Metabolic reprogramming-a breakthrough point in overcoming resistance to BRAF mutant melanoma targeted therapy (Review)

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Received October 30, 2025; Accepted January 21, 2026

DOI: 10.3892/ol.2026.15539

Abstract. Targeted therapy for BRAF-mutant melanoma induces metabolic reprogramming, which drives the development of drug resistance. Studies indicate that following treatment with BRAF inhibitors and/or MEK inhibitors, melanoma cells alter metabolic pathways by modifying various regulatory factors. These adaptations include increased lactate accumulation, enhanced oxidative phosphorylation, elevated glutamine utilization via the tricarboxylic acid cycle, activation of the kynurenine pathway and increased fatty acid synthesis. Collectively, these alterations reshape the tumor microenvironment, suppress ferroptosis and activate alternative signaling pathways, thereby conferring resistance to targeted therapy. This paper systematically reviews the mechanisms underlying therapy-induced metabolic reprogramming in BRAF-mutant melanoma and explores potential combinatorial strategies that target these metabolic vulnerabilities alongside established melanoma therapies. Key metabolic targets with promising therapeutic potential identified include lysine-specific demethylase 1, oxidative phosphorylation components, phosphoglycerate dehydrogenase, indoleamine 2,3-dioxygenase 1 and lipid metabolism enzymes such as fatty acid synthase and 3-hydroxy-3-methylglutaryl-coenzyme a reductase.

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Key words: BRAF-mutant melanoma, targeted therapy, metabolic reprogramming, drug resistance, targeted metabolism

Contents

1. Introduction

Melanoma, a highly aggressive cutaneous malignancy, has a rising global incidence (1,2). Current treatment encompasses surgery, radiation therapy, chemotherapy, immunotherapy and targeted therapy (3). While surgical resection remains the cornerstone for early-stage disease, targeted therapy and immunotherapy have emerged as essential modalities for advanced or metastatic melanoma (4). In recent years, advances in immunotherapy and targeted therapy have brought new hope to patients with melanoma (5). In particular, targeted therapy plays a pivotal role in contemporary melanoma management (6).

BRAF mutations are among the most frequent genetic alterations in melanoma, occurring in ~40-60% of patients with cutaneous melanoma, with the BRAFV600E variant predominating (7). The BRAF gene encodes a serine/threonine protein kinase that plays a crucial role in cellular signaling. The BRAFV600E point mutation results in the substitution of valine for glutamate at position 600, leading to constitutive activation of signaling pathways such as MAPK and thereby driving aberrant cell growth and proliferation (8). Targeted agents, including BRAF inhibitors (e.g., vemurafenib, dabrafenib) and MAPK kinase (MEK) inhibitors (e.g., trametinib), have demonstrated considerable clinical efficacy against this alteration (9). Nevertheless, despite substantial advances in targeted therapies for BRAF-mutant melanoma, the emergence of drug resistance remains a major therapeutic challenge, as tumor cells evade treatment through multiple mechanisms, including

acquired mutations, activation of alternative pathways and modifications of the tumor microenvironment (TME) (10). This review aims to systematically delineate the role of metabolic reprogramming in drug resistance and identify research gaps in the combined targeting of metabolic pathways.

2. Targeted therapy for BRAF-mutant melanoma: Current status and evolving mechanisms of drug resistance

Current evidence indicates that ~50% of patients with melanoma harbor activating BRAF mutations. As a central component of the MAPK cascade, the B-RAF kinase functions as a critical node in the RAS/RAF/MEK/ERK signaling axis, primarily regulating cellular proliferation and survival (9). Oncogenic BRAF mutations lead to constitutive MAPK pathway activation (11), which drives uncontrolled melanoma cell proliferation, evasion of cell death and malignant transformation (12). Given its pivotal role in melanoma initiation, progression, metastasis and therapeutic resistance (13), targeting the MAPK pathway has emerged as a cornerstone of treatment for BRAF-mutant melanoma (14).

Targeted therapies that block the MAPK signaling pathway primarily include BRAF inhibitors (BRAFi) and MEKi (15). BRAFi selectively suppress the mutated BRAF protein, thereby blocking downstream signal transduction and impeding tumor growth (16), whereas MEKi directly inhibit MEK activity to achieve a similar pathway blockade (17). Current clinical practice relies on BRAFi monotherapy or BRAFi/MEKi combination regimens, which have demonstrated substantial efficacy, significantly improving objective response rates and overall survival (18). Notably, the Food and Drug Administration approved vemurafenib and dabrafenib over a decade ago for advanced BRAF-mutant melanoma, with both agents achieving high response rates and even complete tumor regression in a subset of patients (12).

Although drugs targeting the MAPK pathway have made significant progress in melanoma treatment, resistance to targeted therapy remains an obstacle to curative treatment for melanoma. The expansion of research on immune-checkpoint inhibitor-related mechanisms in melanoma underscores the growing clinical importance of understanding immune-metabolic interactions (19). The combination of BRAFi and MEKi as a first-line treatment option for locally advanced or metastatic melanoma with BRAF mutations has demonstrated excellent response rates. However, these responses are not durable and nearly all patients develop resistance (1,2). Statistical analysis revealed that in BRAF-mutated melanoma, the median time to clinically detectable acquired resistance to BRAFi/MEKi was 9-11 months (20).

3. Metabolic reprogramming as a driver of targeted therapy resistance in BRAF-mutant melanoma

Melanoma metabolic reprogramming is intricately linked to targeted therapy resistance (21). As a hallmark of cancer, this process involves the rewiring of cellular metabolic pathways to meet bioenergetic and biosynthetic demands, supporting rapid proliferation and survival (22,23). In melanoma, an aggressive malignancy with high metabolic plasticity, such reprogramming fuels tumor progression and enables adaptation to therapeutic stress (24). Critically, metabolic adaptation not only drives melanoma growth and metastasis but also underlies the development of treatment resistance (21,25).

