BMB
Reports

BMB Rep. 2024; 57(9): 388-399
www.bmbreports.org

Invited Mini Review

Metabolic reprogramming of the tumor microenvironment to enhance immunotherapy

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Immunotherapy represents a promising treatment strategy for targeting various tumor types. However, the overall response rate is low due to the tumor microenvironment (TME). In the TME, numerous distinct factors actively induce immunosuppression, restricting the efficacy of anticancer immune reactions. Recently, metabolic reprogramming of tumors has been recognized for its role in modulating the tumor microenvironment to enhance immune cell responses in the TME. Furthermore, recent elucidations underscore the critical role of metabolic limitations imposed by the tumor microenvironment on the effectiveness of antitumor immune cells, guiding the development of novel immunotherapeutic approaches. Hence, achieving a comprehensive understanding of the metabolic requirements of both cancer and immune cells within the TME is pivotal. This insight not only aids in acknowledging the current limitations of clinical practices but also significantly shapes the trajectory of future research endeavors in the domain of cancer immunotherapy. In addition, therapeutic interventions targeting metabolic limitations have exhibited promising potential as combinatory treatments across diverse cancer types. In this review, we first discuss the metabolic barriers in the TME. Second, we explore how the immune response is regulated by metabolites. Finally, we will review the current strategy for targeting metabolism to not simply inhibit tumor growth but also enhance antitumor immune responses. Thus, we could suggest potent combination therapy for improving immunotherapy with metabolic inhibitors. [BMB Reports 2024; 57(9): 388-399]

INTRODUCTION

Metabolic reprogramming is ability of cancer cells to modify their metabolism and it is one of the hallmarks of tumor that is distinct feature compares with non-cancerous cells (1). This is further defined by the enhancement of absorption and utilization of carbohydrates, lipids, and proteins, resulting in a pro-tumorigenic response concurrent with the acquisition and maintenance of malignant properties. Various factors contribute to this metabolic shift, including the influence of oncogenes, growth factors, hypoxia, and tumor suppressor genes (1, 2). These alterations lead to significant changes in cell metabolism, particularly in glucose, with a marked increase in its absorption rate in cancer cells. For this notion, anti-metabolites therapies have been developed for cancer treatment and some of metabolic inhibitors were developed for cancer cell derangement and can regulate some tumor development. However, for many other observed metabolic derangements in tumor cells, clinical translation has been more challenging. Reasons for this hurdle include the flexibility of cancer metabolic pathways to circumvent points of inhibition, leading to insufficiency of monotherapy; overlap with metabolism of healthy cells, which narrows the therapeutic index; and the difficulty of accessing some tumors of interest — particularly CNS tumors or tumors within a dense environment of supporting cells. Moreover, Metabolic inhibitors can reshape the TME by altering the availability of nutrients and metabolites and this can influence the composition and behavior of immune cells. Thus, we need to understand different angles of metabolites usages including tumor and different immune cells for overcoming the challenges of current therapy.

In this review, we provide a comprehensive summary of the metabolic reprogramming of the TME to enhance immunotherapy. We first discuss the metabolic barrier in TME and how immune evasion is regulated by metabolites. Then, we will review current strategy how to target metabolism in order to not simply inhibit tumor growth but also enhance antitumor immune responses. Finally, we summarize the recent advances in combined immunotherapy and metabolic target inhibitor t and discuss future directions in therapeutic development. Therefore, we can suggest the potent combination therapy for improving immunotherapy with metabolic inhibitors.

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https://doi.org/10.5483/BMBRep.2024-0031

Received 5 February 2024, Revised 27 March 2024, Accepted 21 June 2024, Published online 16 July 2024

Keywords: Immune checkpoint inhibitor, Immunotherapy, Metabolic reprogramming, Metabolism, Tumor microenvironment

ISSN: 1976-670X (electronic edition)

