic profiles, also hold promise. By tailoring treatments to the unique metabolic dependencies of a patient's tumor, it is possible to maximize therapeutic efficacy while minimizing toxicity. For example, tumors with MYC amplification might be particularly sensitive to glycolysis and glutaminolysis inhibitors. In contrast, RAS-mutant tumors might respond better to inhibitors targeting the PI3K/AKT/mTOR pathway and lipid metabolism.Additionally, the metabolic vulnerabilities created by oncogenic reprogramming can be exploited to enhance the efficacy of existing therapies. For instance, many chemotherapeutic agents induce oxidative stress, and cancer cells with upregulated glycolysis and glutaminolysis are often more dependent on antioxidant systems to manage this stress. Inhibiting these metabolic pathways could sensitize cancer cells to oxidative damage induced by chemotherapy, improving treatment outcomes(Chelakkot *et al*., 2023; Matés, Campos-Sandoval, de Los Santos-Jiménez, & Márquez, 2020).

3. Tumor Suppressors and Their Impact on Metabolism

3.1 Key Tumor Suppressors and Their Functions

Tumor suppressors maintain cellular homeostasis by regulating growth, division, and metabolism. These proteins act as brakes on cell proliferation and survival, counteracting the effects of oncogenes and preventing the unchecked growth that leads to cancer. Among the most significant tumor suppressors are p53 and PTEN, which profoundly affect cellular metabolism. Understanding the roles of these tumor suppressors in regulating metabolic pathways is essential for developing therapeutic strategies to exploit metabolic vulnerabilities in cancer cells.The p53 tumor suppressor, often called the "guardian of the genome," is pivotal in maintaining cellular integrity. It is a transcription factor that responds to various cellular stresses, including DNA damage, hypoxia, and oncogene activation. Upon activation, p53 can induce cell cycle arrest, apoptosis, or senescence, thereby preventing the propagation of damaged cells. In addition to these well-known functions, p53 significantly impacts cellular metabolism(Alvarado-Ortiz *et al*., 2021). It promotes oxidative phosphorylation by upregulating the expression of genes involved in mitochondrial function, such as SCO2, which is essential for the assembly of cytochrome c oxidase, a key component of the electron transport chain. Enhancing oxidative phosphorylation, p53 helps maintain a metabolic state less conducive to rapid cell proliferation(Anwar, Shamsi, Mohammad, Islam, & Hassan, 2021).

Moreover, p53 can inhibit glycolysis, the metabolic pathway heavily relied upon by cancer cells, by downregulating the expression of glycolytic enzymes like glucose transporter 1 (GLUT1) and phosphoglycerate mutase (PGM). This dual regulation of oxidative phosphorylation and glycolysis highlights p53's role in promoting metabolic homeostasis and preventing the metabolic reprogramming characteristic of cancer cells. In conditions of nutrient deprivation, p53 can also activate autophagy, a process that recycles cellular components to maintain energy balance. Through these mechanisms, p53 acts as a metabolic checkpoint, ensuring that cells do not proliferate under unfavorable conditions and limiting the metabolic flexibility that cancer cells exploit(Park, Pyun, & Park, 2020).

PTEN (phosphatase and tensin homolog) is another critical tumor suppressor that regulates cellular metabolism, primarily through its antagonistic effects on the PI3K/AKT signaling pathway. PTEN dephosphorylates phosphatidylinositol (3,4,5)-trisphosphate (PIP3), thereby inhibiting the activation of AKT. The PI3K/AKT pathway is a major driver of cellular growth and survival, and its activation leads to increased glucose uptake and glycolysis. By inhibiting this pathway, PTEN reduces glycolytic flux and promotes a metabolic state more reliant on oxidative phosphorylation. This shift is significant because cancer cells often exhibit increased glycolysis even in the presence of oxygen, a phenomenon known as the Warburg effect(Kocianova *et al*., 2022; Urbano, 2021).

Additionally, PTEN influences lipid metabolism by regulating the activity of mTOR (mechanistic target of rapamycin), a downstream target of AKT. mTOR controls protein synthesis and lipid biosynthesis, which are essential for cell growth and proliferation. By inhibiting mTOR activity, PTEN can decrease lipid synthesis and cellular growth, further contributing to its tumor-suppressive functions. Loss of PTEN function, common in many cancers, results in unchecked activation of the PI3K/AKT/mTOR pathway, leading to enhanced glycolysis, lipid synthesis, and overall metabolic reprogramming that supports tumor growth and survival(Zhao, Wang, Liu, & Zhang, 2020).