Studies indicate that targeted inhibition of BRAF-mutant melanoma cells induces profound metabolic shifts, including enhanced oxidative phosphorylation (OXPHOS), increased glutamine flux through the tricarboxylic acid (TCA) cycle, and altered fatty acid (FA) synthesis and catabolism (9). BRAFi and MEKi therapies trigger metabolic reprogramming in BRAF-mutant melanoma cells, thereby conferring resistance (26). Consequently, targeting these adaptive metabolic pathways offers a promising strategy to overcome resistance and suppress tumor progression (21).

In this section, the context of targeted therapy resistance was first outlined, key metabolic adaptations and their mechanistic roles in promoting resistance were then described in detail, and finally, emerging therapeutic targets and translational implications were discussed. Elucidating these metabolic mechanisms not only reveals actionable vulnerabilities but also informs the identification of predictive biomarkers for personalized treatment. Furthermore, growing evidence underscores the interplay between metabolic rewiring and immune dysregulation, highlighting the need to integrate metabolic and immune profiling in future research to develop more effective combinatorial strategies (19).

Lactate accumulation. Lactate accumulation in melanoma cells is closely associated with monocarboxylate transporters (MCTs), a class of membrane proteins responsible for transporting monocarboxylic acids such as lactate and pyruvate (27). MAPK pathway inhibition has been shown to downregulate the expression and activity of specific MCT isoforms, particularly MCT1 and MCT4, thereby impairing lactate efflux and promoting intracellular lactate accumulation (28).

Research into the resistance mechanisms of BRAFV600E mutant melanoma to BRAFi and MEKi revealed that in BRAFi/MEKi-resistant melanoma, lactate accumulation drives the lactylation of lysine specific demethylase 1 (LSD1), thereby promoting its interaction with FOS like 1, AP-1 transcription factor subunit (FosL1) and preventing LSD1 degradation by the E3 ligase tripartite motif containing 21. Lactylated LSD1 and FosL1 jointly regulate gene transcription, inhibiting ferroptosis by interfering with iron uptake mediated by the transferrin receptor (TFR) (29).

Ferroptosis is characterized by iron overload-driven mitochondrial dysfunction, excessive reactive oxygen species (ROS) generation and subsequent peroxidation of polyunsaturated FAs in cellular membranes, ultimately leading to oxidative cell damage (30). Tumor cells can negatively regulate ferroptosis via lactylated LSD1. Inhibition of ferroptosis markedly enhances the oxidative stress resistance of melanoma cells, enabling them to adapt and survive under the pressure of targeted therapy, thereby diminishing the therapeutic efficacy of targeted agents against melanoma (31) (Fig. 1).

Increased mitochondrial OXPHOS. In melanoma, although BRAF mutations initially suppress OXPHOS (11), resistance to targeted therapy is consistently associated with OXPHOS upregulation in both experimental models and clinical specimens of BRAF-mutant melanoma (9,32). This metabolic