BRIEF SUMMARY OF IMMUNOTHERAPY

Immunotherapy has been studied extensively over the past 20-30 year. Especially, immune check point inhibitors (ICIs) for targeting PD-1, PD-L1 or CTLA-4 and these has been shown promising effect of advance solid tumor including melanoma and classical Hodgkin's lymphoma (3-6). Notably, it has well developed many different tumor types, but it still exists several kinds of hurdles and need to resistance several limitations (7, 8) because of TME. For reshaping TME, one emerging field to improve immunotherapy is targeting tumor metabolites. Understanding cancer metabolism is crucial to regulate function of cancer (1) and it can affect to function of immune cells in TME (9). Recently, it is an important to understand metabolic barriers that affect to tumor growth and how those are influences to immune cells for activating or suppressing immune systems. Intrinsically and extrinsically, metabolism profoundly influences the TME, with recent recognition of its impact on immune cell function. These metabolic alterations within immune cells have the potential to significantly compromise the efficacy of the anti-tumor immune response. Consequently, the interaction between metabolites and immune cells emerges as a critical determinant for the success of immunotherapy.

METABOLIC LANDSCAPE OF THE TUMOR MICROENVIRONMENT

Glucose

As we describe in previous, metabolic reprogramming is one of the hallmarks of cancer cells (2). Among the various nutrients, glucose is main source of energy and skeleton for biosynthesis in cells. For cell homeostasis, glucose breakdown to pyruvate via glycolysis, imported into mitochondria via mitochondria pyruvate carrier (MPC) and using it for TCA cycle. Tumor cells use large amount of glucose and produce lactic acid through glycolysis pathway under the oxygen sufficient condition. This is unique features of tumor, and it is known as the Warburg effect (1). This effect was confirmed in most of cancers, and it promotes glucose uptake on cancer cells. Moreover, cancer growth rate and poor prognosis are highly correlated with glucose level and glucose deprivation is one kind of effective treatment for suppression of tumor growth. Furthermore, glucose metabolism influences antitumor immunity. For example, NK cells lose their anti-tumor function gradually during lung tumor development and they are crucial in tumor initiation stage but not control tumor promotion and progression. Mechanistically, NK cell lost function gradually during cancer development by Fructose-1,6-bisphosphatase (FBP-1) mediated inhibition of glycolytic metabolism, thus it promotes tumor immune escape (10). In contrast, glucose sufficient environment enhances anti-tumor T cells effector function. Especially, phosphoenolpyruvic acid (PEP) which is glycolytic metabolite regulate calcium signaling and NFAT signaling for reprogramming T cell function (11). However, tumor uptake a lot of glucose, so there is not enough glucose in TME and eventually T cell function reduced in TME (11). Particularly, glioblastoma tumors upregulate glucose transport GLUT1 into cell and increased glycolytic and glutamine metabolism leading to low levels of glucose and glutamine in the TME (12, 13). Reduced metabolites affected to effector T cells proliferation. In addition, pro-tumoral immune suppressive populations including Tregs, MDSCs, M2 macrophages are enriched (14, 15). In conclusion, we need to find a way to target glucose in tumor cells specifically, rather than immune cells, to enhance the antitumor effect.

Lactate

Lactate is the key metabolite generated from glycolytic metabolism from glucose. This lactate makes the acid environment in TME. This is the one of the important hurdles for immune cells and the role of lactate in immune cells and tumor cells are quite complex in TME. Not only does the highly concentrated lactate within the TME serve as a substrate to supply energy to the malignant cells, but it also works as a signal to activate multiple pathways that enhance tumor metastasis and invasion, as well as immune escape. One example of immune escape is, LDHA-associated lactic acid production and acidification lead to immune evasion and diminish T and NK cell activation and IFN-γ expression through NFAT level reduction (16). Second, Treg-specific deletion of the lactate transporter which is SLC16A1 results in decreased tumor growth. Moreover, targeting lactate metabolism directly through MCT1 inhibition or modulating tumor acidity represents strategies to disrupt this metabolic symbiosis, so it lower the Treg barrier to cancer immunity (17). Furthermore, in hypoxic tumor region, cancer cell secreted lactate and it inhibited function of T cells and promotive immune suppressive cells such as Treg and TAMs. In contrast, sodium lactate induced $CD8^+$ T cell stemness and increasing antitumor effect which is opposite effect with lactic acid. Subcutaneous administration of lactate shows the MC38 tumor growth reduced but the glucose does not. In addition, it promotes ICI (anti-PD-1) therapeutic effect in multiple tumor model including MC38, TC-1 and B16F10 (18). The detachment of lactate from acidic protons inhibits histone deacetylases in $CD8^+$ T cells, thereby transforming them into potent anti-tumor immune cells. Thus, it has the potential to enhancing therapeutic outcomes of immunotherapy including ICI, T cell vaccine and ACT therapy.

