ISSN:2790-1688 Volume-15-(2025)

Cancer Metabolic Reprogramming: From the Warburg Effect to Metabolic-Immune Regulation—Mechanistic Insights and Novel Targeted Therapeutic Strategies

Jinchen Han

Annie Wright Schools, Tacoma, 98403, United States

Abstract. Cancer metabolism has been a benchmark of cancer cells. It has emerged as a critical area of cancer research decades ago, as it reprograms the traditional cellular metabolic cycles that facilitate cancer cells with rapid proliferation and resistance under stressful TME and immune surveillance. This review synthesizes the current understanding of these metabolic alterations, foundational metabolic mechanisms, especially including key signaling pathways and epigenetic modifications. With the Warburg effect as the foundation, the role of metabolites, such as lactate, in shaping the tumor microenvironment to promote immune evasion and tumor progression will be elucidated. Crucial signaling pathways and transcriptional regulators are also explored as pivotal contributors to metabolic reprogramming. Ultimately, this review critically discusses the latest innovative therapeutic strategies targeting cancer metabolism, based on these understandings, and highlights the promising metabolic modulators, especially metformin, for future clinical interventions. By connecting fundamental metabolic biology with emerging precision oncology strategies, particularly metabolism-based combination therapies, this paper outlines potential avenues for improving cancer patient outcomes and advancing personalized therapeutic approaches.

Keywords: Metabolic reprogramming; Metabolism-Based Combination Therapy; Metabolite-Mediated Immune Evasion; Metformin; Tumor Microenvironment.

1. Introduction

Cellular metabolism serves as a fundamental chemical process that sustains life by providing energy and biosynthetic intermediates essential for growth and maintenance. In healthy cells, metabolism is tightly regulated by specific nutrient cues and signaling pathways to meet physiological demands such as muscle protein synthesis (MPS). However, cancer cells overturned the traditional pattern; they exhibit significant metabolic alterations, colloquially known as metabolic reprogramming. This kind of remodeling allows the cancer cell to sustain its rapid proliferation, survive in a hypoxic environment, and evade immune surveillance. Over decades of studies, based on a theory known as the Warburg effect from a century ago, the studies on cancer's metabolic reprogramming have made huge progress and keep advancing and expanding. The Warburg effect indicates that cancer cells preferentially engage in aerobic glycolysis over the more energy-efficient oxidative phosphorylation that cells usually do; they ferment glucose into lactate even when sufficient oxygen is present and mitochondria are completely functioning[1, 2]. This seemingly paradoxical metabolic shift in cancer cells actually helps them in the rapid production of ATP and biosynthetic precursors needed for aberrant cell proliferation, and simultaneously generates metabolites such as lactate that modify the tumor microenvironment (TME) to favor cancer cell survival and immune evasion, that is, an acidic pH environment impairs the functionality of various kinds of immune cells functionality.[1-3]

Recently, the scientific scope has expanded from glucose metabolic reprogramming to encompass alterations in lipid metabolism, amino acid utilization, redox regulation, and one-carbon metabolism.[4-6] These unique alterations enable cancer cells to have complex metabolic flexibility to sustain their malignant phenotype, such as supporting tumor outgrowth, inducing metastasis, and therapeutic resistance. These metabolic shifts are governed by complex epigenetic modifications, signaling networks, and transcriptional regulators, which collectively enhance cancer cells' metabolic plasticity.[2-6]

This review comprehensively synthesizes current knowledge of metabolic rewiring mechanisms, highlighting crucial signaling pathways and epigenetic modifications driving metabolic flexibility in cancer cells. Eventually, we critically discussed emerging therapeutic interventions targeting core metabolic nodes and the immunosuppressive TME, emphasizing the promising role of metabolic modulators, especially metformin. By connecting foundational metabolic biology with innovative clinical strategies, especially metabolism-based combination therapies, this paper aims to illuminate new avenues for precision oncology and improved cancer patient outcomes.

2. Metabolic Foundation: Normal Nutrient-Driven Anabolism vs. Cancer Metabolism

In healthy cells, glucose metabolism undergoes the critical steps of glycolysis to break glucose into pyruvate in the cytosol, then is directed into the mitochondria for oxidation via the tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) when oxygen is sufficient, also known as the Krebs cycle. Eventually, this oxygen-dependent process will produce more than 30 ATP molecules per glucose through the Electron transport chain (ETC). When oxygen is insufficient, the Krebs cycle is shifted to lactic acid fermentation, in which pyruvates from glycolysis are converted into lactate, allowing the glycolysis cycle to continue for a short period. This process produces ATP, accompanied by the accumulation of a lactate byproduct that needs to be removed by oxygen later. This whole metabolism strategy is energy efficient and feedback-sensitive, functionally coupled to cellular demand, and therefore has been the most common way of cellular respiration for thousands of years.