3.2 Metabolic Pathways Controlled by Tumor Suppressors

The metabolic pathways controlled by tumor suppressors like p53 and PTEN are crucial for maintaining cellular energy balance and preventing the uncontrolled growth characteristic of cancer. Oxidative phosphorylation, regulated by p53, is a highly efficient way to generate ATP, the cell's energy currency, and it supports cellular activities that require sustained energy production. By promoting oxidative phosphorylation, p53 ensures that cells efficiently produce energy while minimizing the production of reactive oxygen species (ROS), which can cause cellular damage(Shi & Dansen, 2020).

In contrast, the PI3K/AKT/mTOR pathway, inhibited by PTEN, promotes glycolysis and lipid synthesis, which are critical for rapidly dividing cells. Glycolysis provides ATP

quickly, albeit less efficiently than oxidative phosphorylation, and generates intermediates necessary for biosynthetic processes. Lipid synthesis, also regulated by this pathway, is essential for producing cell membranes and signaling molecules required for cell growth and proliferation. By inhibiting this pathway, PTEN ensures that cells do not excessively rely on glycolysis and lipid synthesis, thereby preventing the metabolic adaptations that support tumorigenesis(Hoxhaj & Manning, 2020).

The therapeutic potential of targeting tumor suppressor pathways to disrupt cancer metabolism is immense. Restoring the function of tumor suppressors or mimicking their activity can reprogram the metabolism of cancer cells, making them less adaptable and more susceptible to treatment. One promising approach involves the use of small molecules or gene therapy to reactivate p53 in tumors where it is mutated or inactivated. Reactivating p53 can restore its ability to promote oxidative phosphorylation, inhibit glycolysis, and induce apoptosis, leading to reduced tumor growth and increased sensitivity to conventional therapies(Hu *et al*., 2021).

Similarly, targeting the PI3K/AKT/mTOR pathway in cancers with PTEN loss can disrupt the metabolic reprogramming that supports tumor survival. Inhibitors of PI3K, AKT, and mTOR are already being investigated in clinical trials, and their combination with other metabolic inhibitors could enhance therapeutic efficacy. For example, combining PI3K/AKT/mTOR inhibitors with glycolysis inhibitors could provide a dual blockade of the metabolic pathways that cancer cells depend on, leading to greater anti-tumor effects(G.-P. Zou *et al*., 2021).Moreover, the integration of metabolic therapies with immunotherapy holds promise. Cancer cells with reprogrammed metabolism often create an immunosuppressive microenvironment, making it difficult for the immune system to mount an effective response. By targeting metabolic pathways regulated by tumor suppressors, it may be possible to modulate the tumor microenvironment and enhance the efficacy of immune checkpoint inhibitors and other immunotherapies(Z. Zou, Tao, Li, & Zhu, 2020).

In conclusion, tumor suppressors such as p53 and PTEN play vital roles in regulating cellular metabolism and maintaining metabolic homeostasis. By promoting oxidative phosphorylation and inhibiting glycolysis and lipid synthesis, these tumor suppressors prevent the metabolic reprogramming that supports cancer cell growth and survival. Understanding the metabolic pathways controlled by tumor suppressors provides a foundation for developing therapeutic strategies that exploit metabolic vulnerabilities in cancer cells. Targeting these pathways can disrupt the metabolic adaptations of cancer cells, offering new avenues for treatment and improving outcomes for patients with cancer.

4. Integrative Approaches for Targeting Metabolic Reprogramming

4.1 Combination Therapies

The complexity of cancer metabolism, driven by the interplay of oncogenes and tumor suppressors, necessitates innovative therapeutic approaches that target multiple facets of metabolic reprogramming. Integrative strategies combining therapies aimed at both oncogenes and tumor suppressors hold promise for disrupting the metabolic dependencies of cancer cells and improving treatment outcomes. Additionally, personalized medicine approaches, guided by the metabolic profiles of individual tumors, and emerging technologies such as CRISPR and metabolic inhibitors, offer new avenues for precise and effective targeting of metabolic pathways in cancer therapy.