Tryptophan

Tryptophan (Trp) metabolism is associated with diverse biological process including protein synthesis to support cell proliferation. Kynurenine pathway (KP) is major pathway for breaking down the free Trp. Its metabolism through the KP plays a crucial role in the regulation of immunity, neuronal function, and intestinal homeostasis. Imbalances in Trp metabolism in cancer have been examined therapeutically targeting the KP, particularly indoleamine-2,3-dioxygenase 1 (IDO1), IDO2 and

tryptophan-2,3-dioxygenase (TDO) that is main rate-limiting enzymes as well as kynurenine monooxygenase (KMO). Trp metabolism promote tumor progression by increasing the malignant properties of cancer cells (19, 20). Moreover, it modulates cancer growth by suppressing antitumor immune response (21, 22). For instance, tryptophan and its metabolites exert varying effects on $CD8^+$ T cells and Treg cells. Tumor-repopulating cells exhibit high expression of IDO1, resulting in abundant kynurenine release. Kynurenine, taken up by $CD8^+$ T cells, induces, and activates the aryl hydrocarbon receptor (AhR), subsequently binding to and upregulating PD-1. This indicates that TRCs potentially drive PD-1 upregulation in $CD8^+$ T cells via a transcellular Kyn-AhR mechanism. Furthermore, in the presence of IDO1, activated Tregs upregulate FoxO3a and sequentially PD-1, perpetuating sustained suppression through the PD-1/PTEN feedback loop. Recent research highlights GTP cyclohydrolase 1 (GCH1) as an inducer of PD-1 elevation in both Tregs and $CD8^+$ T cells, operating through a 5-HTP-AHR-IDO1-dependent mechanism. Consequently, given the role of Trp in regulating the expression of immune checkpoint molecules, Trp metabolism is promising target for combination with ICI therapy.

Glutamine

Glutamine is nonessential amino acid (NEAA) and it provides carbon source for lipid metabolism and Tricarboxylic Acid (TCA) cycle or nitrogen source for nucleotide synthesis and amino acid synthesis (23). Glutamine stands as a critical anaplerotic fuel essential for sustaining the TCA cycle and serves as a pivotal source for lipid synthesis, especially through reductive carboxylation in hypoxic cancer cells (24). Inhibiting glutamine uptake was observed to enhance glucose uptake across various cell types residing within tumors. This finding indicates that glutamine metabolism suppresses glucose uptake, even in the absence of glucose being a limiting factor in the TME. Therefore, the preferential acquisition of glucose and glutamine by immune and cancer cells, respectively, is governed by cell-intrinsic programs. Leveraging the cell-selective partitioning of these nutrients holds potential for developing therapies and imaging strategies aimed at enhancing or monitoring the metabolic programs and activities of specific cell populations within the TME. This insight opens new avenues for targeted interventions and precision metabolic modulation in cancer therapy. The SLC1a5 (ASCT2) which is major glutamine transporter is highly expressed in various cancers such as head and neck squamous cell carcinoma and renal cell carcinoma (25, 26). Similar with glucose, there exists a potential competition for glutamine and its derivatives between cancer and immune cells. This competition may significantly impair antitumor immunity, as evidenced by reduced glutamine levels in culture leading to decreased nucleotide synthesis, thereby attenuating the activation, proliferation, and cytokine production of effector T cells (27). Moreover, glutamine is promoting intertumoral conventional dendritic cell type 1 (cDC1) function and SLC38A2 which is glutamine transporter tunes anti-tumor immunity. Notably, intratumoral glutamine supplementation inhibits tumor growth by regulating cDC1-mediated $CD8^+$ T cell immunity, overcoming therapeutic resistance to ICI and T cell therapy (28). Accordingly, targeting glutamine level in tumor help to improve cancer treatment and immunotherapy.

