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Metabolic reprogramming of immune cells and metabolic intervention in cutaneous tumors

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Highlights:

- Metabolic reprogramming shapes immune cell plasticity and antitumor immune responses.
- Clinical trials of metabolic immunotherapy for melanoma, cSCC, and BCC treatment are summarized.
- Key challenges and future directions for clinical translation of metabolic targeted therapy are highlighted.

Abstract: Immunotherapy has achieved notable advancements in the treatment of cutaneous malignancies. However, challenges such as low response rates and frequent drug resistance remain. The metabolic characteristics of immune cells are closely linked to their fate, activation, and function, exhibiting remarkable plasticity that enables metabolic networks to finely regulate immune cell responses to external stimuli. Consequently, targeting metabolic networks to modulate immune cell phenotypes and augment antitumor immunity has emerged as a pivotal avenue for clinical translation. This article systematically elucidates the functional roles of glucose, lipid, and amino acid metabolic reprogramming in immune cells. It summarizes ongoing clinical trials of metabolic immunotherapy for treating melanoma, cutaneous squamous cell carcinoma (cSCC), and basal cell carcinoma (BCC), while discussing unresolved challenges in the clinical translation of metabolic therapy. This provides theoretical support and research directions for novel metabolic therapeutic strategies.

Keywords: metabolic reprogramming; tumor microenvironment; cancer therapy; cutaneous tumors

1. Introduction

Skin cancer has emerged as the fifth most commonly reported cancer worldwide, exerting considerable strain on global health systems and economies [1]. Immunotherapy has revolutionized the treatment

landscape for advanced cutaneous malignancies, enabling long-term survival for patients [2,3]. However, a substantial proportion of patients fail to derive durable clinical benefit [4]. Fundamental factors influencing immune responses include a complex interplay of tumor-intrinsic features and the functional heterogeneity of immune cells in the tumor microenvironment (TME) [5]. Tumor cells adapt their energy metabolism to thrive in hypoxic and nutrient-deprived microenvironments through a process termed metabolic reprogramming [6]. These metabolic shifts not only provide the bioenergetic and biosynthetic foundation for tumor cell functions but may also critically modulate immune cell proliferation, differentiation, and functional activation, thereby forming an immunosuppressive TME that facilitates tumor growth and metastasis [7].

The metabolic characteristics of immune cells are intrinsically linked to their fate, activation state, and effector functions [8]. Furthermore, immune cells exhibit remarkable metabolic plasticity, which creates therapeutic vulnerabilities that can be pharmacologically targeted [9]. Research into the potential of metabolism-targeting drugs to enhance the metabolic microenvironment for immune cells is a promising area [10]. These drugs have the capacity to positively influence immune function, promote effective anti-tumor immune responses, and enable rational combination therapeutic strategies [11]. Therefore, a comprehensive understanding of the mechanisms through which metabolic reprogramming modulates the delicate balance between protumor and antitumor immune activity, and the potential of metabolic-targeted drugs to modulate patient cancer immune responses toward anti-tumor immune responses, is imperative for the advancement of this concept into clinical practice.

This article provides a concise overview of the metabolic features and pathways of tumor and immune cells in the TME. It focuses on how glucose, amino acid, and lipid metabolism regulate the functions of key immune cells. Clinical trials of metabolic immunotherapy, currently used to treat skin cancer, are summarized to deepen the understanding of how metabolic interventions create a favorable anti-tumor immune microenvironment for skin tumor patients.

2. Metabolism in the TME

The TME comprises tumor cells and diverse immune cells, both of which exhibit substantial metabolic heterogeneity. The interaction between neoplastic cells and immune cells gives rise to an immunosuppressive microenvironment, marked by factors such as hypoxia, nutrient deprivation, waste accumulation, pH drop, and oxidative stress. This microenvironment profoundly influences the fate, activation, and function of immune cells (Figure 1) [12,13].

2.1. Metabolic characteristics of tumor cells

Tumor cells demonstrate elevated metabolic adaptability in the nutrient-deprived TME to satisfy the bioenergetic and biosynthetic requirements for rapid primary tumor growth and metastatic colonization, endowing them with a survival edge over non-cancerous cells [14]. Even in oxygen-replete environments, tumor cells mainly utilize aerobic glycolysis (the Warburg effect) to metabolize glucose and produce lactate [15]. They boost fatty acid uptake and synthesis to preserve membrane integrity and energy homeostasis, while rewiring amino acid metabolism to sustain protein biosynthesis and signal transduction. Tumor cells can also flexibly switch to oxidative phosphorylation (OXPHOS) for energy production based on microenvironmental conditions [16]. These metabolic alterations are critical in transforming glucose,

lipid, and amino acid metabolism, influencing both tumor cell proliferation and TME dynamics. As tumors advance and metastasize, the TME gradually evolves into an immunosuppressive environment [17].

Cutaneous malignancies exhibit distinct metabolic programs that differ from those of other solid tumors, shaped by both cell-intrinsic oncogenic drivers and tissue-specific microenvironmental factors. Melanoma, the most extensively studied skin cancer, is characterized by a pronounced dependence on OXPHOS, even under normoxic conditions. This OXPHOS-high phenotype is sustained by MITF-driven PGC1α expression and confers resistance to glycolysis-targeted therapies while rendering melanoma cells vulnerable to inhibitors of mitochondrial metabolism [18]. In contrast, cutaneous squamous cell carcinoma (cSCC) frequently displays a glycolytic phenotype driven by EGFR/HIF-1α signaling, with elevated lactate production and enhanced expression of monocarboxylate transporter 1 (MCT1)/MCT4 transporters [19].