Other macronutrient metabolism, such as protein metabolism, also operates under strict nutritional and hormonal control. One of the best examples is MPS, activated by the mammalian rapamycin Target 1(mTORC1) signaling pathway—the central hub integrating signals from amino acids, glucose, oxygen, and growth factors to control anabolic processes such as protein, lipid, and nucleotide synthesis—achieving efficient protein translation.[7, 8] Amino acids stimulate this significant pathway through the Ragulator–Rag GTPase complex to achieve lysosomal recruitment and activate the kinase, while growth factor signaling, particularly insulin and IGF-1 pathways, also activate the PI3K–AKT cascade, stimulating the mTORC1 pathway further.[8] Lipid metabolism is another parallel example to illuminate the characteristics of normal cellular metabolism, dynamically regulated according to nutrient status. In the form of fatty acids, lipids are often oxidized through β-oxidation within mitochondria. The process of breakdown of fatty acids yields acetyl-CoA, which then enters the TCA cycle to contribute to ATP production, while in a nutrient excess status, fatty acid synthase and acetyl-CoA carboxylase are transcriptionally upregulated via the mTORC1-SREBP1 axis, ending with a result that lipogenesis is promoted, contributing to membrane biosynthesis and energy storage.[8, 9]

However, cancer cells often display a strikingly different metabolic profile. Even in the presence of ample oxygen, many tumor cells still preferentially convert glucose into lactate through aerobic glycolysis, a phenomenon known as the Warburg effect.[1, 2] Instead of maximizing their ATP energy production, cancer cells prioritize carbon flux through glycolysis to supply precursors for anabolic processes, their biosynthetic requirements of uncontrolled proliferation. The excess carbon has then been used for the de novo generation of nucleotide synthesis, lipid production, and amino acid biosynthesis through multiple branching signaling pathways.[1] Moreover, during aerobic glycolysis, NADH in the pyruvate is then converted to NAD+ by the lactate dehydrogenase, enabling the glycolysis cycle to be highly active and continuous, further supporting the growth and proliferation demand of the cancer cell by this rapid biosynthesis.[1] Theories that low ATP production is the cost of maintaining high fluxes through anabolic pathways also support the rationalization of cancer cells' unique metabolism reprogramming.[1] In fact, in many cancer research and models, it's been proven that tumors and other rapidly proliferating cells relying on the

Warburg effect can sustain intracellular ATP levels comparable to or even greater than those of non-cancerous cells.[2]

3. Cancer cells are dependent on metabolic reprogramming to acquire survival advantages.

Cancer cells have now obtained critical advantages that promote their uncontrolled growth, massive proliferation, survival under stressful environments, resistance to therapeutic strategies, and metastasis potential, through epigenetic modifications, aberrant signaling, and transcriptional control. Specifically, DNA methylation and histone acetylation, these epigenetic modifications, silence the tumor suppressor genes, and activate metabolic programs such as glycolysis and serine synthesis.[10, 11] At the same time, dysregulated signaling pathways like PI3K–AKT, mTOR, and IGF-1 will enhance the metabolism while suppressing apoptosis, ensuring cancer cells maintain to withhold massive proliferation in a nutrient-scarce tumor environment. [5, 8] Transcription factors can further magnify these effects by upregulating crucial metabolic genes and further support the cancer cell to live in metabolic stress.[4, 12] Furthermore, this cancer metabolic reprogramming simultaneously brought cancer cells advantages beyond those intrinsic metabolic adaptations. Cancer cells reshape the TME to enhance survival and immune evasion further. The stabilization of HIF-1α under hypoxic conditions can upregulate glycolytic genes and lactate transporters, which will further support tumor progression by acidifying the tumor environment.[2, 13] It lowers the pH value in the tumor environment and impairs cytotoxic T cell and NK cell activity, promoting immune evasion.[10, 14] Similarly, the activation of the NF-κB and GCN2 pathways can help cancer cells with angiogenesis formation and adaptive immunity suppression, such as impairing amino acid metabolism in immune cells and limiting their effector functions. [1-3, 6, 14]

3.1 Metabolic reprogramming products alter tumor cell epigenetics

Changes in the expression or activity of epigenetically modifying enzymes are closely related to metabolic reprogramming in cancer cells.[10] Epigenetic modifications encompass DNA methylation, succinylation, acetylation, lactylation, and regulation by noncoding RNAs with metabolites as substrates.[10, 11] These processes play essential roles in both physiological and psychological development, and their dysregulation has been implicated in the onset and progression of numerous diseases.[10] In cancer metabolism and the progression of the malignancy, epigenetic modifications regulate genes without changing the DNA sequence; there are three main aspects of epigenetic modifications: metabolites as substrates for epigenetic enzymes, oncometabolites disrupt epigenetic regulation, and epigenetic changes rewire metabolism.[10, 11, 15, 16]

Methylation. There are several metabolites acting as substrates for chromatin-modifying enzymes. S-adenosylmethionine (SAM) is an example; it is a methyl donor for DNA methyltransferases and histone methyltransferases, contributing to the production of S-adenosylhomocysteine, which is crucial to the methylation potential, sustaining the oncogenic chromatin landscapes.[10] Tumors often upregulate one-carbon metabolism to sustain SAM levels and reinforce methylation programs, which are highly related to the promotion of tumor progression, especially when hijacked.[10, 15] Metabolic mutations in cancer could produce aberrant metabolites, also known as oncometabolites. It interferes with normal epigenetic regulation by inhibiting α-ketoglutarate (α-KG)-dependent dioxygenases.[16] D-2-hydroxyglutarate is a typical example; it's a metabolite produced by neomorphic mutations in isocitrate dehydrogenase 1 or 2 often accumulates and inhibits α-KG–dependent dioxygenases in affected tumors, leading to the widespread hypermethylation of DNA and histones, which contributes to tumor progression by inducing CpG island methylator phenotype, preventing cellular differentiation.[16]