Arginine

Arginine, a pivotal amino acid, intricately participates in diverse cellular processes, contributing to nitric oxide and polyamine synthesis while a nutrient-responsive kinase strongly implicated in carcinogenesis. Although classified as a non- or semi-essential amino acid because normal cells can synthesize arginine from citrulline and aspartate via ASS1 (argininosuccinate synthase 1) and ASL (argininosuccinate lyase), it retains its status as an essential dietary supplement and a potential target for therapeutic depletion. Dysregulation of arginine metabolism is prevalent in various cancers, with arginine playing a crucial role in both the urea cycle and polyamine synthesis pathways, vital for diverse biochemical and potential signaling functions. Remarkably, transcriptional suppression of ASS1 occurs in over 70% of tumors, resulting in cellular dependence on external arginine (29). This forms the basis for arginine-deprivation therapy. The defective arginine synthesis, achieved through the knockdown of ASS1 expression, represents a common metabolic vulnerability in cancer and is often referred to as arginine auxotrophy. Depleting extracellular arginine in arginine-auxotrophic cancer cells induces mitochondrial dysfunction and reprograms transcription. Critical enzymes in arginine metabolism, including NO synthase and arginase, exhibit notable upregulation in various cancer cells, as well as in tumor associated M2 macrophages known for promoting tumor progression (30). In contrast, argininosuccinate synthetase 1 is frequently deficient in many tumors, heightening the reliance of cancer cells on external sources of arginine (31). This metabolic dependency extends to T cells, where arginine availability significantly influences their proliferation and function, highlighting its pivotal role in immune responses (32). Elevation of L-arginine levels triggers comprehensive metabolic shifts, leading to a transition from glycolysis to oxidative phosphorylation in activated T cells. This elevation also promotes the generation of central memory-like cells that possess higher survival capacity and exhibit anti-tumor activity in a mouse model (33). In addition, NK cell proliferation and cytotoxicity were decreased by L-arginine deprivation (34). Moreover, depletion of L-arginine induced higher MDSC induction. Even though positive impact of L-arginine on effector cell survival and anti-tumor functionality presents a potential therapeutic avenue, especially for enhancing adoptive cell therapies, tumor growth also affects by arginine. Thus, we need to find a way to regulate arginine metabolism in immune cells specifically to enhance the function of immune cells without affecting the tumor growth.

Lipids

Lipids are vital energy source and form the fundamental components of cellular structure. It also can be the intra or extracellular molecule as well. Within mammalian cells, fatty acids (FAs) can be acquired either via direct uptake from the surrounding microenvironment or synthesized *de novo* using nutrients like glucose or glutamine. A recognized hallmark of cancer cell metabolism is lipidomic remodeling, which involves substantial alterations in fatty acid transport, *de novo* lipogenesis, storage as lipid droplets (LDs), and the utilization of β-oxidation to generate ATP. In the context of cancer progression, cells may exhibit a reliance on either lipid uptake or *de novo* synthesis pathways. This phenomenon can be happened depending on the tumor types. Targeting lipid metabolism can slow down the metastatic disease as well. Exogenous fatty acid uptake needs specialized transporter such as CD36 and FABPs which facilitate efficient movement across the plasma membrane. CD36 is known as fatty acid translocase (FAT) and its expression increased in most of tumors. High CD36 is corelates with poor prognosis in some kinds of tumor types and it promotes increased FA uptake and storage (35, 36). Deletion of CD36 in tumors are enough to regulated tumor growth and migration (37). Especially, CD36 is important to liver metastasis which is highly aggressive tumor. Its expression in tumor correlates with M2 macrophages differentiation which makes more immunosuppressive microenvironment. An analysis via protein array revealed an elevation in fatty acid-binding protein 4 (FABP4) expression within omental metastases in contrast to primary ovarian tumors. Notably, the absence of FABP4 significantly hindered metastatic tumor expansion in mice, highlighting its pivotal role in driving ovarian cancer metastasis (38, 39). These findings underscore the contribution of adipocytes in furnishing fatty acids crucial for accelerated tumor growth, emphasizing lipid metabolism and transport as promising targets for therapeutic intervention in cancers where adipocytes play a significant role in the microenvironment (38, 40). Cytoplasmic acetyl-CoA is the main substrate of the FA synthesis derived from citrate or acetate. Cancer cells upregulate acetyl-CoA synthetase 2 (ACSS2) in order to generate acetyl-CoA from acetate under the hypoxia