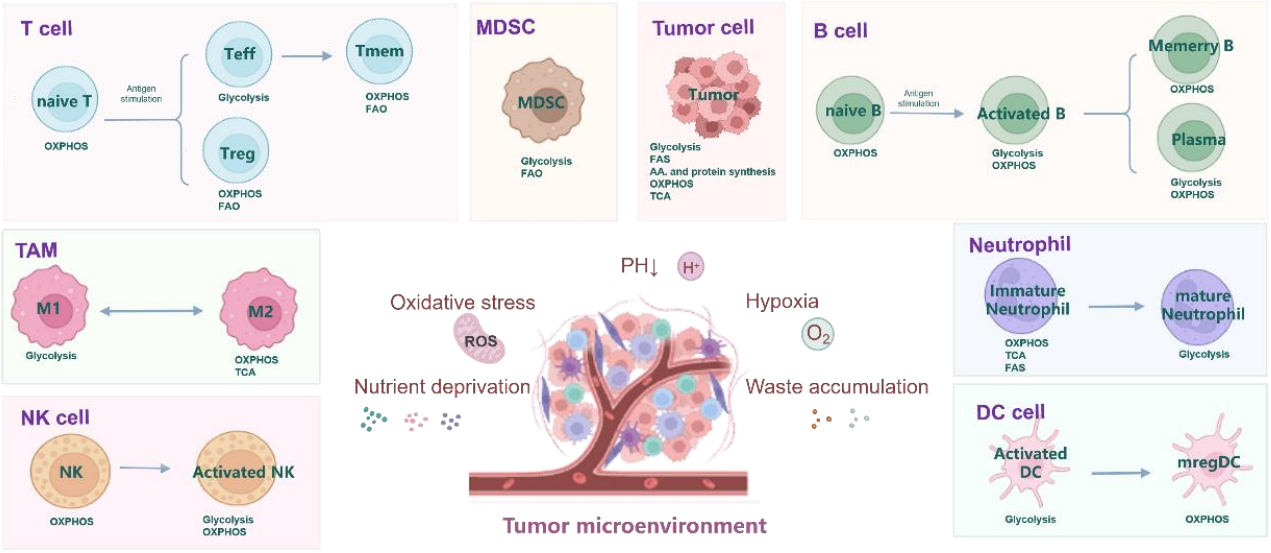

Figure 1. Metabolic plasticity of immune cells in the tumor microenvironment. Immune cell metabolism is dynamically rewired upon activation and differentiation. Naive T cells rely on OXPHOS, while effector T cells shift to aerobic glycolysis and memory T cells favor FAO. B cells upregulate both glycolysis and OXPHOS upon activation, with plasma cells maintaining dual fluxes and memory B cells adopting intermediate OXPHOS. M1 macrophages are glycolysis-dependent; M2 macrophages depend on OXPHOS. MDSCs exhibit glycolysis with elevated FAO. Activated NK cells enhance both glycolysis and OXPHOS. DC activation requires glycolysis, whereas mregDCs upregulate OXPHOS and acquire immunosuppressive functions. Tumor-infiltrating neutrophils are glycolysis-dependent. Tumor-immune metabolic crosstalk remodels the TME into an immunosuppressive niche characterized by nutrient deprivation, metabolite accumulation, hypoxia, oxidative stress, and acidification.

2.2. Metabolic characteristics of immune cells

Immune cells are central regulators of the tumor immune microenvironment, exhibiting substantial disparities in energy metabolism between their resting and activated states [20].

T cells dominate antitumor immunity and serve as key effectors in cancer immunotherapy. Classified by lineage markers and functionality, T cells mainly comprise cytotoxic T lymphocyte ($CD8^+$) and helper T lymphocytes ($CD4^+$) subsets. Naive T cells have minimal energy requirements in the resting state, relying

primarily on OXPHOS to generate adenosine triphosphate (ATP) for sustaining fundamental biological processes. Upon antigen stimulation, T cells differentiate into effector T cells (Teff) and sharply boost nutrient uptake and glycolytic flux, meeting the high bioenergetic and biosynthetic requirements for rapid proliferation and cytotoxic activity [21]. Memory T cells (Tmem) manifest metabolic characteristics analogous to those of naive T cells; however, they demonstrate a propensity to store lipids and depend on fatty acid oxidation (FAO) to preserve functional readiness [22]. Treg cells primarily rely on FAO and OXPHOS, enabling them to sustain immunosuppressive functions within the nutrient-deprived TME [23]. Restricting glycolysis and promoting a metabolic shift to OXPHOS is critical for Treg differentiation and function, highlighting the divergent metabolic requirements governing Teff and Treg activity [24].

Tumor-associated macrophages (TAMs) are indispensable TME components, polarized into proinflammatory antitumor (M1) and immunosuppressive protumor (M2) phenotypes, with polarization tightly linked to metabolic programming. M1 macrophages rely mainly on glycolysis, accompanied by impaired tricarboxylic acid (TCA) cycle and OXPHOS activity [25]. Conversely, M2 macrophages predominantly depend on OXPHOS for energy production [26]. Within the TME, signaling molecules such as lactate drive macrophage polarization toward the M2 phenotype, which mediates immunosuppression and facilitates tumor proliferation and metastasis [27].

Myeloid-derived suppressor cells (MDSCs) are heterogeneous immature myeloid cells with potent immunosuppressive functions. In the hypoxic TME, MDSCs depend mainly on glycolysis, while displaying elevated fatty acid uptake and activated FAO, alongside increased mitochondrial mass, upregulated FAO-related enzymes and higher oxygen consumption rates. Multiple metabolic mechanisms—including nutrient competition and metabolic toxin secretion-collectively support their robust immunosuppressive activity [28,29].

Natural killer (NK) cells are pivotal innate antitumor effectors, mediating cytotoxicity, secreting cytokines and interacting with other immune cells via membrane receptors. Their metabolism is dynamically regulated during development and activation: resting NK cells depend on OXPHOS to maintain homeostasis, whereas activated NK cells significantly upregulate both glycolysis and OXPHOS to sustain cytotoxic function. Notably, glycolysis is essential for the synthesis of interferon-gamma (IFN-γ) and granzyme B [30,31].

Dendritic cells (DCs) bridge innate and adaptive immunity and trigger lymphocyte activation and differentiation. Quiescent DCs rely on OXPHOS, while activation and maturation induce robust glycolysis, supported by glycogen storage and fueling fatty acid synthesis. However, tumor antigen uptake prompts rapid DC activation and maturation, and the immunosuppressive TME drives the formation of regulatory mregDCs. This unique DC subset upregulates OXPHOS in the TME, maintaining its immunosuppressive phenotype [32,33].

The metabolic profiles of B cells vary according to activation status. Naive B cells remain quiescent with extremely low basal metabolism, while antigen stimulation triggers massive nutrient uptake and biomass accumulation. Activated B cells upregulate both glycolysis and OXPHOS to support rapid growth, biosynthesis, proliferation, and differentiation. Plasma cells consume large amounts of glucose for antibody synthesis and secretion, relying on both glycolysis and OXPHOS for energy. Memory B cells maintain low metabolic activity with moderate OXPHOS levels [34,35].

Neutrophils are critical immune regulators that drive cancer development and progression. During early differentiation, neutrophil progenitors depend heavily on mitochondrial oxidative metabolism for

ATP generation. In the hypoxic, nutrient-poor TME, mature neutrophils rewire glycolysis to sustain phagocytosis, oxidative bursts, granule release and neutrophil extracellular trap formation. These functions enable neutrophils to modulate macrophage recruitment, inflammation, angiogenesis, tumorigenesis and immune activation [36,37].

Collectively, immune cells exhibit striking metabolic diversity aligned with their lineage and function in the TME. Naive and memory T cells, resting NK cells, and quiescent B cells maintain low bioenergetic demands and primarily rely on OXPHOS for homeostasis. Upon activation, effector T cells, M1 macrophages, mature neutrophils, and activated B cells undergo rapid metabolic reprogramming toward aerobic glycolysis to support proliferation, cytokine secretion and cytotoxicity. In contrast, immunosuppressive populations—including Tregs, M2 macrophages, MDSCs, and mregDCs—preferentially utilize FAO and OXPHOS, exhibiting reduced glycolytic dependence that enables their persistence and suppressive activity within the nutrient-limited, lactate-rich tumor microenvironment. This functional dichotomy highlights a central paradigm in immunometabolism: glycolysis fuels pro-inflammatory effector functions, while oxidative metabolism (FAO/OXPHOS) supports immune suppression and long-term persistence. Critically, these metabolic programs are not fixed but dynamically remodeled by microenvironmental cues such as hypoxia, lactate, and nutrient competition. Understanding this metabolic-functional coupling across immune lineages not only reveals fundamental principles of immune biology but also unmasks context-dependent vulnerabilities that can be therapeutically exploited.