Acetylation. One of the most prominent histone modifications, acetylation, plays a critical role in regulating chromatin accessibility and gene transcription. Catalyzed by histone acetyltransferases and the CBP/p300 family, this histone-modifying process is known for the acetylating lysine residues on

histone H3 and H4 tails, especially H3K18, H3K27, H3K9, and H4K5, to loosen chromatin structure and promote transcriptional activation.[17, 18] Moreover, bromodomain-containing "reader" proteins such as BRD4 often attach to acetylation marking sites to enhance transcriptional outputs further.[17] The dysregulation of CBP/p300 activity can be found in various malignancies, including acute myeloid leukemia, which indicates it's its strong oncogenic relevance.[17] In addition to these, histone deacetylases like the Rpd3S complex, guided by H3K36me3 methylation marks through the Eaf3 chromodomain and Rco1 PHD finger, deacetylate histones H3 and H4 while sparing marks like H3K9ac, function as "erasers" by removing acetyl groups to maintain transcriptional fidelity.[18] Overall, acetylation in cancer is not only a permissive mark for transcription but also a compact process that integrates metabolic cues and epigenetic signals to control oncogenic gene expression.[17, 18]

Lactylation. Lactate accumulation is always a highly noted aspect of cancer, and lactylation is an emerging epigenetic modification that directly links to it. As glycolysis is elevated in cancer cells described by the Warburg effect, the significant intracellular lactate accumulation acts as a signaling molecule and substrate for histone lactylation, especially on histone H3 at lysine 18.[19] Lactylation is the addition of a lactyl group to lysine residues on histones, catalyzed by the same histone acetyltransferase p300 that mediates histone acetylation[20]. It can achieve the enzymatic overlap between metabolic-epigenetic pathways, activate transcription of genes involved in tumor progression, and immune evasion. Notably, Histone lysine lactylation has been shown to reprogram tumor-associated macrophages (TAMs) toward an M2-like phenotype, enhancing the immunosuppressive character of the tumor microenvironment (TME), continuing suggesting the metabolic reprogramming and immune dysfunction role of lactylation.[19]

Succinylation. A similar concept can also apply to the mutations in succinate dehydrogenase (SDH) and fumarate hydratase (FH), which are also α-KG–dependent demethylases and histone-modifying enzymes, altering the epigenetic landscape to support the cancer cell plasticity.[11, 16] A post-translational modification that adds a succinyl group derived from succinyl-CoA to lysine residues is protein succinylation.[21] This succinylation alters protein structure and function by introducing a negative charge and a bulky group. In cancer cells, mitochondrial metabolism is often dysregulated so that succinyl-CoA availability can be greatly enhanced, causing the hyper-succinylation of metabolic enzymes, especially in those in the TCA cycle and ETC[21]. The significance of this metabolic enzyme succinylation is the boost of their enzymatic activity that reinforces the anabolic programs and supports cancer cell proliferation.[11, 16, 21]

3.2 Signalling pathways

3.2.1 The mTOR signaling pathway is the basis of nutrient sensing and regulation in cancer.

The mechanistic target of the rapamycin (mTOR) signaling pathway is the basis of nutrient sensing and regulation. As one of the most critical regulators of cancer cell metabolism, mTOR complex 1 (mTORC1) integrates signals from amino acids, glucose, and other growth factors to drive anabolic growth and proliferation. mTORC1 often functions as a downstream effector for the PI3K/Akt pathway and Ras/Raf/Mek/Erk (MAPK) pathway, which are frequently mutated oncogenic pathways that will be discussed in detail in the proliferation and survival pathways section.[8, 22] Through those pathways, mTORC1 can be hyperactivated, leading to even greater cancer progression independent of nutrient status[8]. The mutation/dysregulation of mTOR itself can also contribute to tumorigenesis and enhance glycolysis, sometimes even resistance to clinical methodologies.[8, 22] Moreover, mTOR complex 2 (mTORC2) also plays a crucial role in cancer metabolism. mTORC2 is effective in activating Akt, driving pro-proliferative processes, and promoting glycolysis and glutaminolysis with mTORC1, while also inhibiting apoptosis. [8, 22]

Another important regulatory pathway is the General Control Nonderepressible 2 (GCN2) pathway, which can be triggered by amino acid starvation. GCN2 often uses uncharged tRNAs as the indicator of amino acid scarcity, selectively upregulating stress-adaptive genes, which can promote survival under metabolic stress.[6] This is significant in the context of a poorly vascularized tumor

microenvironment (TME) since it enables tumor cells to endure amino acid deprivation and restore metabolic balance.[6] GCN2 is also known for its ability to disable immune cells' functions, impairing the effect of immune cells such as T cells and antigen-presenting cells, and resistance towards immunosuppression therapy.[6]

This metabolic balance-maintaining ability can also be observed in AMP-activated protein kinase (AMPK), a metabolic checkpoint in cancer. Instead of sensing amino acid starvation, AMPK senses energy depletion through an increased AMP/ATP ratio.[4] When sensing energy depletion, AMPK will activate and suppress energy-consuming anabolic processes by directly inhibiting mTORC1 and activating catabolic programs such as fatty acid oxidation and autophagy.[4] However, AMPK is often suppressed or mutated; without this balancing factor, cancer cells can maintain high biosynthetic activity even under metabolic stress.[4] The characteristics of AMPK make it a promising tumor suppressor and a therapeutic target, especially in metabolism-based cancer strategies, such as metformin, which will be discussed in detail later in the text.