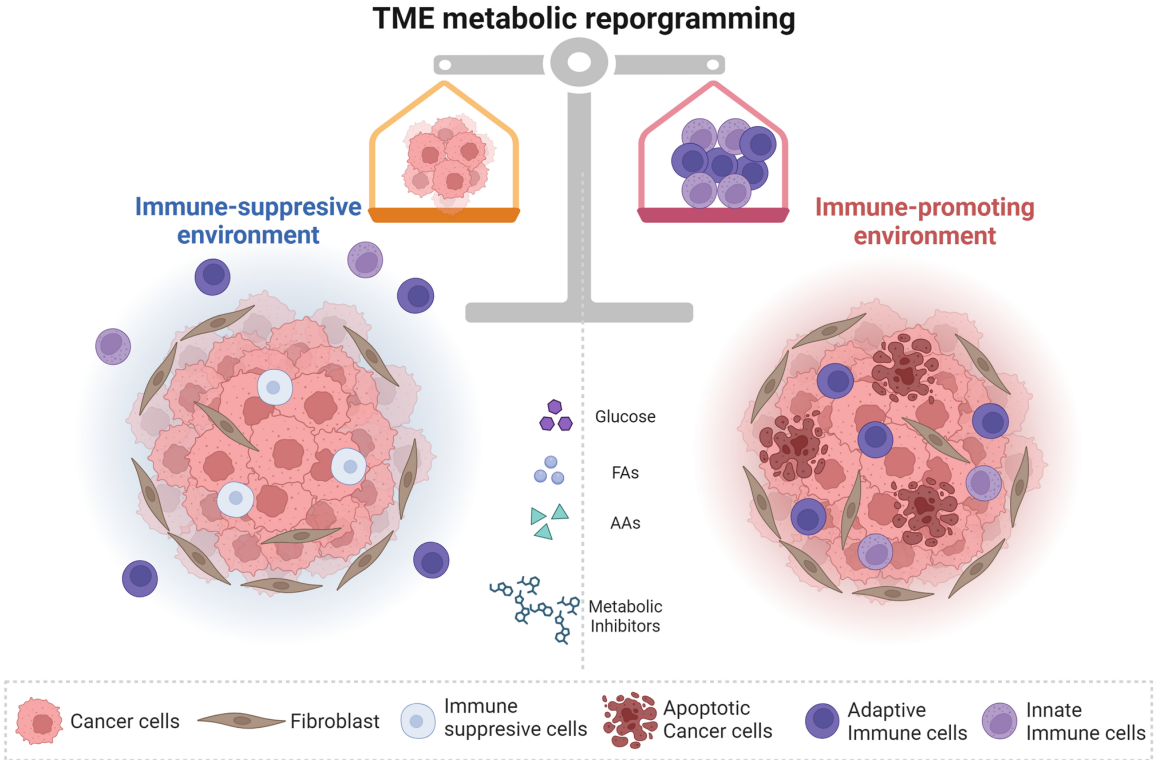

Fig. 1. Metabolic reprogramming by metabolites or inhibitors in the tumor microenvironment. Tumor and immune cells share metabolites such as glucose, lactic acid, tryptophan, or lipids in the TME. Some metabolites can induce an immune-suppressive environment by metabolically driving tumor escape or an immune-promoting environment by enhancing effector cells for tumor elimination. To modulate the TME, supplements such as glucose, fatty acids, or amino acids are required, or inhibitors are needed to reduce metabolic pathways for promoting immune cells. FAs, fatty acids; AAs, amino acids. Adapted from "Tumor Comparison (Layout)" by BioRender.com (2024). Retrieved from https://app.biorender.com/biorender-templates.

or lipid depletion environment. Therefore, the targeting of lipid metabolism either exogenous or endogenous could also be a promising therapeutic approach to overcome tumor resistance to most common treatments. The accumulation of lipids within the TME not only fosters immune evasion and inflammation but also serves as a crucial energy source for rapidly proliferating cells. In tumors, abnormal lipid accumulation is associated with T cell dysfunction, exhaustion, elevated proportions of Tregs, and alterations in memory T cells, alongside heightened T cell recall responses. Furthermore, lipids influence macrophage functions, displaying increased plasticity in certain instances and, conversely, leading to diminished macrophage differentiation, thereby promoting tumor growth. The presence of lipid droplets has been correlated with the infiltration of natural killer NK cells and an increase in metastasis. Similarly, triglyceride accumulation in DCs contributes to downregulated antigen presentation and heightened immune evasion. Taken together, lipid is promising metabolic target for immunotherapy because of opposite role in immune cells and tumor.