3. Metabolic reprogramming of immune cells

Immune cell metabolic reprogramming in the TME is governed by a complex and interconnected network of glucose, amino acid, and lipid metabolism (Figure 2). These pathways not only fuel the energetic and biosynthetic demands for immune activation, but also serve as critical nodes of immunoregulatory control (Figure 3).

3.1. Glucose metabolism

Glucose metabolism serves as a core metabolic pathway regulating immune cell function and differentiation. Tumor cells and immune cells compete intensely for limited nutrient resources; glucose deprivation directly inhibits glycolysis in immune cells, thereby impairing their tumor-killing capacity. Restoring glycolytic activity in tumor-infiltrating immune cells can reactivate their anti-tumor function. Specifically, low glucose levels suppress mammalian target of rapamycin (mTOR) signaling, glycolytic flux, and IFN-γ production in T cells [38]. Immune checkpoint inhibitors targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death-ligand 1 (PD-L1) reverse TME glucose depletion, promoting T cell glycolysis and IFN-γ secretion [39]. Elevating the level of phosphoenolpyruvate (PEP), a key glycolytic intermediate, rescues impaired glycolysis in tumor-infiltrating lymphocytes, sustains T-cell receptor (TCR)-induced Ca^{2+} signaling and nuclear factors of activated T cells (NFAT) activation, and ultimately enhances T-cell effector function [40]. Furthermore, glucose restriction promotes Treg differentiation via hypoxia-inducible factor (HIF)-1α-dependent pathways. Tregs drive T-cell senescence and impair effector T-cell function by inhibiting the DNA damage response [41,42].

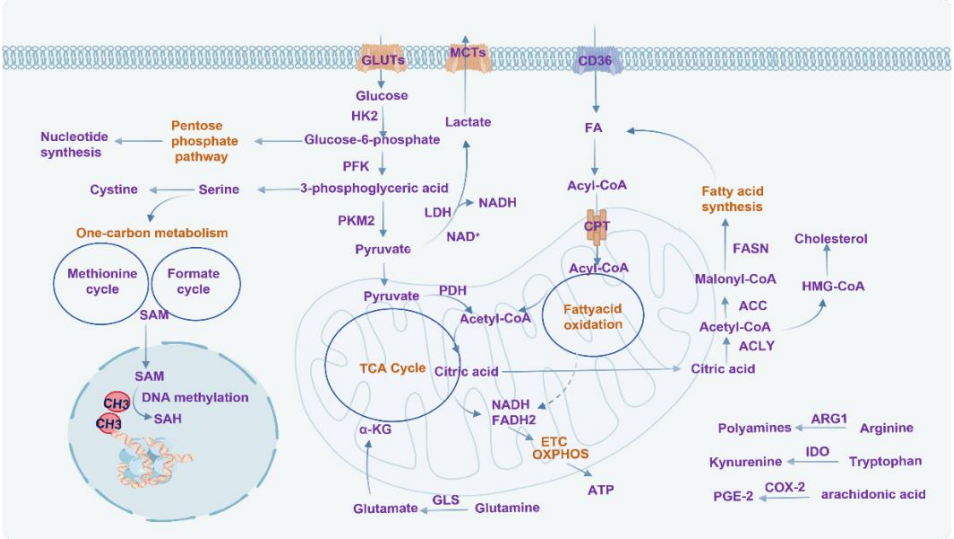

Figure 2. Overview of glucose, amino acid, and lipid metabolic pathways. Glucose enters cells via GLUT transporters and is metabolized through glycolysis. Pyruvate is either converted to lactate via LDH and exported by MCTs, or enters mitochondria to fuel the TCA cycle. Glycolytic intermediates are diverted into the pentose phosphate pathway and serine-one-carbon metabolism to support nucleotide, amino acid, and lipid biosynthesis. Fatty acid metabolism involves CD36-mediated uptake and CPT-driven β-oxidation, or de novo synthesis from citrate via ACLY, ACC, and FASN. Amino acids—including arginine, glutamine, leucine, and methionine—are integrated into bioenergetic and biosynthetic pathways that collectively orchestrate immune cell activation, proliferation, and antitumor function. Abbreviation: GLUT, glucose transporter; LDH, lactate dehydrogenase; PFK, phosphofructokinase; ACLY, ATP-citrate lyase; ACC, acetyl-CoA carboxylase; FASN, fatty acid synthase; CPT, carnitine palmitoyltransferase; SAH, S-adenosylhomocysteine; COX-2, cyclooxygenase-2; GLS, glutaminase; FA, fatty acid; ETC, electron transport chain.

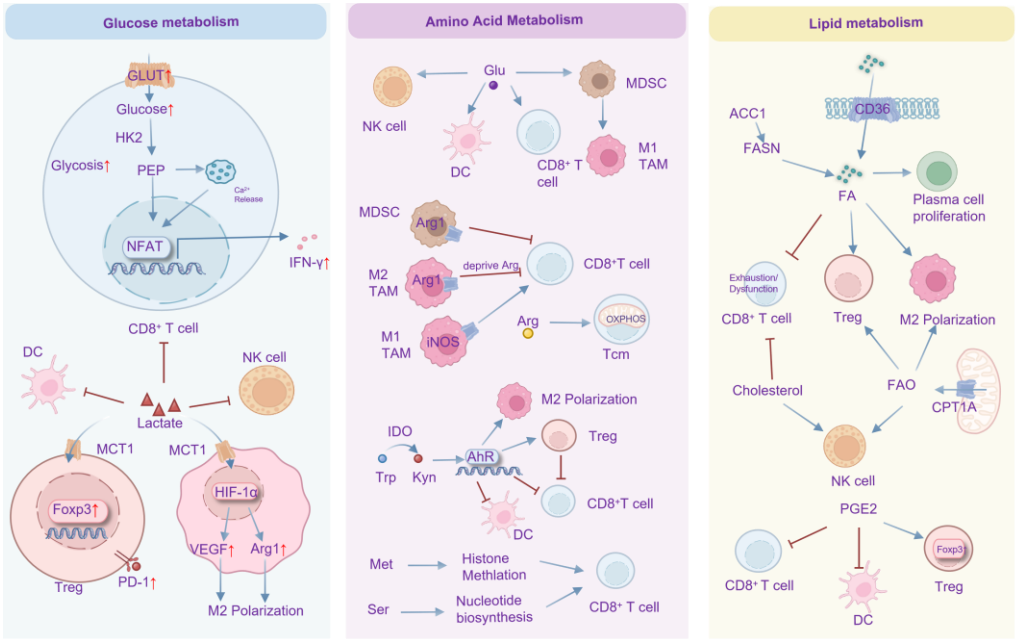

Figure 3. Overview of immunometabolic mechanisms in the TME: glucose, amino acid, and lipid metabolism differentially regulate immune cell function.