Last but not least, the Insulin-like Growth Factor-1 (IGF-1) signaling pathway. This pathway has a great connection with the mTOR and PI3K pathways; when IGF-1 binds to IGF1R, its receptor, IGF-1 will activate the PI3K–AKT signaling cascade, which then stimulates mTORC1 to promote various anabolic biosynthesis[8]. IGF-1 signaling is often found upregulated through receptor overexpression in malignancies, which creates a metabolic environment that supports rapid tumor growth while also possessing resistance to metabolic stress and nutrient-limited conditions[8].

3.2.2 Anabolic metabolism alters the proliferation and survival pathways in cancer cells.

Signaling pathways in charge of coordinating anabolic metabolism with growth and survival signals are crucial; the phosphoinositide 3-kinase (PI3K)–AKT signaling pathway is a great example since it's one of the most frequently dysregulated pathways in human cancer.[5] As mutations happen in PI3K or AKT, the hyperactivation of this pathway will allow constitutive glucose uptake, while glycolytic enzymes will be upregulated, and macromolecule biosynthesis will follow.[5] The PI3K-AKT axis often activates downstream targets such as mTORC1 and inhibits FOXO transcription factors, which leads to a growth-favorable metabolic state for cancer cells even in tumor environments that are nutrient-resource-scarce.[5, 8] This ability made PI3K a major therapeutic target; this metabolic reprogramming not only offers cancer cells a proliferative advantage but also resistance to apoptosis, making this signal pathway a main focus in metabolism-focused oncology.

Another signaling pathway that helps cancer cells to quickly proliferate and survive in harsh conditions is the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway. This pathway is often triggered by pro-inflammatory cytokines such as TNF-α, IL-1β, ROS, or other microbial components.[14] The activation of this pathway can facilitate aerobic glycolysis and increase glucose flux, which is a basic component of cancer metabolism. Moreover, this metabolic-inflammation axis can regulate lipid metabolism and antioxidant defenses, promoting angiogenesis while suppressing adaptive immunity.[14]

3.2.3 Transcriptional Control and Metabolic Gene Expressions Signaling Pathways

Transcriptional regulators that modulate metabolic gene expression can often be affected by cancer cells. Through oncogenic programs, they often satisfy the cancer cells' needs of rapid proliferation under a metabolic stress environment, sometimes even with metastatic potential. One crucial transcriptional driver of cancer metabolism is the MYC proto-oncogene, which is often amplified or overexpressed in tumors.[12] The upregulation of key enzymes such as HK2 and LDHA in glycolysis and other macronutrient metabolisms can be attributed to MYC, while MYC also contributes to ribosome biogenesis and mitochondrial translation in the tumor to enhance the biosynthetic capacity[5, 12]. Moreover, MYC induces transporters SLC1A5 and enzymes that feed into the TCA cycle, driving the serine synthesis pathway(SSP) in cancer cells under nutrient deprivation conditions; this enables MYC to maintain redox balance and biomass production while in nutrient-scarce environments.[5]

KRAS is another frequently mutated crucial oncogene, especially in pancreatic and lung cancers. Similarly, KRAS can enhance aerobic glycolysis by upregulating glucose transporters and glycolytic enzymes, such as activating the expression of the glucose transporter GLUT1.[4]. It can also drive the flux into the pentose phosphate pathway (PPP), which will lead to NADPH production and nucleotide synthesis[4]. KRAS can also aid tumors under stressful conditions. When mutated, KRAS can stimulate macropinocytosis and autophagy, which helps nutrient scavenging from the tumor microenvironment.[4]

Some developmentally conserved pathways contribute to the transcriptional control of cancer metabolism beyond oncogenes. The first one is the Notch pathway, which is known for regulating cell fate and stemness. When hyperactive in a tumor, Notch signaling can support tumor-initiating cells and metastatic potential by regulating mitochondrial respiration and glucose utilization.[10] Similarly, the Wnt/β-catenin pathway can activate transcriptional programs that favor anabolic metabolism; in an aberrant status, Wnt signaling promotes metabolic plasticity, supporting the resistance and evasion of cancer cells towards therapy and the immune system, especially in colon and liver cancers, modulating the metabolic plasticity.[13] Last but not least, the Hypoxia-inducible factor 1-alpha (HIF-1α) is a key transcriptional regulator of the hypoxic response. In tumors, HIF-1a can drive the expression of genes involved in glycolysis (GLUT1, LDHA), lactate export (MCT4), and angiogenesis (VEGF); eventually leading to the cancer cell adapting to the hypoxic tumor microenvironment.[2]