TARGETING METABOLIC PATHWAY USING INHIBITOR OR SUPPLEMENTS

Targeting metabolism as a direct means to inhibit cancer cell growth and proliferation represents a straightforward approach to augment the efficacy of immunotherapy. Nevertheless, as mentioned above, tumor metabolism exerts a profound influence other factor in the TME as well. The heightened metabolic activity of cancer cells, coupled with a disorganized and dysfunctional vasculature, contributes to hypoxia and nutrient depletion in the TME. This, in turn, triggers competition for oxygen and nutrients among various cells within the TME, including both cancer and immune cells. Beyond depriving immune cells of essential nutrients, tumor metabolism contributes to the generation of immunosuppressive metabolites. These include lactic acid, reactive oxygen species (ROS), kynurenine, polyamines, adenosine, and cholesterol, all of which actively suppress antitumor immunity. Consequently, interventions targeting tumor metabolism hold the potential to enhance immunotherapy by fostering a tumor microenvironment more conducive to an effective antitumor immune response (Fig. 1). Here, we will describe two different aspects that is inhibitors and supplements how they can modulate TME for enhancing immunotherapy in preclinical model. Pharmacological inhibitor for targeting tumor were as summarized in Table 1.

Inhibition of metabolic pathways

Recent findings suggest that manipulation of glucose metabolism can represent a valuable tool to limit cancer cell growth and to help the immune system to elicit an efficient and protective response to cancer cells. Both pharmacological approaches and diets with a low carbohydrate content are under evaluation to limit glucose availability in metabolic processes for a future application as co-adjuvant strategies to improve cancer immunotherapies. For targeting glucose metabolism, several drugs are available and holds an advantage. Over the years, numerous glycolysis inhibitors have been developed. In particular, 2-DG is a glucose analog and a competitive inhibitor of glycolysis (41) in which the 2-hydroxyl group is replaced by hydrogen. 2-DG blocks the activity of different enzymes related to glycolysis, result in cell death. Hyperglycemic condition aggravates cancer cell proliferation, inflammatory conditions, and viral infection (42). 2-DG exerts its mechanism by competing with glucose for hexokinase (HK) binding, subsequently converting to 2-DG-6-phosphate (2-DG-6-P) via phosphorylation. The accumulation of 2-DG-6-P within cells impedes phosphor-glucose isomerase (PGI) activity, thereby curtailing glucose uptake and downstream metabolic pathways, ultimately leading to ATP depletion and cell death. Under conditions of diminished cellular energy supply, 2-DG induces metabolic stress, leading to the inhibition of immune cell functions and concurrent downregulation of pivotal immune-related genes. These effects underscore the impact of 2-DG on immune cell activity and gene expression, elucidating its relevance in immune modulation. In contrast to a prior study demonstrating 2-DG's role in promoting memory T cell differentiation through glycolysis inhibition, our findings revealed that 2-DG treatment significantly enhanced the antitumor activity of human T cells, particularly against tumor cells ex-

Table 1. Summarizes pharmacological inhibition of metabolic pathway for targeting TME

Target metabolites	Inhibitors	Specific target	Reference
Glucose	2-DG	HK1/2	(80)
	STF-31	GLUT1	(81)
	WZB-117	GLUT1	(44)
	BAY-876	GLUT1	(82)
	Glutor	GLUT	(83, 84)
Lactic acid	AZD3965	MCT	(85)
	NCI-006	LDH	(46)
Trytophan	Epacadostat	IDO1	(86)
	BAY-2416964	Aryl hydrocarbon receptor (AhR)	(50)
Glutamine	V-9302 (Benzylserine)	ASCT2 (SLC1A5)	(52)
	DON (JHU083)	GLS1/2	(56)
	CB-839	GLS	(67)
Lipid	C75	FASN	(87)
	TVB-2640	FASN	(88)
	TOFA	ACC	(89)
	Statin (simvastatin, lovastatin)	HMGCR	(90)
	Avasimibe	ACAT	(79)

List of pharmacological inhibitors that target the tumor growth inhibition.