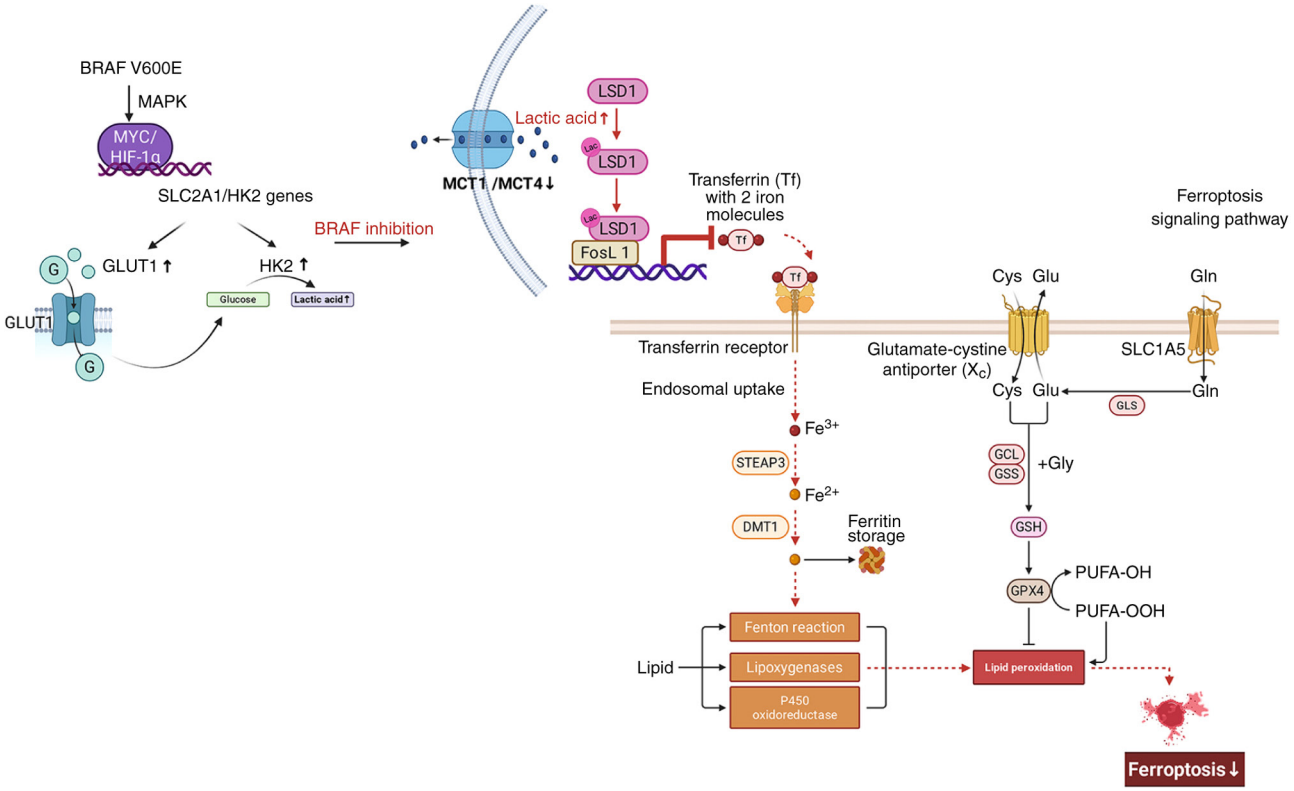

Figure 1. Lactic acid accumulation induces targeted therapy resistance by inhibiting ferroptosis. After the MAPK signaling pathway is inhibited, suppression of MCTs expression and activity impairs intracellular lactate efflux, leading to lactate accumulation. This accumulated lactate drives the lactylation of LSD1. The lactylated LSD1, in conjunction with FosL1, regulates gene transcription, which interferes with TFR-mediated iron uptake to inhibit ferroptosis. This inhibition of ferroptosis significantly enhances the resistance of melanoma cells to oxidative stress. MAPK, mitogen-activated protein kinase; MCTs, monocarboxylate transporters; LSD1, lysine-specific demethylase 1; FosL1, Fos-like antigen 1; TFR, transferrin receptor.

shift enhances tumor invasion and metastatic potential, thereby driving resistance to MAPK pathway inhibitors (11). Furthermore, the phenotypic plasticity accompanying OXPHOS activation may complicate this metabolic adaptation and contribute to acquired resistance against BRAFi and MEKi (e.g., trametinib, cobimetinib, binimetinib) (33) (Fig. 2).

OXPHOS-driven bioenergetic adaptation. The BRAFV600E mutation leads to microphthalmia-associated transcription factor (MITF) inactivation via ERK1/2-mediated phosphorylation or direct RAF binding, which in turn suppresses the transcription of peroxisome proliferator-activated receptor gamma Coactivator 1α (PGC1α), a master regulator of mitochondrial biogenesis and function (34). Consequently, under constitutive MAPK signaling, reduced MITF and PGC1α levels attenuate oxidative metabolism. Conversely, BRAF/MAPK pathway inhibition restores MITF expression and activity, thereby upregulating PGC1α and its downstream targets (35).

Following MAPK pathway inhibition by BRAF-targeted therapeutics, ATP citrate lyase (ACLY) expression is enhanced via sterol regulatory element binding transcription factor 1 transcriptional activation. ACLY enhances histone acetyltransferase p300 (EP300) activity by supplying sufficient acetyl-CoA. This increases histone acetylation at MITF binding sites, thereby promoting transcription via the MITF-PGC1α axis. The MITF-PGC1α axis activation activates OXPHOS. Expression of MITF and PGC1α correlates with OXPHOS genes, and PGC1α drives increased glutamine and serine metabolism dependency, thereby enhancing OXPHOS (36). Melanoma cells can enhance energy production and biosynthetic capacity by boosting OXPHOS, leading to bioenergetic adaptation that sustains their survival and proliferation (37). Furthermore, MITF, a transcription factor specific to the typical melanocyte lineage, is induced and promotes downstream PGC1α-dependent OXPHOS. This pathway also represents a classic signaling cascade involved in adaptive resistance to MAPK inhibitor-targeted therapies in melanoma (12,38) (Fig. 2).

Elevated OXPHOS drives redox adaptation through ROS modulation. Beyond the MITF-PGC1α axis, BRAF inhibitors promote OXPHOS via alternative mechanisms. For instance, while the BRAFV600E mutation suppresses OXPHOS through constitutive kinase activation, pharmacological BRAF inhibition reverses this effect and induces OXPHOS upregulation (21). Following MAPK blockade treatment, upregulation of the OXPHOS-associated lincRNA enhancer also promotes metabolic shift from glycolysis to OXPHOS (39).

Enhanced OXPHOS inevitably elevates mitochondrial ROS production. Rather than merely tolerating high ROS levels, drug-resistant melanoma cells establish a remodeled redox homeostasis characterized by moderately elevated ROS. This adapted state functions not only as a selective survival advantage but also as a key signaling node that supports resistance. Specifically, ROS can activate parallel survival pathways, such as the PI3K/AKT cascade, enabling cell proliferation even under BRAF or MEK inhibition (12,40). Concurrently, ROS