4. Therapeutic Strategies Targeting Cancer Metabolism/ Future View

4.1 From Mechanism to Medicine: The Therapeutic Promise of Metabolic Rewiring

Over the past few decades, many different therapeutic interventions have been revealed based on the discovered mechanisms of cancer metabolism. From earlier sections, cancer cells use epigenetic reprogramming, nutrient-sensing disruption, and transcriptional overdrive to collectively achieve their demand for immortality. These mechanisms provide a foundation for therapeutic strategies today that are able to target cancer cell metabolism directly or reprogram the TME to achieve immune activation. However, this exploration journey has faced multiple challenges along the way so far, especially on the pathways involved in mTOR, PI3K, and AMPK, which these essential signaling pathways for normal cell function, hindering the effectiveness of therapeutic approaches. The complexity of the metabolic plasticity of tumor cells is another main challenge, which is the redundancy in nutrient supply routes and adaptive epigenetic regulation in cancer cells, often limiting the efficacy of single-agent inhibitors. It was not until recent years that this situation began to improve; with a better understanding of the TME, strategic combination therapies, particularly those integrating immune with metabolism-targeted therapies, started to emerge, bringing several new candidates into the clinical testing and practice of cancer.

4.2 Targeting Core Metabolic Nodes in Cancer

A direct strategy is the inhibition of glycolysis, a fundamental characteristic of cancer metabolism, the Warburg effect. Now, therapeutic agents targeting key glycolytic enzymes such as hexokinase 2 and LDHA and glucose transporters such as GLUT1 and GLUT3 can be applied to limit the carbon supply to biosynthetic pathways.[23, 24] And these agents can also reduce the immunosuppressive lactate burden in the TME, disabling the evasion of cancer from the immune system. A specific example is GLUT1 inhibition; the use of selective small-molecule inhibitor BAY-876 can greatly reduce GLUT1 and HIF-1α expression, therefore decreasing glycolytic flux, lowering cancer cells' proliferation rate, and inducing apoptosis by boosting mitochondrial activity.[23, 24] Moreover, another notable therapeutic target, LDHA, has been increasingly investigated in preclinical studies. The inhibitors of LDHA, such as FX11, can also achieve a similar effect of impairing tumor growth

through the inhibition of the proliferation pathway PI3K-Akt that cripples cellular redox control and diminishes ATP production in effector T cells. [24, 25]

Beyond the fundamental glucose metabolism, amino acid metabolism has also been highly targeted. Glutamine is the basic carbon and nitrogen source for tumor cells to synthesize nucleotide and control redox; with that said, glutaminase inhibitors CB-839 has been used to block glutaminase activity, entering clinical trials for renal cell carcinoma and triple-negative breast cancer, and possessing an indirect influence towards transcriptional factors such as MYC and KRAS since they often enhance glutamine uptake and SSP activity in tumor.[24] Tryptophan metabolism, specifically IDO1, IDO2, and TDO2, these key enzymes, has to be emphasized in the chapter on amino acids as their hyperactivation is highly correlated with immune suppression and cancer-favor TME.[6, 23, 26] Here, a crucial repurposed antidiabetic drug, metformin, will be introduced. In recent studies, metformin has shown its anti-tumor immunity to repress SLC7A5, a key tryptophan transporter in colorectal cancer cells, through the inhibition of MYC.[26] This successfully reduces the tumor cell tryptophan uptake, supporting the immune $CD8^+$ T cells' cytotoxic activity that requires tryptophan uptake.[26] What's especially notable is that this is not the only anti-tumor ability of metformin; its main anti-tumor immunity, which has already been clinically applied, will be discussed in the following sections.

4.3 Metformin as a Central Player in Metabolic–Immune Reprogramming

Metformin, one of the most promising metabolic modulators, stands out among all metabolism-targeting agents due to its safety profile and often dual mechanism of action, even the cross-talk of multiple signaling axes previously discussed. Clinically and epidemiologically, metformin has shown its profound potential for cancer treatment and prevention through substantial evidence. The meta-analyses of diabetic patient cohorts have consistently reported reduced cancer incidence and improved overall survival associated with metformin treatment, especially in gastrointestinal, gynecological, and hematologic malignancies.[27, 28] Metformin possesses multiple direct effects on cancer cells' metabolic mechanisms. Within the ETC, metformin inhibits mitochondrial complex I, therefore controlling the ATP supply for tumor growth; simultaneously, it raises the AMP/ATP ratio in cancer cells, activating AMP-activated protein kinase (AMPK) that subsequently suppresses mTORC1, downregulating anabolic biosynthesis processes crucial for cancer cell proliferation.[8, 29] The significance of this therapeutic mechanism of metformin is that it provides a robust therapeutic rationale for targeting multiple oncogenic signaling cascades simultaneously while being efficient. [5, 29, 30]

At the same time, metformin's capacity to reprogram immune responses has become increasingly evident. Wabitsch et al. revealed that metformin-induced mitochondrial stress leads to the release of mitochondrial DNA (mtDNA) into the cytosol; it activates the cGAS–STING pathway, which significantly enhances type I interferon responses, priming the TME for improved immune surveillance.[31] Moreover, Pusceddu et al. also reported that metformin suppresses OXPHOS in TAMs, which promotes their repolarization from an M2-like immunosuppressive phenotype toward a pro-inflammatory M1-like state.[32] Metformin, at this point, not only enhances $CD8^+$ T cell infiltration but also synergizes with immune checkpoint inhibitors to improve antitumor efficacy, manifesting its multifaceted immune ability to modulate both cancer cell-intrinsic metabolism and extrinsic immune responses.[31-33]