Activated immune cells typically exhibit a widespread increase in glycolytic flux, with corresponding upregulation of glucose transporters and key glycolytic enzymes, all of which modulate immune cell activation and function [43]. Activated T cells primarily rely on increased GLUT expression to enhance glucose uptake and metabolism for biosynthetic demands. Glut1 deficiency blocks glucose uptake and glycolysis, reduces Teff cell proliferation and their ability to induce inflammatory diseases *in vivo* [44]. Hexokinase 2 (HK2), the rate-limiting enzyme initiating glycolysis, catalyzes glucose phosphorylation into glucose-6-phosphate. HK2 deficiency in immune cells impairs effector function, thereby weakening antitumor immunity. Nuclear factor (NF)-κB-inducing kinase enhances T cell glycolysis and effector activity by regulating reactive oxygen species levels and inhibiting HK2 autophagic degradation, significantly boosting anti-tumor immunity and adoptive T cell therapy efficacy [45]. The purinergic receptor P2Y12 maintains HK2 stability via the phosphoinositide 3-kinase (PI3K)/Akt pathway and suppresses HK2 lysosomal degradation, thereby promoting T cell activation and immune responses [46]. Immune checkpoints such as Tim-3 can also suppress HK2 expression in macrophages through the signal transducer and activator of transcription 1 (STAT1) pathway, reducing the secretion of TNF-α and IL-1β [47]. Pyruvate kinase M2 (PKM2) catalyzes the final glycolytic step, converting PEP to pyruvate. PKM2 activation reinforces $CD8^+$ T-cell recall and anti-tumor functions, diminishes tumor-infiltrating Tregs, and elevates the effectiveness of adoptive cell therapy [48].

Lactate accumulation induced by the Warburg effect acts as a key metabolic regulator that influences immune cell function by modulating intracellular signaling pathways [15]. Lactate accumulation directly inhibits the expansion and cytokine secretion of $CD8^+$ T cells, reducing cytotoxicity. In contrast, Tregs take up lactate from the TME via monocarboxylate transporters (MCTs), upregulating PD-1 expression to sustain immunosuppressive function and proliferation [49–51]. In macrophages, lactate induces vascular endothelial growth factor (VEGF) and arginase 1 expression via HIF-1α, driving immunosuppressive M2-like polarization; inhibiting lactate production shifts macrophages toward anti-tumor M1-like phenotypes [52,53]. For NK cells, lactate decreases intracellular pH and induces apoptosis; inhibiting LDHA activity effectively restores NK cell anti-tumor function [54]. In DCs, lactate not only promotes antigen degradation and impairs antigen presentation, but also binds to GPR81 to trigger Ca^{2+} mobilization, suppressing IFN-α production in plasmacytoid DCs and thus weakening anti-tumor immune responses [55–57]. Furthermore, activated B cells deprive T cells of glucose and secrete lactate via elevated glycolytic activity, inhibiting T cell cytokine production and proliferation [58].

3.2. Amino acid metabolism

Glutamine, a precursor for multiple metabolic pathways, regulates immune cell proliferation, differentiation, and redox homeostasis. Glutamine deprivation inhibits T cell activation and IL-2/IFN-γ secretion, impairs Th1/Th17 cell expansion, and simultaneously promotes $FoxP3^+$ regulatory T cell generation [59,60]. Inhibition of glutamine metabolism impairs MDSC expansion and recruitment, correlating with downregulated colony stimulating factor 3 (CSF3) expression [61]. Suppressing glutamine metabolism in MDSCs directly reprograms them into inflammatory macrophages, boosting antitumor immunity [61]. Glutamine also regulates NK cell metabolic programs and effector functions by activating mTORC1 to maintain c-Myc expression [62]. For DCs, glutamine is the most highly demanded amino acid; intratumoral glutamine supplementation reinforces conventional DC1 (cDC1)-mediated $CD8^+$ T cell immunity, suppresses tumor growth, and overcomes resistance to checkpoint blockade

and T cell-based immunotherapies [63]. Additionally, glutamine is catabolized into α-ketoglutarate (αKG) and lactate; glutamine deprivation reduces lactate conversion from glutamine, impairs the NAD^+/NADH balance in TAMs, and suppresses M1 polarization [64,65].

Arginine metabolism also synergistically regulates immune cell activation and immune responses. Elevated L-arginine levels trigger a metabolic shift in T cells from glycolysis to mitochondrial OXPHOS pathways, enhancing T cell survival, antitumor activity and memory cell formation [66]. Low arginine conditions induce T cell metabolic and transcriptional reprogramming via the ATF4-SLC7A11-GSH axis, conferring Treg-like immunosuppressive properties to activated T cells [67]. Tumor cells and MDSCs express high levels of arginase 1 (Arg1), competitively absorbing arginine while secreting elevated ornithine, creating a high-ornithine, low-arginine metabolic environment. This metabolic imbalance inhibits T cell proliferation, signal transduction, and anti-tumor activity, ultimately diminishing response to immune checkpoint blockade (ICB) therapy [68]. Arginine metabolism also distinguishes TAM phenotypes: M1 macrophages catabolize arginine to nitric oxide (NO) via inducible nitric oxide synthase (iNOS), suppressing tumor progression and enhancing T cell immune activity; whereas M2 macrophages overexpress Arg1 to diminish NO generation and drive immunosuppression [69,70]. Pimozide, a 3-oxoacid CoA-transferase 1 (OXCT1) inhibitor, suppresses Arg1 expression and protumor TAM polarization, reducing $CD8^+$ T cell exhaustion and slowing tumor growth [71]. Moreover, arginine deprivation suppresses NK cell proliferation and IFN-γ secretion, while ARG1 blockade restores arginine levels and boosts antitumor immunity in an NK cell-dependent fashion [72,73].

Tryptophan metabolism exerts a crucial immunosuppressive effect in cancer. Tryptophan deficiency induces T cell dysfunction and Treg infiltration, facilitating tumor immune evasion [74]. Kynurenine accumulation itself activates the aryl hydrocarbon receptor (AhR), promoting Treg differentiation and inhibiting $CD8^+$ T cells via PD-1 upregulation [75]. Targeting indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) to block tryptophan breakdown into kynurenine effectively reverses T cell dysfunction [74]. High IDO1 expression in tumor cells and MDSCs causes Trp depletion in the TME, inducing Treg expansion to promote tumor proliferation [76]. IDO1 mediates immune evasion by inducing DCs to secrete Treg-recruiting chemokines [57]. IDO inhibition enhances the sensitivity of NK cells and suppresses tumor growth [77].

Methionine, an essential sulfur-containing amino acid, serves as the primary precursor of S-adenosylmethionine (SAM)—a core methyl donor critical for epigenetic and post-translational regulation. Tumor cells upregulate methionine transporter expression to enhance methionine uptake, thereby depleting its levels in the TME. Methionine deprivation reduces methyl donor availability, alters histone H3 lysine 79 (H3K79me2) in $CD8^+$ T cells, and triggers T cell apoptosis and dysfunction. Methionine supplementation enhances H3K79me2 and STAT5 expression in T cells, reviving and strengthening antitumor immunity [78].

Other amino acids also play vital roles in immune regulation. Serine promotes glutathione (GSH) synthesis and supports one-carbon metabolism essential for Teff responses. Serine deprivation or pathway inhibition impairs purine biosynthesis and T cell proliferation [79]. Notably, Tregs depend on GSH to suppress serine metabolism and maintain suppressive function. Limiting serine availability restores $FoxP3^+$ expression and inhibitory capacity of Gclc-deficient Tregs [80].