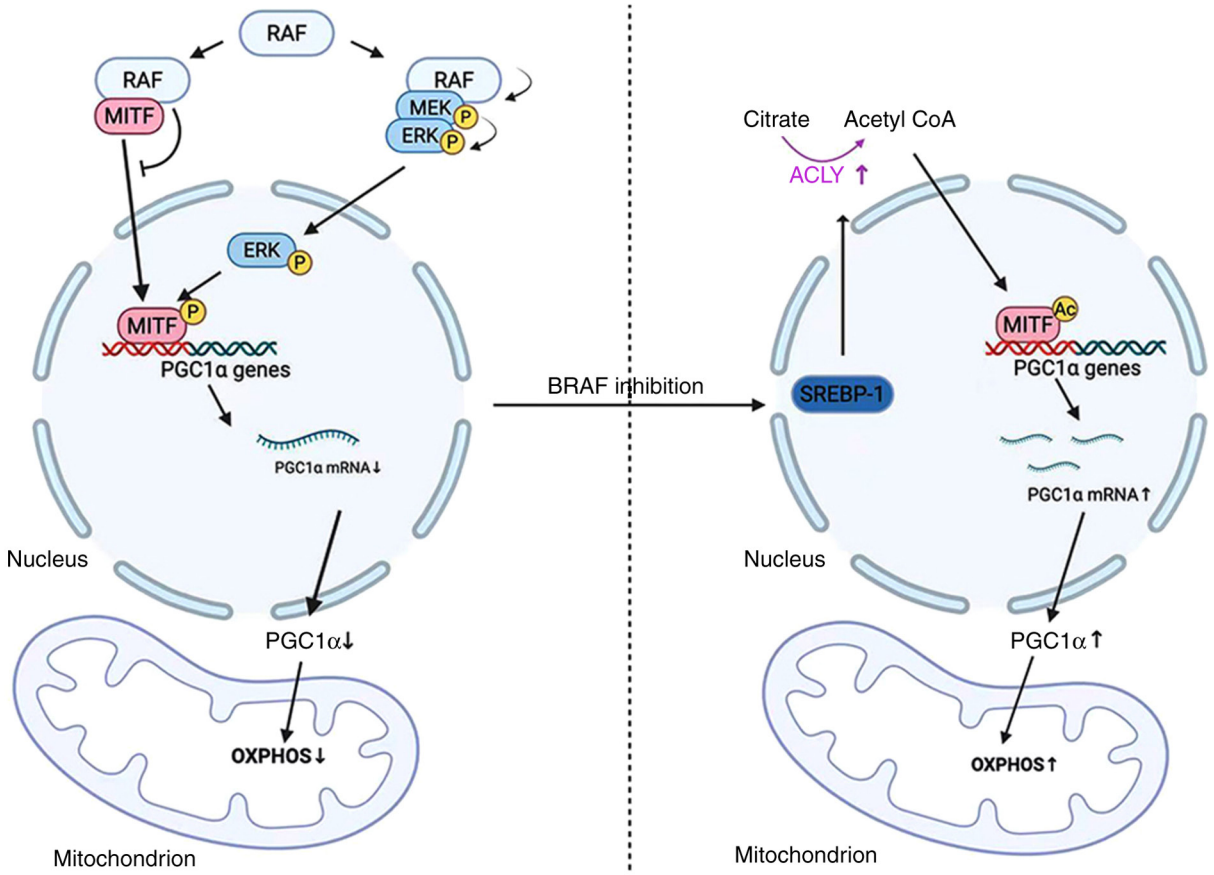

Figure 2. OXPHOS enhancement leads to targeted therapy resistance by boosting metabolism. Following MAPK pathway inhibition, SREBP-1-mediated transcriptional activation increases ACLY expression, which elevates acetyl-CoA levels. This leads to enhanced EP300 activity and subsequent activation of the MITF-PGC1α axis, ultimately resulting in enhanced OXPHOS and augmented tumor invasion and metastatic capacity. MAPK, mitogen-activated protein kinase; SREBP-1, sterol regulatory element-binding protein 1; ACLY, ATP-citrate lyase; EP300, E1A binding protein p300; MITF, melanocyte-inducing transcription factor; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; OXPHOS, oxidative phosphorylation.

stimulates compensatory antioxidant responses, including the NFE2 like bZIP transcription factor 2/antioxidant response element pathway, which enhances cellular ROS-buffering capacity and limits oxidative damage (40). Furthermore, ROS contributes to the epigenetic remodeling of resistant cells through mechanisms involving DNA methylation and histone modification (41). Thus, through fine-tuned regulation of OXPHOS-derived ROS, melanoma cells achieve a redox-adapted state that sustains proliferation and confers acquired resistance to targeted therapy.

Altered amino acid metabolism

Increased glutamine utilization via the TCA cycle. In BRAF-inhibited melanoma cells, since glucose is primarily converted to lactate, glutamine serves as an alternative carbon source, fueling the TCA cycle by conversion to α-ketoglutarate (α-KG), with glutamine consumption leading to reduced α-KG levels. α-KG serves as a crucial cofactor for Jumonji C-domain-containing histone demethylases, which rely on α-KG for catalytic activity to promote histone demethylation and maintain a differentiated cellular state (42). In the TME, reduced α-KG levels therefore directly inhibit histone demethylation, subsequently leading to a hypermethylated epigenetic landscape that drives cellular dedifferentiation and increased resistance to targeted therapies in melanoma cells (12). This creates a dual role for glutamine metabolism in resistance: While fueling the TCA cycle as an energy source, its consumption simultaneously depletes a key epigenetic cofactor (α-KG), locking cells into a resistant, dedifferentiated phenotype (Fig. 3). However, melanoma cells that acquire resistance to BRAFi exhibit high dependence on glutamine for proliferation, suggesting that glutamine metabolism may play context-dependent, seemingly opposing roles at different stages of therapeutic resistance, acting as both a fuel source and an epigenetic regulator (12).