Nevertheless, despite the broad therapeutic promise of metformin, recent studies have also indicated some of the limitations of metformin, especially the adaptive resistance mechanisms of cancer cells in long-term treatment. Prolonged metformin exposure can lead to reversible resistance, mediated by super-enhancer (SE)-driven transcriptional reprogramming, upregulating the prostaglandin reductase 1, a critical factor in restoring cell cycle progression and glycolytic activity, eventually counteracting metformin's antiproliferative effects.[33] This SE-mediated resistance highlights the epigenetically rewiring ability of cancer cells to escape blockade while metformin initiates cytostatic pressure through AMPK activation and mitochondrial inhibition.[33]

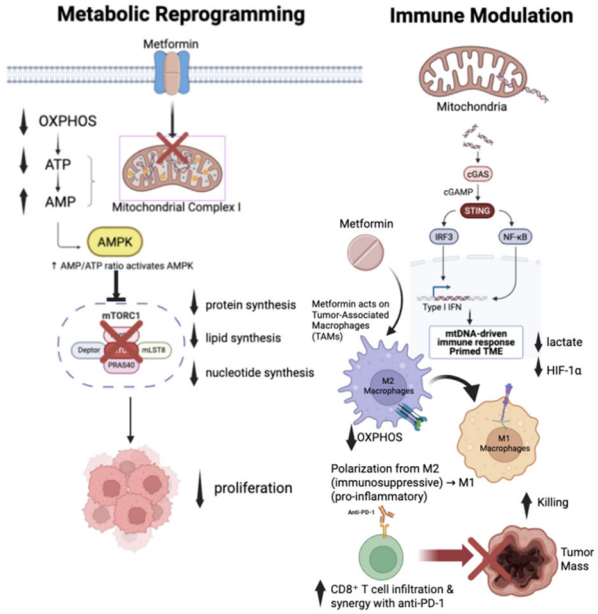

Figure 1: Metformin-mediated metabolic and immune reprogramming in cancer

Metformin exerts dual anti-tumor effects by targeting cancer cell metabolism and modulating immune responses. Left: Metformin inhibits mitochondrial complex I, reducing OXPHOS and ATP levels, leading to AMPK activation and subsequent mTORC1 inhibition. This downregulates biosynthetic pathways and suppresses tumor proliferation. Right: Metformin induces mitochondrial stress, triggering mtDNA release and activation of the cGAS–STING pathway. At the same time, metformin enhances type I interferon production and primes the TME, while metformin reprograms tumor-associated macrophages (TAMs) from an immunosuppressive M2 to a pro-inflammatory M1 phenotype, lowering lactate and HIF-1α levels. Lastly, metformin promotes synergy with immune checkpoint blockade to enhance $CD8^+$ T cell–mediated tumor clearance.

4.4 Targeting the Tumor Microenvironment (TME): Lactate, Hypoxia, and Immunosuppression

The GLUT1 inhibition also has applications in the TME, as it can sensitize tumors to immune checkpoint inhibitors through the optimization of the lactate tumor microenvironment.[23] The inhibition of glucose uptake by the GLUT1 agents will lead to a decrease in lactate secretion and rebalance of the pH in TME. The GLUT1 inhibitor BAY-876 mentioned can efficiently deal with the lactate-driven immunosuppression in glioblastoma through fewer TAMs and Tregs, enhanced production of IFN-γ, and increased CTL infiltration in orthotopic models.[34] This optimization of the TME by BAY-876 is therefore achieved through restraining inflammation-mediated growth, enhancing CTL and helper T cell activity, activating antigen presentation, and prompting long-term immunosurveillance.[23, 24, 34] Moreover, some preclinical studies have shown that in triple-negative breast cancer, BAY-876-mediated glycolytic suppression can reduce PD-L1 glycosylation, leading Tregs toward an immunostimulatory phenotype, therefore enhancing the efficacy of PD-1/PD-L1 blockade in cancer cells.[35]

Metformin, similarly, is also a crucial modulator of the TME. Besides the lactate accumulation, hypoxia-targeted therapies are also particularly effective, and metformin once again plays a role here. The downregulation of mTORC1 by metformin mentioned above can lead to a decrease in tumor glycolytic flux, therefore significantly reducing lactate production; but what's more is that metformin's inhibition on mitochondrial respiration which can reduce oxygen consumption while triggering AMPK, indirectly alleviating hypoxia and suppressing HIF-1α stabilization.[2, 27, 29, 30] Moreover, metformin's ability to modulate inflammatory signaling and redox balance is equally important; it reduces nuclear factor NF-κB activity, which decreases the pro-inflammatory cytokines while limiting chronic inflammation-driven immunosuppression.[29] Beside these direct effects, the AMPK activation driven by metformin shifts macrophage polarization away from

immunosuppressive M2 phenotypes towards a more pro-inflammatory and anti-tumor M1 state, turning the whole TME into a more active and immune-specific place.[27, 29, 30]