3.3. Lipid metabolism

Lipid metabolism is a cornerstone of immunometabolism, acting not only as a vital energy source and cellular structural component, but also mediating signal transduction, gene expression, and tumor immune regulation. CD36, a ubiquitous membrane fatty acid transporter, dominates exogenous fatty acid uptake. In tumor-infiltrating $CD8^+$ T cells, CD36-mediated fatty acid uptake induces lipid peroxidation and ferroptosis, reducing cytotoxic cytokine secretion and impairing antitumor activity [81]. Further studies reveal that CD36 modulates mitochondrial fitness via peroxisome proliferator-activated receptor (PPAR)β signaling, supporting Treg survival and function [82]. Targeted deletion of CD36 in Tregs reduces intratumoral Treg infiltration, enhances anti-tumor immune responses, and inhibits tumor progression. Moreover, CD36-mediated enhancement of fatty acid oxidation drives M2-like polarization, creating a highly immunosuppressive TME [83]. CD36-mediated lipid uptake enhances FAO in MDSCs to support their immunosuppressive functions [84]. CD36 also participates in B-cell autophagy, and its deficiency dampens humoral immunity by impairing plasma cell differentiation, proliferation, mitochondrial function and OXPHOS [85].

ACC1, the rate-limiting enzyme for fatty acid synthesis that converts acetyl-CoA to malonyl-CoA, exerts pleiotropic effects on T cells. ACC1-regulated lipid droplet accumulation drives $CD8^+$ T cell dysfunction in tumors, whereas ACC1 deficiency enhances memory $CD4^+$ T cell formation by regulating fatty acid biosynthesis [86]. As another pivotal enzyme for de novo long-chain fatty acid synthesis, FASN supports Treg maturation and the production of inflammatory cytokines by $CD4^+$ T cells. FASN inhibition also reduces major histocompatibility complex class I (MHC-I) degradation, enhances $CD8^+$ T cell infiltration, and exerts synergistic antitumor effects with PD-L1 immune checkpoint blockade [87,88].

Abnormal cholesterol metabolism induces endoplasmic reticulum stress and elevates PD-1 expression in $CD8^+$ T cells, thereby impairing their antitumor activity; reducing excessive cholesterol accumulation restores T cell cytotoxic function [89]. Inhibiting cholesterol synthesis blocks macrophage M2 polarization, promoting tumor cell apoptosis and inhibiting their proliferation and migration [90]. Cholesterol efflux via ATP-binding cassette transporters regulates macrophage reprogramming: genetic ablation of ABC transporters reverses TAM tumor-promoting activity and curbs tumor progression [91]. Conversely, elevated TME cholesterol and intracellular cholesterol accumulation in NK cells boost membrane lipid raft formation, enhancing immune signaling and anti-tumor capacity [92].

FAO is highly active in immune cells and shapes their functional phenotypes. Activation of PPARα and PPARδ/β upregulates FAO enzymes in T cells, maintaining memory phenotypes and IFN-γ secretion for long-term antitumor function [22,93,94]. Leptin-STAT3 signaling-mediated FAO elevation inhibits glycolysis and impairs $CD8^+$ T cell antitumor activity. PPAR-γ signaling further activates STAT3-dependent FAO to promote tumor progression. Upregulated carnitine palmitoyltransferase 1A (CPT1A) drives increased FAO in DCs, suppressing IL-6/IL-12 secretion and promoting Treg generation [95]. Studies have also shown that NK cells can enhance fatty acid uptake and upregulate CPT1A expression; CPT1A-deficient NK cells exhibit reduced proliferation and impaired anti-cancer defense due to defective actin cytoskeleton rearrangement [96]. PPAR-γ-dependent FAO mediates TAM protumor polarization, and the FAO inhibitor etomoxir blocks IL-4-induced M2 macrophage polarization [93,97].

Fatty acid metabolites are also involved in immune cell regulation. Prostaglandin E2 (PGE2) exerts crucial and complex effects in the TME by binding to its receptors EP2 and EP4, significantly impacting immune cell functions, facilitating immune evasion, and promoting tumor development. Typically, PGE2 weakens granule-dependent cytotoxicity, enhances immunosuppressive cell activity, upregulates immune checkpoints and promotes inhibitory cytokine secretion [98]. PGE2 signaling drives M1-to-M2 macrophage polarization and tumor immune escape [99], while the PGE2–lymphocyte-specific protein tyrosine kinase (LCK) axis acts as a critical barrier to NK cell activation [100]. Blocking the PGE2-EP2/EP4-cDC1 axis restores cDC1 function, reactivates local $CD8^+$ T cell responses, and elicits antitumor immunity [101].

Table 1 summarizes the key metabolic pathways, corresponding cell types, experimental interventions, metabolic alterations, and subsequent immune functional outcomes. Collectively, glucose metabolism—through GLUT1, HK2, PKM2, and metabolites (lactate, PEP)—directly dictates the balance between effector function and exhaustion in T cells, while shaping the suppressive capacity of Tregs, the polarization of macrophages, and the functional integrity of DCs, NK cells, and B cells. Amino acid metabolism exerts equally profound and context-dependent effects: glutamine sustains c-Myc-driven proliferation in effector lymphocytes but supports MDSC plasticity and TAM polarization; arginine metabolism distinguishes M1 from M2 macrophages and dictates T cell memory potential; tryptophan catabolism via IDO-kynurenine-AhR axis enforces immune tolerance; and methionine availability links nutritional status to epigenetic remodeling in $CD8^+$ T cells. Lipid metabolism, meanwhile, exhibits marked functional duality. CD36-mediated fatty acid uptake induces $CD8^+$ T cell ferroptosis yet sustains Treg stability and M2-TAM polarization; ACC1 and FASN link de novo lipogenesis to T cell dysfunction or memory fate; cholesterol metabolism exerts distinct regulatory effects on $CD8^+$ T cell exhaustion and NK cell-mediated anti-tumor immunity; and FAO, via CPT1A and PPAR signaling, supports persistence in memory T cells but promotes immunosuppression in DCs, TAMs, and Tregs. PGE2 signaling further amplifies this immunosuppressive network via EP2/EP4 receptors, impairing cDC1 function and $CD8^+$ T cell reinvigoration.

This growing body of mechanistic evidence has illuminated a broad spectrum of metabolically vulnerable nodes—ranging from glucose transporters and glycolytic enzymes to amino acid sensors, lipid transporters, and nuclear metabolic sensors—that are amenable to pharmacological intervention. Importantly, many of these nodes are not only functionally validated in preclinical cutaneous tumor models but also exhibit context-specific dependencies that can be exploited therapeutically. These insights have propelled the translation of metabolic strategies into early-phase clinical investigation, particularly in melanoma and, to a lesser extent, non-melanoma skin cancers. In the following section, we provide a comprehensive overview of completed and ongoing clinical trials targeting glucose, glutamine, arginine, tryptophan, and lipid metabolism—both as monotherapies and in combination with immunotherapies—and discuss the translational challenges and opportunities that shape the future of metabolic intervention in cutaneous malignancies.