Increased glutamine synthesis via the serine pathway. In BRAF-mutant melanoma following BRAFi treatment, upregulation of phosphoglycerate dehydrogenase (PHGDH) and activation of the serine synthesis pathway have been observed (43). PHGDH is the key enzyme in *de novo* serine synthesis, responsible for converting 3-phosphoglycerate into serine (44). Serine indirectly participates in glutathione (GSH) synthesis by converting into glycine, making serine supply critical for maintaining intracellular GSH levels (45). Elevated GSH suppresses ferroptosis by reducing intracellular ROS production. Tumor cells can significantly enhance their oxidative stress defense capacity and increase resistance to targeted therapies by negatively regulating ferroptosis (46). Consequently, PHGDH upregulation correlates with resistance to melanoma targeted therapies and may represent a therapeutic

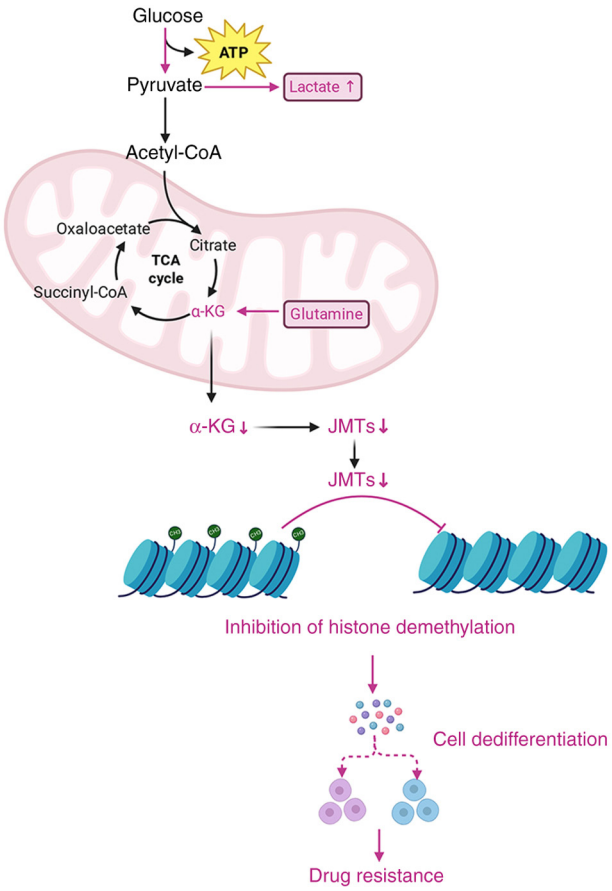

Figure 3. Increased utilization of glutamine through the TCA cycle leads to histone demethylation, thereby inducing resistance to targeted therapies. Following MAPK pathway inhibition, glutamine utilization via the TCA cycle increases. As an alternative carbon source, glutamine is converted into α-KG to fuel the TCA cycle. This enhanced consumption results in decreased α-KG levels. As α-KG serves as a critical cofactor for JMJs, its depletion in the tumor microenvironment inhibits histone demethylation and subsequently promotes cellular dedifferentiation. TCA, tricarboxylic acid. MAPK, mitogen-activated protein kinase; TCA, tricarboxylic acid; α-KG, α-ketoglutarate; JMJs, Jumonji C-domain-containing histone demethylases.

target (43,44). Notably, the serine synthesis pathway intersects with glutamine metabolism. Glutamine-derived nitrogen is utilized in serine and glycine synthesis, and the resulting GSH is critical for mitigating oxidative stress that may arise from altered mitochondrial metabolism (e.g., enhanced OXPHOS). Thus, the co-upregulation of glutamine utilization and serine synthesis forms an integrated metabolic network that supports redox balance and epigenetic adaptation, collectively fostering a resistant phenotype.

Activation of the kynurenine metabolic pathway. Indoleamine is the primary metabolite of tryptophan, influencing the TME and immune response through multiple mechanisms to promote melanoma drug resistance (47). During BRAFi and MEKi therapy, tumor cells may activate the indoleamine metabolic pathway to enhance survival and proliferation, thereby diminishing targeted treatment efficacy (12). In treatment-sensitive melanoma cells, BRAFi therapy reduces indoleamine 2,3-dioxygenase (IDO) expression levels. However, IDO expression may increase in BRAFi-resistant cells. IDO expression is elevated not only in patient biopsies of primary and metastatic melanoma but also in

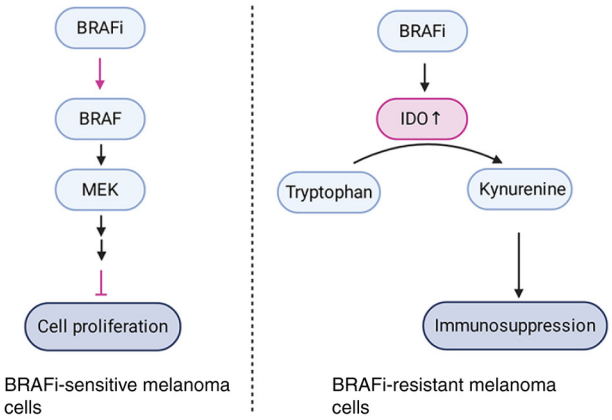

Figure 4. Activation of the kynurenine pathway leads to targeted therapy resistance by suppressing immune responses. Upon inhibition of the MAPK signaling pathway, the kynurenine metabolic pathway is activated, leading to the conversion of tryptophan into kynurenine by IDO. The resulting accumulation of kynurenine establishes an immunosuppressive microenvironment, which promotes tumor cell growth and confers drug resistance. MAPK, mitogen-activated protein kinase; IDO, indoleamine 2,3-dioxygenase.

IDO mRNA levels during BRAFi resistance (48). Tryptophan is metabolized into kynurenine by enzymes such as IDO (49). Research shows that the accumulation of kynurenine not only promotes the formation of a TME but also activates the aryl hydrocarbon receptor, thereby inducing the differentiation of induced regulatory T cells and myeloid-derived suppressor cells (50). Single-cell transcriptional profiling further supports that metabolic cues can reshape key immune-regulatory pathways, such as IL27RA-mediated immunomodulation (51). Kynurenine promotes Treg generation, further suppressing immune responses and thereby favoring tumor cell growth and drug resistance (40) (Fig. 4).