4.5 Toward Combination Therapies and Precision Oncology

Most drugs are only applicable to a specific type of cancer, and cancer cells can reroute metabolic flux through alternative pathways, enabling them to survive and proliferate even when nutrient supplies are restricted. This heterogeneity of cancer emphasizes the importance of combination therapies and technology; there are already substantial studies that have proven the antitumor efficacy of metformin, anti-PD-1, and phenformin combined with LDH inhibitors.[5, 24] The combination of metformin with 4SC-202 synergistically promotes apoptosis via the intrinsic pathway, which upregulates multiple key pro-apoptotic molecules and downregulates anti-apoptotic proteins.[30] Moreover, combining metformin with simvastatin induces necroptosis, as evidenced that Ripk1 and Ripk3 proteins expression increased, and HMGB-1 was released.[30] Pusceddu et al. have also indicated the antitumor activity potential of metformin with lanreotide ATG in both non-diabetic and diabetic patients. [32] Similarly, Wabitsch et al. suggested the significant contribution of metformin to the critical regulation of CD8+ T cell metabolism in ICI therapy.[31] All these substantial pieces of evidence keep suggesting that distinct yet complementary mechanisms of metformin, when combined with specific agents or therapy, effectively modulate cancer cell death pathways and immune response.

Furthermore, targeting cancer and immune cell metabolism can have a synergistic effect with anti-tumor immunity; this has been proven that combined immunomodulatory chemotherapeutic agent docetaxel with arginine, successfully prompted the anti-tumor phenotypes of DCs, and reduced the proliferation of MDSCs in their living models of breast cancer.[3, 6] Moreover, combining LSD1 inhibitors with anti-PD-1 immunotherapy can also effectively suppress tumor progression as they can reverse immune evasion mechanisms and enhance anti-tumor immune responses.[10] Similarly, dual epigenetic therapy using DNMT inhibitors together with HDAC inhibitors has demonstrated efficacy in mouse models of non-small cell lung cancer as well; the researchers successfully improved the responsiveness of NSCLC tumors to immunotherapy.[10] All of these combination therapeutic strategies highlight the potential of targeting modulation to restore immune surveillance and amplify the effects of immune checkpoint blockade.

In addition to the traditional therapeutic strategies, the use of modern technology of CRISPR-Cas9 can also have meaningful applications in this study.[10] Researchers have developed a CRISPR-Cas9-based acetyltransferase capable of activating promoters and enhancers within the epigenome. This powerful tool for manipulating gene regulation provides a precise therapeutic strategy for targeting site-specific epigenetic disorders.[10] Over and above that, a TME-responsive bispecific aptamer-based nanoassembly was built to reveal the efficacy and synergistic effects of PAE-tagged aptPD-L1 and aptCTLA-4 combined with BAY-876, once again suggesting the promising significance of integrating new technology in precision oncology today. [35]

5. Conclusion

Profound metabolic reprogramming is one of the most notable characteristics of cancer cells; as a fundamental adaptation to their harsh survival environment, supporting their uncontrolled proliferation and immune evasion. The Warburg effect has demonstrated how cancer cells uniquely prioritize aerobic glycolysis, leveraging metabolic flexibility to manipulate the TME and sustain their needs. The intricate interplay of epigenetic modifications and the key signaling pathways with critical transcriptional regulators further emphasizes cancer's metabolic complexity while offering numerous potential targets for therapeutic intervention and prevention.

Recent therapeutic advancements targeting metabolic vulnerabilities and immunosuppressive microenvironments, have significantly promoted the current oncology research progress. The promising therapeutic agent Metformin has proven this therapeutic prospect by modulating core

metabolic pathways, limiting immunosuppressive metabolites, and synergizing with established therapies; it bridges cancer metabolism, immunity, and precision oncology. Currently, emerging therapeutic strategies have more or less possessed synergetic effects with other agents, targeting lactate transport, amino acid metabolism, and mitochondrial function.

Looking forward, in order to enhance therapeutic efficacy further, integrating metabolism-targeted interventions with immunotherapy and precision oncology will likely define the next era of cancer treatment. Future efforts should focus on more clinical research and studies that clarify and verify the metabolic heterogeneity across cancer types, refining biomarkers for patient stratification by optimizing drug combinations. Eventually, the deep mechanistic understanding of metabolic reprogramming and therapeutic agents presented in this review not only advances foundational cancer biology but also further the progress toward more effective, personalized therapeutic strategies against cancer.

References

[1] Liberti, M.V. and J.W. Locasale, The Warburg Effect: How Does it Benefit Cancer Cells? Trends in Biochemical Sciences, 2016. 41(3): p. 211-218.

[2] Barba, I., L. Carrillo-Bosch, and J. Seoane, Targeting the Warburg Effect in Cancer: Where Do We Stand? International Journal of Molecular Sciences, 2024. 25(6).

[3] Xia, L., et al., The cancer metabolic reprogramming and immune response. Molecular Cancer, 2021. 20(1).

[4] Faubert, B., A. Solmonson, and R.J. DeBerardinis, Metabolic reprogramming and cancer progression. Science, 2020. 368(6487).

[5] Li, Z. and H. Zhang, Reprogramming of glucose, fatty acid and amino acid metabolism for cancer progression. Cellular and Molecular Life Sciences, 2015. 73(2): p. 377-392.

[6] Yang, L., et al., Amino acid metabolism in immune cells: essential regulators of the effector functions, and promising opportunities to enhance cancer immunotherapy. Journal of Hematology & Oncology, 2023. 16(1).

[7] Han, J., The Regulatory Role of Nutrients in Muscle Protein Synthesis (MPS) and Muscle Protein Breakdown (MPB) with Resistance Exercise. MedScien, 2024. 1(9).