Combination therapies represent a promising approach for targeting metabolic reprogramming in cancer. By simultaneously targeting oncogenic pathways that drive metabolic adaptations and restoring or mimicking the function of tumor suppressors that regulate metabolic homeostasis, it is possible to achieve synergistic effects that enhance therapeutic efficacy. For example, combining inhibitors of glycolysis, such as 2-deoxyglucose (2-DG) or hexokinase inhibitors, with agents that inhibit oncogenic signaling pathways like PI3K/AKT or RAS/MAPK can disrupt the metabolic adaptations of cancer cells and induce cell death. This combinatorial approach targets multiple vulnerabilities within cancer cells and reduces the likelihood of resistance development, which often occurs with single-agent therapies(Pal, Sharma, Mathew, & Jaganathan, 2022; Shuvalov, Daks, Fedorova, Petukhov, & Barlev, 2021).

4.2 Personalized Medicine

Moreover, personalized medicine holds great potential for optimizing cancer treatment based on the unique metabolic profiles of individual tumors. Advances in genomic and metabolomic technologies have enabled the characterization of metabolic alterations specific to different cancer types and even within individual tumors. By profiling the metabolic landscape of a patient's tumor, clinicians can identify key metabolic dependencies and tailor treatment strategies accordingly. For instance, tumors with elevated glycolytic activity may benefit from therapies that target glycolysis, whereas tumors with defects in oxidative phosphorylation may require strategies to enhance mitochondrial function or inhibit compensatory metabolic pathways(Moindjie, Rodrigues-Ferreira, & Nahmias, 2021).

Furthermore, emerging technologies are revolutionizing the precision with which metabolic pathways can be targeted in cancer therapy. CRISPR-Cas9 gene editing technology, for example, allows for precise manipulation of oncogenes and tumor suppressors implicated in cancer metabolism. Researchers can use CRISPR to knockout or modify specific genes involved in metabolic reprogramming, thereby elucidating their roles and potential as therapeutic targets. This technology also holds promise for developing novel gene therapies aimed at restoring tumor suppressor function or disrupting oncogenic signaling pathways in a targeted manner(Selvakumar *et al*., 2022).

In addition to gene editing technologies, metabolic inhibitors represent another class of emerging therapies that enable precise targeting of metabolic pathways in cancer cells. These inhibitors selectively disrupt enzymes or metabolic processes essential for cancer cell survival and growth. For example, glutaminase inhibitors, an enzyme critical for glutaminolysis, have shown efficacy in preclinical models by starving cancer cells of essential nutrients and inducing cell death. Similarly, inhibitors targeting key enzymes in lipid metabolism or mitochondrial function are being explored for their potential to disrupt the metabolic dependencies of cancer cells(Srivastava *et al*., 2022).

Integrating these emerging technologies with existing therapeutic modalities represents a paradigm shift in cancer treatment, offering new opportunities to overcome the challenges posed by metabolic heterogeneity and adaptive

resistance mechanisms. By combining insights from genomic profiling, metabolomics, and advanced imaging techniques, clinicians can develop multidimensional profiles of tumor metabolism that inform personalized treatment decisions. This holistic approach improves the precision and efficacy of therapies and minimizes the potential for off-target effects and toxicity associated with conventional treatments.Furthermore, the development of companion diagnostics that assess the metabolic status of tumors can facilitate the implementation of personalized medicine approaches in clinical practice. These diagnostics enable real-time monitoring of metabolic changes in response to therapy, allowing clinicians to adapt treatment regimens based on the evolving metabolic landscape of the tumor. For example, positron emission tomography (PET) imaging with radiotracers specific to metabolic pathways can provide valuable information about tumor metabolism and response to targeted therapies.

5. Future Directions and Conclusion

Targeting metabolic reprogramming in cancer therapy presents both challenges and promising opportunities for future research and clinical applications. Understanding these complexities is crucial for advancing treatment strategies that exploit the roles of oncogenes and tumor suppressors in cancer metabolism.

5.1 Challenges and Opportunities

One of the significant challenges in targeting metabolic reprogramming is the heterogeneity of cancer cells within tumors. Cancer cells exhibit diverse metabolic profiles that can evolve over time, leading to resistance against targeted therapies. Overcoming this challenge requires a deeper understanding of the molecular mechanisms driving metabolic adaptations and the development of combination therapies that target multiple metabolic pathways simultaneously.

Another challenge lies in translating preclinical findings into effective clinical applications. While promising therapeutic targets have been identified in preclinical studies, their efficacy and safety in human patients need to be rigorously evaluated through clinical trials. Furthermore, identifying biomarkers that accurately predict metabolic vulnerabilities in individual tumors is essential for selecting patients most likely to benefit from targeted therapies.Despite these challenges, several opportunities for future research abound. Technological advances, such as single-cell metabolomics and high-throughput screening platforms, offer new tools for dissecting the metabolic heterogeneity of tumors and identifying druggable targets. Integrating these technologies with computational modeling and artificial intelligence can enhance our understanding of complex metabolic networks and facilitate the discovery of novel therapeutic strategies.