Altered lipid metabolism. Lipid metabolic reprogramming constitutes an adaptive cellular response to metabolic stressors such as glucose deprivation and hypoxia. In melanoma, this process is characterized by enhanced *de novo* FA synthesis, enabling tumor cells to dynamically adapt to the evolving TME (52). Lipid metabolic reprogramming also plays multiple roles in melanoma progression and targeted therapy resistance. Numerous studies support its role in regulating melanoma cell differentiation states and promoting resistance to targeted therapies. Drugs targeting lipid metabolic reprogramming show strong therapeutic potential in drug-resistant melanoma (53). Research indicates that lipid metabolic reprogramming occurs in vemurafenib (BRAFi)-treated melanoma cells (54), inducing or maintaining resistance by altering the lipid composition and biophysical properties of cancer cell membranes (55) (Fig. 5).

Increased FA synthesis. Acetyl-CoA serves as the primary substrate for FA synthesis. ACLY facilitates the production of oxaloacetate and cytoplasmic acetyl-CoA, acting as a pivotal enzyme linking glycolysis and lipid synthesis (56). BRAF-mutant melanomas exhibit elevated ACLY expression following MAPK inhibition, leading to increased FA synthesis (37).

FAs can be utilized for synthesizing bioactive lipids that support cell proliferation and survival by acting as second messengers in signaling pathways. For instance,

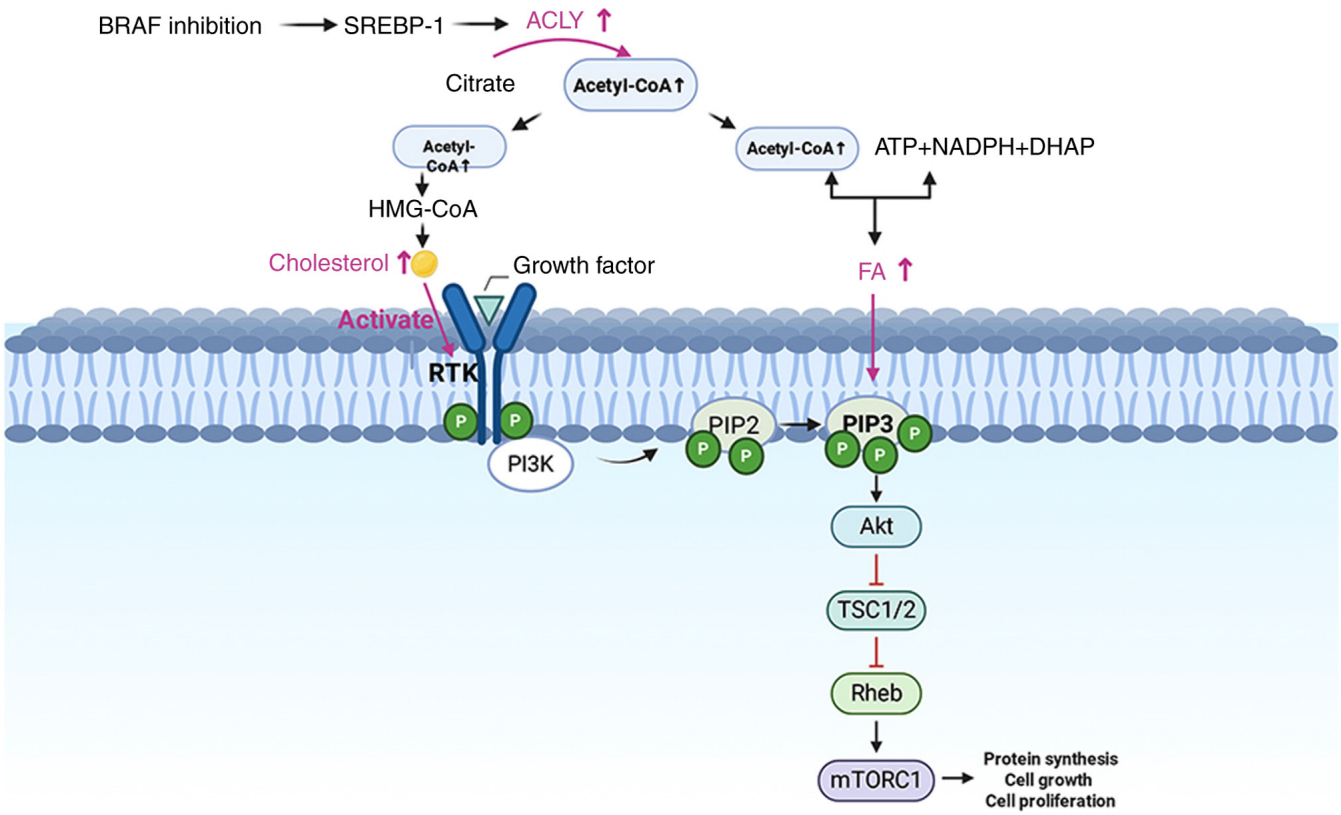

Figure 5. Altered lipid metabolism (increased fatty acid synthesis and cholesterol accumulation) leads to targeted therapy resistance by activating the PI3K/AKT pathway. PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B.

phosphatidylinositol, composed of an inositol ring, glycerol backbone and two FA chains, is one of the most characteristic signaling-related lipids (53). Phosphatidylinositol (3,4,5)-trisphosphate facilitates the recruitment of AKT to the plasma membrane, where AKT is subsequently activated by pyruvate dehydrogenase kinase 1 and the mTOR complex 2 (mTORC2), the latter being hyperactivated downstream of PI3K signaling. The PI3K-AKT-mTOR pathway is one of the most common signaling pathways and plays a crucial role in the acquisition of resistance to targeted therapies in melanoma. Furthermore, increased expression of various G protein-coupled bioactive lipid receptors participates in regulating migratory signaling in melanoma, such as activation of cyclic AMP/PKA, MAPK and PI3K pathways, which may represent an important mechanism for the failure of targeted therapy (53,57).