[8] Saxton, R.A. and D.M. Sabatini, mTOR Signaling in Growth, Metabolism, and Disease. Cell, 2017. 169(2): p. 361-371.

[9] Menendez, J.A. and R. Lupu, Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. Nature Reviews Cancer, 2007. 7(10): p. 763-777.

[10] Xu, X., et al., Metabolic reprogramming and epigenetic modifications in cancer: from the impacts and mechanisms to the treatment potential. Experimental & Molecular Medicine, 2023. 55(7): p. 1357-1370.

[11] Sun, L., H. Zhang, and P. Gao, Metabolic reprogramming and epigenetic modifications on the path to cancer. Protein & Cell, 2021. 13(12): p. 877-919.

[12] Stine, Z.E., et al., MYC, Metabolism, and Cancer. Cancer Discovery, 2015. 5(10): p. 1024-1039.

[13] Pate, K.T., et al., Wnt signaling directs a metabolic program of glycolysis and angiogenesis in colon cancer. The EMBO Journal, 2014. 33(13): p. 1454-1473.

[14] Mao, H., X. Zhao, and S.-c. Sun, NF-κB in inflammation and cancer. Cellular & Molecular Immunology, 2025.

[15] Miranda-Gonçalves, V., et al., Metabolism and Epigenetic Interplay in Cancer: Regulation and Putative Therapeutic Targets. Frontiers in Genetics, 2018. 9.

[16] Xu, W., et al., Oncometabolite 2-Hydroxyglutarate Is a Competitive Inhibitor of α-Ketoglutarate-Dependent Dioxygenases. Cancer Cell, 2011. 19(1): p. 17-30.

[17] Geffen, Y., et al., Pan-cancer analysis of post-translational modifications reveals shared patterns of protein regulation. Cell, 2023. 186(18): p. 3945-3967.e26.

[18] Guan, H., et al., Diverse modes of H3K36me3-guided nucleosomal deacetylation by Rpd3S. Nature, 2023. 620(7974): p. 669-675.

[19] Chen, H., et al., NBS1 lactylation is required for efficient DNA repair and chemotherapy resistance. Nature, 2024. 631(8021): p. 663-669.

[20] Chen, Y., et al., Metabolic regulation of homologous recombination repair by MRE11 lactylation. Cell, 2024. 187(2): p. 294-311.e21.

[21] Liang, L., et al., Alterations in PD-L1 succinylation shape anti-tumor immune responses in melanoma. Nature Genetics, 2025. 57(3): p. 680-693.

[22] Mossmann, D., S. Park, and M.N. Hall, mTOR signalling and cellular metabolism are mutual determinants in cancer. Nature Reviews Cancer, 2018. 18(12): p. 744-757.

[23] De Martino, M., et al., Cancer cell metabolism and antitumour immunity. Nature Reviews Immunology, 2024. 24(9): p. 654-669.

[24] Stine, Z.E., et al., Targeting cancer metabolism in the era of precision oncology. Nature Reviews Drug Discovery, 2021. 21(2): p. 141-162.

[25] Xu, K., et al., Glycolysis fuels phosphoinositide 3-kinase signaling to bolster T cell immunity. Science, 2021. 371(6527): p. 405-410.

[26] Huang, X., et al., Metformin Reprograms Tryptophan Metabolism to Stimulate CD8+ T-cell Function in Colorectal Cancer. Cancer Research, 2023. 83(14): p. 2358-2371.

[27] Pernicova, I. and M. Korbonits, Metformin—mode of action and clinical implications for diabetes and cancer. Nature Reviews Endocrinology, 2014. 10(3): p. 143-156.

[28] O'Connor, L., et al., Association of metformin use and cancer incidence: a systematic review and meta-analysis. JNCI: Journal of the National Cancer Institute, 2024. 116(4): p. 518-529.

[29] Foretz, M., et al., Metformin: From Mechanisms of Action to Therapies. Cell Metabolism, 2014. 20(6): p. 953-966.

[30] Hua, Y., et al., Metformin and cancer hallmarks: shedding new lights on therapeutic repurposing. Journal of Translational Medicine, 2023. 21(1).

[31] Wabitsch, S., et al., Metformin treatment rescues CD8+ T-cell response to immune checkpoint inhibitor therapy in mice with NAFLD. Journal of Hepatology, 2022. 77(3): p. 748-760.

[32] Pusceddu, S., et al., Safety and antitumor activity of metformin plus lanreotide in patients with advanced gastro-intestinal or lung neuroendocrine tumors: the phase Ib trial MetNET2. Journal of Hematology & Oncology, 2023. 16(1).

[33] Ye, J., et al., Metformin escape in prostate cancer by activating the PTGR1 transcriptional program through a novel super-enhancer. Signal Transduction and Targeted Therapy, 2023. 8(1).

[34] Li, T., et al., Metabolism/Immunity Dual‐Regulation Thermogels Potentiating Immunotherapy of Glioblastoma Through Lactate‐Excretion Inhibition and PD‐1/PD‐L1 Blockade. Advanced Science, 2024. 11(18).

[35] Ren, X., et al., Inhibition of glycolysis-driven immunosuppression with a nano-assembly enhances response to immune checkpoint blockade therapy in triple negative breast cancer. Nature Communications, 2023. 14(1).