Table 1. Metabolic reprogramming of immune cells.

Metabolic pathway	Cell type	Intervention	Metabolic effect	Immune functional outcome	Reference
Glucose metabolism	T cell	Checkpoint blockade antibodies	Restores glucose availability, enabling T-cell glycolysis	Restores IFN-γ production in T cells	[39]
	T cell	PEP	Sustains TCR-mediated Ca^{2+}-NFAT signaling	Sustains T cell effector functions	[40]*
	T cell	Glycolysis inhibition	Inhibits glycolysis via a HIF-1α-dependent transcriptional program	Suppresses Th17 cell development while promoting Treg generation	[41]
	T cell	STAT signaling	Inhibits the DNA damage response and STAT signaling pathways	Abrogates Treg-induced T-cell senescence	[42]
	T cell	GLUT1 deficiency	Abrogates increased glucose uptake and glycolysis	Reduces Teff cell survival and differentiation	[44]
	T cell	NF-κB-inducing kinase	Prevents autophagic degradation of HK2 by regulating cellular ROS levels	Promotes $CD8^+$ T-cell metabolism and function	[45]*
	T cell	P2RY12	Inhibits HK2 degradation via activation of the PI3K/Akt pathway	Enhances T cell activation and immune responses	[46]
	TAM	Tim-3	Inhibits HK2 expression in macrophages via the STAT1 pathway	Reduces TNF-α and IL-1β production	[47]
	T cell	PKM2 agonists	Enhances effector T-cell glycolytic metabolism	Enhances effector T-cell activation while reducing $FoxP3^+$ Tregs	[48]*
	T cell	Lactic acid	Attenuates metabolism in infiltrating CTLs	Reduces cytokine production in CTLs	[50]*
	Treg	MCT1	Tregs take up lactic acid via MCT1	Promotes NFAT1 nuclear translocation and PD-1 upregulation	[51]
	TAM	Lactic acid	Induces expression of arginase 1 and VEGF	Induces M2-like polarization of TAMs	[52]*
	NK cell	LDHA	The SIX1/LDHA axis promotes lactate accumulation	Leads to NK cell dysfunction	[54]
	DC	Lactate	Attenuates intracellular Ca^{2+} mobilization via GPR81 receptor	Impairs effective pDC activation	[57]
	DC	Lactate	DC conditioning by lactate accelerates antigen degradation	Impairs cross-presentation and adaptive immune function	[55]
	B cell	Lactate accumulation	Activated B cells deprive T cells of glucose and produce lactic acid	Suppresses T cell cytokine production and proliferation	[58]*
Arginine metabolism	T cell	Glutamine	Depletion of glutamine	Blocks T lymphocyte proliferation and cytokine production	[59]
	Treg	Glutamine	Impairs glutamine-dependent nucleotide synthesis	Promotes the generation of $FoxP3^+$ regulatory T cells	[60]

Table 1. *Cont.*

Metabolic pathway	Cell type	Intervention	Metabolic effect	Immune functional outcome	Reference
	MDSC	CSF3	Inhibiting glutamine metabolism in MDSCs	Leads to conversion of MDSCs to inflammatory macrophages	[61]
	NK cell	SLC7A5	Glutamine withdrawal results in loss of c-Myc protein	Reduces cell growth and impairs NK cell responses	[62]
	DC	SLC38A2	Glutamine supplementation augments cDC1 metabolic function	Augments $CD8^+$ T cell immunity, overcomes resistance to immunotherapy	[63]
	T cell	Arginine	Elevating L-arginine levels shifts metabolism from glycolysis to OXPHOS	Promotes generation of central memory-like T cells	[66]*
	T cell	Arginine	Low arginine levels activate the ATF4-SLC7A11-GSH axis	Confers Treg-like immunosuppressive capacities upon activated T cells	[67]
	MDSC	Arg1	Blunts Arg1-mediated metabolic suppression	Shifts immune landscape toward a pro-inflammatory environment	[102]
	TAM	Arg1	Inhibiting OXCT1 suppresses Arg1 expression	Inhibits TAM protumor polarization, slows tumor growth	[71]
	MDSC	Arg1	Inhibiting FFAR2 reduces Arg1 expression and arginine consumption in MDSCs	Reverses T cell dysfunction	[68]
	NK cell	Arginine	Low arginine levels	Inhibit NK cell proliferation and IFN-γ production	[72]
Tryptophan metabolism	T cell	IDO, TDO	Targeting IDO/TDO to inhibit tryptophan breakdown to kynurenine	Reverses significant immunosuppression	[74]
	Treg and TAM	AHR	Blocking AHR to suppress kynurenine-mediated metabolic signaling	Suppresses immunosuppression in Tregs and TAMs	[75]*
	DC	IDO1	IDO1 regulates Trp metabolism in DCs and secretes chemokines	Recruits Tregs, mediating immune evasion	[103]
Methionine catabolism	T cell	Methionine	Methionine supplementation improves H3K79me2 and STAT5 expression	Increases T cell immunity	[78]*
Serine metabolism	Treg	Serine	Cellular serine limitation	Restores FoxP3 expression and suppressive capacity in Gclc-deficient Tregs	[80]*
	T cell	Serine	Serine provides glycine and one-carbon units for nucleotide biosynthesis	Supports proliferating T cells	[79]
Lipid metabolism	T cell	CD36	Blockade of the oxidized lipid-CD36 axis	Suppresses intratumoral $CD8^+$ T-cell exhaustion	[81]*
	Treg	CD36	Blocking CD36-PPAR-β signaling inhibits mitochondrial fitness and NAD production	Inhibits Treg function	[82]*

Table 1. *Cont.*

Metabolic pathway	Cell type	Intervention	Metabolic effect	Immune functional outcome	Reference
Lipid metabolism	TAM	CD36	CD36 activates signaling and STAT6 pathway, promoting metabolic reprogramming	Drives TAM polarization to the M2 phenotype	[97]
	MDSC	CD36	Genetic depletion of CD36 inhibits oxidative metabolism activation	Inhibits induction of immunosuppressive function in MDSCs	[84]
	B cell	CD36	CD36 deficiency impairs OXPHOS and mitochondrial mobilization in B cells	Reduces plasma cell formation and proliferation	[85]
	TAM	CD36	IL-34 induces CD36-mediated elevations in FAO	Drives M2-like polarization of TAMs	[83]
	T cell	ACC1	Inhibiting ACC1 restores FAO capacity and enhances ATP production in $CD8^+$ T cells	Improves stemness and persistence	[104]
	T cell	ACC1	ACC1 regulates de novo fatty acid biosynthesis	Determines the memory potential of $CD4^+$ T cells	[86]
	T cell	FASN	FASN inhibition decreases MHC-I degradation	Promotes cancer cell killing by $CD8^+$ T cells	[88]
	Treg	FASN and SREBP activity	Inhibiting SREBPs-mediated lipid synthesis	Suppresses Treg functional maturation	[87]
	T cell	Cholesterol	Reducing excessive cholesterol accumulation	Restores $CD8^+$ T cytotoxic function and suppresses tumor growth	[89]*
	TAM	Cholesterol efflux	Increased cholesterol efflux promotes IL-4-mediated metabolic reprogramming	Inhibits IFN-γ-induced gene expression in macrophages	[91]
	TAM	Cholesterol	Inhibiting cholesterol synthesis	Blocks macrophage M2 polarization and promotes tumor cell apoptosis	[90]
	NK cell	Cholesterol	Cholesterol accumulation in NK cell	Activates anti-tumor effector functions	[92]
	T cell	CPT1A	PPARα/δ agonists upregulate the FAO rate-limiting enzyme CPT1A	Enhances efficacy of adoptive $CD8^+$ T-cell therapy	[94]*
	T cell	FAO	Leptin and PD-1 activate STAT3 to increase FAO and inhibit glycolysis	Inhibits $CD8^+$ Teff cell function	[105]
	DC	CPT1A	Upregulating CPT1A to drive FAO in DCs	Suppresses IL-6/IL-12, culminating in Treg generation	[95]*
	NK cell	CPT1A	CPT1A deficiency impairs FAO in NK cell	Reduces NK cell proliferation and anti-cancer protection	[96]
	TAM	FAO	PPAR-γ-dependent upregulation of FAO	Mediates pro-tumor polarization of TAMs	[93]
	T cell and Treg	PGE2	PGE2 impairs $CD8^+$ T cell metabolism and function	Inhibits proliferation/cytotoxicity, increases FoxP3, stimulates Tregs	[98]
	DC	PGE2	Blockade of the PGE2-EP2/EP4 axis prevents cDC1 metabolic dysfunction	Reinvigorates anti-cancer $CD8^+$ T-cell responses for tumor control	[101]*