Cholesterol accumulation. Intracellular cholesterol accumulation has been observed in BRAFV600E-mutant melanoma cells following MAPKi treatment. Mechanistically, MAPK pathway inhibition promotes the activation of receptor tyrosine kinases, leading to enhanced phosphotyrosine (p-Tyr) signaling. This in turn stimulates downstream pathways such as PI3K-AKT, thereby providing an alternative survival mechanism that sustains tumor growth under therapeutic pressure. Notably, dysregulated cholesterol metabolism appears to drive the activation of these kinases coordinately (58). The resultant PI3K-AKT pathway activation is recognized as a key mechanism of adaptive resistance to targeted therapy in melanoma (12).

4. Therapeutic targeting of metabolic pathways in drug-resistant BRAF-mutant melanoma

Targeted metabolic changes combined with MPAKi are crucial for the treatment of drug-resistant BRAF mutant melanoma. Below are the corresponding drugs identified for different metabolic pathways that can improve melanoma treatment (Table I).

Targeting lactic acid accumulation. LSD1 inhibition (LSD1i)-induced ferroptosis not only directly eliminates melanoma cells but also enhances host antitumor immunity against drug-resistant disease. Mechanistically, therapy-induced lactate accumulation drives lysine lactylation of LSD1, which in turn suppresses ferroptosis, an iron-dependent form of regulated cell death. The TFR serves as a key downstream effector mediating LSD1i-triggered remodeling of the TME. Consequently, combining LSD1 inhibition with TFR blockade can overcome acquired resistance to BRAFi/MEKi in melanoma by establishing a positive feedback loop that restores and amplifies ferroptotic cell death (29).

Targeting OXPHOS. Combining OXPHOS inhibitors (OPIs) with targeted therapies can block tumor cell energy metabolism and inhibit signaling pathways, producing synergistic effects that overcome melanoma resistance and more effectively kill tumor cells (29).

In BRAF-mutant melanoma, resistance to MEKi is primarily mediated by elevated OXPHOS activity, which mTORC1i can counteract. Mechanistically, both BRAF- and NRAS-mutant

Table I. Drugs that can be combined with MAPKi are available for BRAF-mutant melanoma resistant to targeted therapy.

Drug	Drug type	Target	Metabolic pathways	(Refs.)
-	LSD inhibitor	LSD1	Lactic acid accumulation	(3)
Diclofenac	NSAIDs	-	OXPHOS	(4)
Lumiracoxib	NSAIDs	-	OXPHOS	(4)
AZD8055	mTORC inhibitor	mTORC	OXPHOS	(4-6)
AZD2014	mTORC inhibitor	mTORC	OXPHOS	(4-6)
XCT790	PGC1α inhibitor	PGC1α	OXPHOS	(4)
SR-18292	PGC1α inhibitor	PGC1α	OXPHOS	(4)
Phenformin	Mitochondrial respiratory complex I inhibitor	Mitochondrial respiratory complex I	OXPHOS	(4)
ONC212	Mitochondria inhibitor	Mitochondria	OXPHOS	(37)
FK866	NAMPT inhibitor	NAMPT	OXPHOS	(4)
GMX1778	NAMPT inhibitor	NAMPT	OXPHOS	(4)
-	PHGDH inhibitor	PHGDH	Serine pathway	(7)
1-methyl-tryptophan	IDO inhibitor	IDO	Kynurenine pathway	(56,57)
Orlistat	FASN inhibitor	FASN	FA synthesis	(8)
Physostigmine	HMGCR inhibitor	HMGCR	Cholesterol accumulation	(49,59,60)

FASN, fatty acid synthase; FA, fatty acid; HMGCR, 3-hydroxy-3-methylglutaryl-CoA reductase; IDO, indoleamine 2,3-dioxygenase; LSD1, lysine-specific demethylase 1; mTORC, mechanistic target of rapamycin complex; NAMPT, nicotinamide phosphoribosyltransferase; NSAIDs, non-steroidal anti-inflammatory drugs; OXPHOS, oxidative phosphorylation; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1α; PHGDH, phosphoglycerate dehydrogenase.

melanomas promote MITF expression and upregulate the transcriptional coactivator PGC1α, leading to enhanced OXPHOS. mTORC1 inhibitors such as AZD8055 and AZD2014 induce nuclear exclusion of MITF, thereby suppressing PGC1α expression and OXPHOS activity. Similarly, direct targeting of PGC1α with compounds such as XCT790 or SR-18292 reduces mitochondrial mass and function, restoring MEKi sensitivity in OXPHOS-highly resistant melanomas (21).

Other promising OXPHOS-targeting strategies include novel OPIs and phenformin, as well as nicotinamide phosphoribosyltransferase (NAMPT) inhibitors (e.g., FK866 and GMX1778). Given that NAD^+ levels are significantly elevated in BRAFi-resistant melanoma, NAMPTi effectively reduce NAD^+ availability and have been shown to improve survival in preclinical models (21). Additionally, the mitochondrial-targeting agent ONC212 exhibits potent growth-inhibitory effects against vemurafenib-resistant melanoma cells, supporting its potential for inclusion in multimodal therapeutic regimens (11).

Of note, non-steroidal anti-inflammatory drugs such as diclofenac and lumiracoxib also demonstrate OPI activity in melanoma cells, and their combination with BRAFi has been shown to delay the onset of BRAFi resistance (21).