5.2 Clinical Applications

The potential clinical applications of targeting metabolic reprogramming are extensive and encompass various aspects of cancer treatment. Personalized medicine approaches, guided by the metabolic profiles of individual tumors, hold promise for tailoring therapies to the specific metabolic vulnerabilities of each patient's cancer. Clinicians can optimize treatment regimens to maximize efficacy and minimize side effects by stratifying patients based on their metabolic phenotypes.Moreover, combination therapies targeting oncogenes and tumor suppressors offer synergistic benefits for disrupting metabolic dependencies in cancer cells. Clinical trials evaluating these combination approaches are essential for determining their safety and efficacy in different cancer types and patient populations. Furthermore, integrating metabolic inhibitors with existing standard-of-care treatments, such as chemotherapy and immunotherapy, can enhance therapeutic outcomes and overcome treatment resistance.

Collaboration between basic scientists, clinicians, and pharmaceutical companies is essential to translate research findings into clinical practice. Establishing robust preclinical models that recapitulate the metabolic features of human tumors is crucial for predicting therapeutic responses and guiding clinical trial design. Additionally, ongoing investment in biomarker discovery and companion diagnostics will facilitate the implementation of personalized treatment strategies based on tumor metabolism.

5.3 Conclusion

In conclusion, targeting oncogenes and tumor suppressors for metabolic reprogramming represents a promising approach to the treatment of cancer. By understanding how these genetic alterations influence metabolic pathways, researchers and clinicians can develop innovative therapies that selectively target cancer cells while sparing normal tissues. The integration of advanced technologies, personalized medicine approaches, and combination therapies holds great potential for overcoming the challenges associated with metabolic heterogeneity and treatment resistance in cancer.

Moving forward, continued research efforts are needed to unravel the complexities of cancer metabolism and identify new therapeutic targets. By harnessing the power of oncogenes and tumor suppressors to reprogram cancer cell metabolism, we can pave the way for more effective and personalized cancer therapies. Ultimately, exploiting these molecular pathways promises to improve treatment outcomes and represents a paradigm shift towards precision medicine in oncology.

References

1. Alvarado-Ortiz E, de la Cruz-López KG, Becerril-Rico J, *et al*. Mutant p53 gain-of-function: role in cancer development, progression, and therapeutic approaches. Front Cell Dev Biol. 2021;8:607670.
2. Anwar S, Shamsi A, Mohammad T, Islam A, Hassan MI. Targeting pyruvate dehydrogenase kinase signaling in the development of effective cancer therapy. Biochim Biophys Acta Rev Cancer. 2021;1876(1):188568.
3. Aquila S, Santoro M, Caputo A, *et al*. The tumor suppressor PTEN as molecular switch node regulating cell metabolism and autophagy: implications in immune system and tumor microenvironment. Cells. 2020;9(7):1725.
4. Asl ER, Amini M, Najafi S, *et al*. Interplay between MAPK/ERK signaling pathway and MicroRNAs: A crucial mechanism regulating cancer cell metabolism and tumor progression. Life Sci. 2021;278:119499.
5. Bartolacci C, Andreani C, El-Gammal Y, Scaglioni PP. Lipid metabolism regulates oxidative stress and ferroptosis in RAS-driven cancers: a perspective on cancer progression and therapy. Front Mol Biosci. 2021;8:706650.
6. Bhardwaj V, He J, Jain A. Glutamine stabilizes myc via