All findings originating from cutaneous tumor models (primarily melanoma) are marked with an asterisk (*).

4. Metabolic intervention in the treatment of skin tumors

Owing to the intimate crosstalk between cellular metabolism and anti-tumor immunity, therapeutic strategies targeting glucose, amino acid and lipid pathways open a new avenue for cutaneous cancer treatment. Here, we summarize clinical trials of metabolic therapies in skin cancers, including both monotherapies and combination therapies with immunotherapies (Table 2).

Table 2. Clinical trials of metabolic intervention in skin cancer.

Metabolic pathway	Treatment	Monotherapy or in combination with	Conditions	Phase	Status	Reference
Glucose metabolism	Metformin	Pembrolizumab (anti-PD-1 antibody)	Advanced melanoma	I	Recruiting	NCT03311308
	Metformin	Dacarbazine	Melanoma	II	Terminated	NCT02190838 [106]
	Metformin, rosiglitazone	Nivolumab or pembrolizumab (anti-PD-1 antibody)	Solid tumors (melanoma)	II	Recruiting	NCT04114136 [107]
	Metformin	Vemurafenib (BRAF inhibitor)	Melanoma	I/II	Recruiting	NCT01638676 [108]
	Metformin	Dabrafenib, trametinib (MEK inhibitor)	Melanoma	I/II	Withdrawn	NCT02143050
	Metformin	Photodynamic therapy	Skin squamous cell carcinoma	-	-	[109]
	Metformin	Monotherapy	Skin squamous cell carcinoma	-	-	[110]
	Digoxin	Vemurafenib	Melanoma	I	Completed	NCT01765569
Glutamine metabolism	CB-839 (GLS1 inhibitor)	Nivolumab (anti-PD-1 antibody)	Solid tumors (melanoma)	I/II	Terminated	NCT02771626 [111]
	Troriluzole (modulates glutamate)	Ipilimumab (anti-CTLA-4) and nivolumab	Metastatic melanoma	II	Terminated	NCT04899921
Arginine metabolism	ADI-PEG 20 (pegylated arginine deiminase)	Monotherapy	Advanced melanoma	I/II	Completed	NCT00520299
	ADI-PEG 20	Nivolumab and ipilimumab	Uveal melanoma	I	Completed	NCT03922880
	ADI-PEG 20	Monotherapy	Metastatic melanoma	II	Completed	NCT00450372
	ADI-PEG 20	Cisplatin	Metastatic melanoma	I	Completed	NCT01665183
	ADI-PEG 20	Monotherapy	Metastatic melanoma	I	Completed	NCT00029900
	INCB001158 (arginase inhibitor)	Pembrolizumab	Advanced or metastatic solid tumors (melanoma)	I	Completed	NCT02903914 [112]
	PEG-BCT-100 (recombinant human arginase 1)	Monotherapy	Melanoma	I	Completed	NCT02285101 [113]
Tryptophan metabolism	Indoximod (IDO1/2 inhibitor)	Nivolumab, ipilimumab or pembrolizumab	Advanced or metastatic melanoma	I/II	Completed	NCT02073123
	Indoximod	Monotherapy	Relapsed or refractory solid tumors (melanoma)	I	Terminated	NCT00739609 [114]

Table 2. *Cont.*

Metabolic pathway	Treatment	Monotherapy or in combination with	Conditions	Phase	Status	Reference
Tryptophan metabolism	Indoximod	Pembrolizumab or nivolumab	Melanoma	II	Terminated	NCT03301636
	Indoximod	Nivolumab, ipilimumab or pembrolizumab	Advanced or metastatic melanoma	I/II	Completed	NCT02073123
	Epacadostat (IDO1 inhibitor)	MELITAC 12.1 (Multipeptide melanoma vaccine)	Advanced melanoma	II	Completed	NCT01961115
	Epacadostat	Pembrolizumab	Unresectable or metastatic melanoma	III	Completed	NCT02752074 [115]
	Epacadostat	Ipilimumab	Unresectable or metastatic melanoma	I/II	Terminated	NCT01604889 [116]
	Epacadostat	Nivolumab	Advanced melanoma	I/II	Completed	NCT02327078
Lipid metabolism	Lovastatin	Interferon alfa-2b	Malignant melanoma	II	Withdrawn	NCT00963664
	Statins	Monotherapy	Melanoma	IV	Not yet recruiting	NCT06785974
	Aspirin	Monotherapy	Melanoma	II	Completed	NCT04062032
	Aspirin	Ipilimumab or pembrolizumab	Melanoma	II	Completed	NCT03396952
Combined metabolic pathways	INCB001158 plus epacadostat	Pembrolizumab	Advanced solid tumors (melanoma)	I/II	Terminated	NCT03361228
Other methods	Exercise	Immunotherapy	Cutaneous cancers (melanoma, cSCC, merkel cell carcinoma)	-	Recruiting	NCT06008977
	Fasting mimicking diet	-	Melanoma	-	-	NCT03454282
	Dietary intervention (varies in fiber content)	Pembrolizumab or nivolumab	Metastatic melanoma	II	Active, not recruiting	NCT04645680 [117]
	Mediterranean diet	Immunotherapy	Metastatic melanoma	-	Recruiting	NCT06236360
	Ketogenic diet	Immunotherapy	Melanoma	-	Recruiting	NCT06391099
	A whole-foods, fiber-rich diet and a ketogenic diet	-	Melanoma	I	Terminated	NCT03950635
	A low-fat, balanced diet	-	Nonmelanoma tous skin cancer	II	-	NCT00003097

A growing number of clinical trials are investigating metabolic interventions—either as monotherapies or in combination with immunotherapies-across a spectrum of cutaneous malignancies. Agents targeting glucose metabolism (metformin, digoxin), glutamine metabolism (CB-839, troriluzole), arginine metabolism (ADI-PEG 20, INCB001158), tryptophan metabolism (indoximod, epacadostat), and

lipid metabolism (statins, aspirin) have been assessed in phase I–III trials, with variable outcomes ranging from completed and active to terminated or withdrawn. Notably, the majority of these trials focus on melanoma, underscoring both the leading role of this tumor type in immunometabolic research and the relative scarcity of evidence in non-melanoma skin cancers. Emerging non-pharmacological interventions —including exercise, fasting-mimicking diets, and dietary modifications—are also being explored as adjunctive strategies to modulate systemic metabolism and enhance immunotherapy responses. Despite several terminated or negative trials (epacadostat-pembrolizumab in melanoma), ongoing studies continue to refine patient selection, biomarker development, and rational combination regimens. These efforts collectively highlight the translational potential and persistent challenges of integrating metabolic targeting into the standard of care for cutaneous malignancies.