Targeting the serine metabolic pathway. Inhibition of PHGDH acts synergistically with MAPK pathway blockade in melanoma. By suppressing *de novo* serine synthesis, PHGDH targeting reduces GSH production, thereby increasing oxidative stress in tumor cells. This mechanism restores sensitivity to MAPKi in resistant cells. Consequently, co-inhibition of PHGDH and MEK in MEKi-resistant melanoma reduces cellular oxidative stress tolerance and suppresses proliferation (43).

Targeting the tyrosinase metabolic pathway. In vitro studies demonstrate that the IDO1 inhibitor 1-methyl-tryptophan reduces clonogenic capacity in both parental and BRAF-inhibitor-resistant melanoma cells (48), suggesting that IDO1 inhibition represents a promising therapeutic strategy for patients with BRAFi-resistant melanoma (50).

Targeting FA synthesis. FA synthase (FASN), a key multifunctional enzyme complex, drives *de novo* lipogenesis, the metabolic process that converts carbohydrates into FAs. The FASN inhibitor orlistat, which targets this pathway, is presently under investigation in combination with BRAFi for the treatment of melanoma (58).

Targeting cholesterol metabolism. In preclinical studies, inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR)-the rate-limiting enzyme in the mevalonate pathway that converts HMG-CoA to mevalonate during cholesterol biosynthesis-have been investigated for their potential to overcome targeted therapy resistance in melanoma. Cholesterol depletion disrupts receptor-mediated endocytosis and endosomal trafficking, and suppresses key survival pathways such as AKT signaling. Notably, in melanoma cells treated with MAPK pathway inhibitors, cholesterol depletion abrogates p-Tyr signaling activation and synergistically enhances cytotoxic effects both *in vitro* and *in vivo* (49,59). These findings support the combination of MAPKi with

cholesterol-lowering agents to achieve more durable responses in hyper-MAPK-driven tumors by counteracting adaptive resistance. Consistent with this, Wang *et al* (60) reported that physostigmine, an HMGCR-targeting agent, exerts anticancer activity and sensitizes melanoma cells to BRAFi.

5. Discussion

Despite the significant clinical success achieved by targeted therapies against BRAF-mutant melanoma, the inevitable emergence of drug resistance continues to be a major barrier to long-term patient survival. This review systematically synthesizes evidence illustrating how melanoma cells undergo profound metabolic reprogramming following MAPK pathway inhibition, thereby developing resistance. Key adaptations include intracellular lactate accumulation, enhanced mitochondrial OXPHOS, increased reliance on glutamine and serine metabolism, activation of the kynurenine pathway, and alterations in lipid metabolism involving increased FA synthesis and cholesterol accumulation. These shifts are not merely correlative; they actively drive resistance by rewiring energy production, suppressing cell death pathways like ferroptosis, shaping an immunosuppressive TME and activating bypass survival signals. A critical appraisal of the literature, however, reveals complexities and even apparent contradictions. For instance, while glutamine depletion in the TME is linked to histone hypermethylation and dedifferentiation, which favor resistance, other evidence indicates that glutamine addiction itself can be a metabolic vulnerability in resistant clones. This duality underscores that the role of specific metabolites may be context-dependent, varying with the temporal stage of therapy (early adaptive vs. late acquired resistance) and the particular tumor ecosystem, necessitating more nuanced, time-resolved metabolic profiling in future studies. Recent single-cell studies indicate that metabolic adaptation may also dictate responsiveness to immune-checkpoint blockade, with transmembrane protein 71 identified as a key immunomodulatory determinant (61). Therefore, understanding how metabolic pathways interface with immune signaling is essential for developing more durable therapeutic strategies.

Based on the compiled evidence, several metabolic targets emerge as particularly promising for therapeutic intervention. The inhibition of LSD1, whose lactylation is directly fueled by therapy-induced lactate accumulation, presents a compelling strategy to reinstate ferroptosis and remodel the TME. Targeting OXPHOS, a common adaptive node upregulated via the MITF-PGC1α axis and other mechanisms, holds broad potential, especially using agents like mTORC1 inhibitors or novel OPIs, which can reverse the bioenergetic adaptation of resistant cells. Similarly, PHGDH, the gatekeeper of serine synthesis, represents a lethal vulnerability when co-inhibited with MAPK blockade, as it cripples the GSH-mediated antioxidant defense. In the immunosuppressive landscape, IDO1 inhibition stands out for its potential to reverse kynurenine-mediated T-cell suppression and improve immunotherapy or targeted therapy efficacy. Finally, disrupting lipid metabolism via FASN or HMGCR inhibitors offers a route to counteract the PI3K-AKT-mTOR pathway activation driven by increased FAs and cholesterol.

Translating these insights into clinical practice faces significant hurdles. First, toxicity remains a major concern, as many metabolic pathways are essential in normal tissues. Second, tumor heterogeneity and metabolic plasticity may lead to rapid adaptive resistance. Third, robust predictive biomarkers are lacking for patient stratification. Future efforts should prioritize combination strategies, such as pairing metabolic inhibitors with MAPK or immune checkpoint blockade, and leverage single-cell multi-omics and metabolic imaging to guide dynamic, personalized treatment regimens.

Acknowledgements

Not applicable.

Funding

This work was partly supported by the National Natural Science Foundation of China (grant no. ZR2021MH290) and the Shandong Provincial Medical and Health Science and Technology Development Program (grant no. 202104030578).

Availability of data and materials

Not applicable.

Authors' contributions

XZ was involved in the study conceptualization, literature search and drafting the manuscript. FC contributed to conceptualization and provided resources. HL was involved in study supervision and manuscript writing - review and editing. Data authentication is not applicable. All authors have read and agreed to the published version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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