alpha-ketoglutarate and regulates paclitaxel sensitivity. Med Oncol. 2022;39(12):227.
7. Cai Y, Chen H, Tang X, *et al*. The relationship between amino acid and lipid metabolism in oleaginous eukaryotic microorganism. Appl Microbiol Biotechnol. 2022;106(9):3405-17.
8. Cao H, Chen X, Wang Z, *et al*. The role of MDM2-p53 axis dysfunction in the hepatocellular carcinoma transformation. Cell Death Discov. 2020;6(1):53.
9. Capuozzo M, Santorsola M, Bocchetti M, *et al*. p53: from fundamental biology to clinical applications in cancer. Biology. 2022;11(9):1325.
10. Chelakkot C, Chelakkot VS, Shin Y, Song K. Modulating glycolysis to improve cancer therapy. Int J Mol Sci. 2023;24(3):2606.
11. Donati G, Amati B. MYC and therapy resistance in cancer: risks and opportunities. Mol Oncol. 2022;16(21):3828-54.
12. Hoxhaj G, Manning BD. The PI3K-AKT network at the interface of oncogenic signalling and cancer metabolism. Nat Rev Cancer. 2020;20(2):74-88.
13. Hu J, Cao J, Topatana W, *et al*. Targeting mutant p53 for cancer therapy: direct and indirect strategies. J Hematol Oncol. 2021;14:1-19.
14. Jin J, Byun JK, Choi YK, Park KG. Targeting glutamine metabolism as a therapeutic strategy for cancer. Exp Mol Med. 2023;55(4):706-15.
15. Kocianova E, Piatrikova V, Golias T. Revisiting the Warburg effect with focus on lactate. Cancers. 2022;14(24):6028.
16. Kontomanolis EN, Koutras A, Syllaios A, *et al*. Role of oncogenes and tumor-suppressor genes in carcinogenesis: a review. Anticancer Res. 2020;40(11):6009-15.
17. Li J, Eu JQ, Kong LR, *et al*. Targeting metabolism in cancer cells and the tumour microenvironment for cancer therapy. Molecules. 2020;25(20):4831.
18. Martínez-Reyes I, Chandel NS. Cancer metabolism: looking forward. Nat Rev Cancer. 2021;21(10):669-80.
19. Matés JM, Campos-Sandoval JA, de Los Santos-Jiménez J, Márquez J. Glutaminases regulate glutathione and oxidative stress in cancer. Arch Toxicol. 2020;94(8):2603-23.
20. Moindjie H, Rodrigues-Ferreira S, Nahmias C. Mitochondrial metabolism in carcinogenesis and cancer therapy. Cancers. 2021;13(13):3311.
21. Ngoi NY, Eu JQ, Hirpara J, *et al*. Targeting cell metabolism as cancer therapy. Antioxid Redox Signal. 2020;32(5):285-308.
22. Pal S, Sharma A, Mathew SP, Jaganathan BG. Targeting cancer-specific metabolic pathways for developing novel cancer therapeutics. Front Immunol. 2022;13:955476.
23. Park JH, Pyun WY, Park HW. Cancer metabolism: phenotype, signaling and therapeutic targets. Cells. 2020;9(10):2308.
24. Selvakumar SC, Preethi KA, Ross K, *et al*. CRISPR/Cas9 and next generation sequencing in the personalized treatment of Cancer. Mol Cancer. 2022;21(1):83.
25. Sharma S, Agnihotri N, Kumar S. Targeting fuel pocket of cancer cell metabolism: A focus on glutaminolysis. Biochem Pharmacol. 2022;198:114943.
26. Shi T, Dansen TB. Reactive oxygen species induced p53 activation: DNA damage, redox signaling, or both? Antioxid Redox Signal. 2020;33(12):839-59.
27. Shuvalov O, Daks A, Fedorova O, Petukhov A, Barlev N. Linking metabolic reprogramming, plasticity and tumor progression. Cancers. 2021;13(4):762.
28. Srivastava A, Srivastava P, Mathur S, *et al*. Lipid metabolism and mitochondria: Cross talk in cancer. Curr Drug Targets. 2022;23(6):606-27.
29. 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.
30. Vaupel P, Multhoff G. Revisiting the Warburg effect: historical dogma versus current understanding. J Physiol. 2021;599(6):1745-57.
31. Wang Z, Liu F, Fan N, *et al*. Targeting glutaminolysis: new perspectives to understand cancer development and novel strategies for potential target therapies. Front Oncol. 2020;10:589508.
32. Zhao C, Wang B, Liu E, Zhang Z. Loss of PTEN expression is associated with PI3K pathway-dependent metabolic reprogramming in hepatocellular carcinoma. Cell Commun Signal. 2020;18:1-11.
33. Zou GP, Yu CX, Shi SL, *et al*. Mitochondrial dynamics mediated by DRP1 and MFN2 contributes to cisplatin chemoresistance in human ovarian cancer SKOV3 cells. J Cancer. 2021;12(24):7358.
34. Zou Z, Tao T, Li H, Zhu X. mTOR signaling pathway and mTOR inhibitors in cancer: progress and challenges. Cell Biosci. 2020;10(1):31.