5. The challenges and prospects of metabolic therapy

5.1. Current difficulties and limitations

Although immunometabolic research has delineated the intimate links between cellular metabolism and immunity, three fundamental roadblocks continue to impede clinical translation.

5.1.1. Insufficient precision in the intervention

The inherent complexity of cellular metabolism and immune regulation predisposes metabolite or pathway-directed interventions to context-dependent, bidirectional immunomodulation. Elevated extracellular lactate levels in the TME drive intracellular lactate accumulation in T cells, thereby suppressing the secretion of proinflammatory cytokines. Notably, this effect is restricted to activated cytotoxic T cells; Tregs rely on the transcription factor FoxP3, which represses c-Myc signaling to facilitate a metabolic shift toward OXPHOS, ensuring Treg functionality in the TME [118]. This complexity underscores the need for spatiotemporal precision in metabolic intervention targets to avoid unintended effects. In cutaneous tumors, this requirement is further accentuated by disease-specific metabolic landscapes–such as OXPHOS dependency in melanoma and ultraviolet—induced lipid remodeling in cSCC—which mandate tailored rather than universally applied metabolic interventions.

5.1.2. Treatment-related toxicities

Given the high degree of metabolic pathway sharing among malignant and normal cells, metabolic interventions may trigger severe treatment-related adverse events. For instance, the broad-spectrum glutamine antagonist 6-diazo-5-oxo-L-norleucine (DON) demonstrated potent efficacy in cancer treatment but was unfortunately discontinued due to severe gastrointestinal toxicity [119]. Similarly, the IDO1/2 inhibitor Indoximod was prematurely terminated owing to an unfavorable risk–benefit ratio [114]. Consequently, next-generation metabolic therapies must precisely target metabolic vulnerabilities to effectively exert antitumor effects and achieve precision medicine.

5.1.3. Translational limitations of preclinical models

Conventional murine models and two-dimensional cultures struggle to fully replicate the metabolic and immune characteristics of the human tumor microenvironment. Inherent discrepancies between human

and murine immuneI-metabolic networks impede clinical translation. Future efforts must develop more pathophysiologically representative experimental models, combined with organoid systems and human sample validation, to enhance the predictive value of basic research.

5.2. The future direction and outlook

5.2.1. Application of innovative technologies

Cutting-edge biochemical tools, including single-cell RNA sequencing, single-cell metabolomics, spatial metabolomics, redox metabolomics and metabolic flux analysis, enable the identification of key metabolic pathways, biomarkers, and therapeutic targets. The integration of single-cell metabolomics with proteomics allows for detailed characterization of metabolic states and functional heterogeneity among immune cell subpopulations within the tumor microenvironment. Spatial metabolomics techniques reveal the complexity of metabolite distribution within tissues *in situ*, elucidating the spatial logic of metabolic competition and symbiosis between immune and tumor cells. Dynamic tracking technologies, exemplified by metabolic flux analysis, provide real-time insights into the flow and plasticity of intracellular metabolic pathways. AI-driven multi-omics integration is being employed to map systematic metabolic regulatory networks, aiming to identify key hubs influencing global immune responses and metabolically actionable leverage points.

5.2.2. Next-generation metabolic biomarkers

Metabolites, as potential biomarkers, directly provide insights into the TME, including immune cell activity, metabolic demands of tumor cells, and their interactions. Lactic acid and PGE2 have emerged as research hotspots due to their roles in regulating immune cell function and promoting immunosuppressive environments [50,52–56]. Immunotherapy efficacy closely correlates with TME metabolic traits; quantifying specific metabolite levels allows prediction of patient immunotherapy responses, facilitating personalized regimens, eliminating ineffective treatments and boosting clinical efficiency.

5.2.3. Combination intervention strategies

To overcome the limitations of monotherapy and tumor metabolic adaptation, combination intervention strategies have become an inevitable choice. First, targeting multiple metabolic pathways simultaneously may weaken tumor cells' adaptive responses to metabolic interventions, leading to enhanced therapeutic outcomes. For instance, concurrent inhibition of IDO and arginase metabolism synergistically treats advanced solid tumors. Second, combining metabolic interventions with immunotherapy—such as pairing glutaminase inhibitors with immune checkpoint inhibitors—can reverse immunosuppression. Ultimately, integrating innovative technologies, intelligent algorithms, and personalized diagnostics/therapeutics to establish a dynamic, precision metabolic immunotherapy system represents the key pathway to breakthroughs in cancer treatment.

6. Conclusion

Tumor and immune cells exhibit significant metabolic heterogeneity and plasticity, jointly sculpting the immunological landscape of the TME through multiple metabolic pathways. This review systematically delineates the metabolic characteristics of immune cells, dissects regulatory functions of core metabolic pathways (glucose, amino acid, and fatty acid metabolism), and summarizes clinical trials of metabolic interventions in cutaneous neoplasms. Despite basic research demonstrating the immense potential of metabolic modulators in cancer therapy, metabolic therapies in cutaneous cancer have shown suboptimal performance in clinical trials. Insufficient targeting, adverse treatment reactions, and limitations of preclinical models represent major challenges currently facing metabolic therapies. Future advancements in innovative technologies will enable researchers to more precisely identify tumor metabolic vulnerabilities and dynamic metabolic alterations. Identifying and validating metabolic biomarkers are essential prerequisites for achieving precision medicine in tumor metabolism. Furthermore, combined strategies of metabolic intervention and immunotherapy will emerge as a future trend in cancer treatment.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors confirm that during the preparation of this manuscript, they used ChatGPT (GPT-4, OpenAI) to assist in checking language errors and improving sentence clarity. No other AI tools were used. The authors take full responsibility for the content of the manuscript.

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Authors' contribution

Conceptualization, Q.T. and C.P.; resources, N.L. and Q.T.; data curation, N.L. and Q.T.; writing—original draft preparation, Q.T.; writing—review and editing, Q.T. and C.P.; visualization,C.P., J.L.; supervision, C.P. and J.L.; project administration, C.P. and J.L.; funding acquisition, C.P. and J.L. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

Cong Peng holds the position of Editorial Board Member for *Advanced Cancer Research* and has not peer reviewed or made any editorial decisions for this paper.

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