pressing high levels of NKG2D ligands. Additionally, we observed that 2-DG played a crucial role in alleviating the immunosuppression of T cells induced by tumor-released galectins. Taken together, our results propose a novel metabolic reprogramming strategy involving the administration of 2-DG during the *ex vivo* expansion of T cells. We posit that T cells treated with 2-DG could prove effective for T cell-based immunotherapies against cancer (43). Recently, a novel class of small molecules with high selectivity against glucose transporter 1 (Glut1) and favorable pharmacokinetic and pharmacodynamic characteristics has emerged. The pharmacological blockade of Glut1 such as STF-31, WZB-117 and BAY-876 stands out as a promising strategy, offering the potential to enhance both a sustained immune response and reduce tumor growth (44). Especially, BAY-876 pharmacokinetics data is available both *in vitro* and *in vivo*, and it has been tested several different tumor models and helpful to reduce tumor growth (45). Therefore, impairing glucose metabolism in tumor can give the benefit to immunotherapy.

The LDH inhibitor NCI-006, distinguished by its heightened specificity and efficacy, is poised as a promising therapeutic agent with anticipated *in vivo* effects (46). Moreover, N-hydroxyindole drugs have demonstrated efficacy in diminishing the growth of pancreatic and cervical cancer cells *in vitro* (47). Notably, when combined with gemcitabine, they exhibit an augmented apoptosis rate in pancreatic cancer cell lines (48). These findings underscore the potential of NCI-006 and N-hydroxyindole drugs as candidates for further exploration in cancer treatment. Monocarboxylate transporters (MCTs) function as proton-linked transporters, facilitating the movement of various monocarboxylic acid metabolites, such as pyruvate, L-lactate, and ketone bodies, across the plasma membrane with protons. In tumor metabolism, MCT1/4 subtypes dominate, presenting promising targets for anticancer interventions. Inhibitors or gene knockout of MCT1 can disrupt lactate-fueled respiration in mitochondria. MCTs play a vital role in maintaining metabolic homeostasis within the tumor microenvironment. MCT1, with a high affinity for lactate, is preferentially expressed in respiratory cancer cells that uptake lactate (49). Conversely, MCT4, with low lactate affinity, facilitates lactate export from glycolytic cancer cells and is upregulated under hypoxic conditions. Disrupting communication between oxidative and glycolytic cancer cells through MCT1 inhibitors has been shown to inhibit breast cancer growth and promote myeloma cell death. The application of MCT inhibitors demonstrates efficacy in reducing the invasive and migratory capacity of various cancer cell types, including glioma, cervical squamous carcinoma, melanoma, triple-negative breast cancer, and pancreatic ductal adenocarcinoma cells. MCT inhibitors exhibit the potential to diminish glycolysis, lactic acid levels, and tumor growth while concurrently bolstering the immune response. This is manifested by increased tumor infiltration with $CD8^+$ T and NK cells, illustrating the multifaceted impact of MCTs as therapeutic targets in cancer treatment.

For targeting Trp metabolism, we can do pharmacological inhibition of IDO1 and/or TDO2 by using IDO1 inhibitor. Within TME Indoleamine IDO1 is broadly expressed in multiple cell types in cancers, and it is also used in clinical trials. Indoximod as an IDO1 pathway antagonist, multiple other IDO1 inhibitors have been generated to inhibit the ligation of Kyn with AhR. Beside of this, other IDO1 inhibitors target to have higher affinity for IDO1 than Trp or deplete the catalytic stie of IDO1 such as epacadostat. To test those inhibitors shows that immunotherapeutic effect in mouse tumor models, but epacadostat which is the most recent inhibitor cannot enhance ICI therapy. Additionally, blocking of Aryl hydrocarbon receptor (AhR), which is activated by Kynurenine, activation using synthetic AhR modulator. AhRs are key to control T cell differentiation and BAY 2416964 is an AhR antagonist with potent and selective inhibition of ligand induced AhR activation. It exhibits proinflammatory immunomodulatory effects, leading to effective tumor inhibition both *in vitro* and *in vivo* (50). Trp metabolism is good candidate to target cancer treatment because effect on tumor and immune cells are opposite. Therefore, we need to do reverse translational research to understand MOA of current inhibitor, then we can figure out how to improve current therapeutic strategies.

Decreasing glutamine availability administration of V-9302 has been shown to increase glucose uptake by both cancer cells and immune cells in allograft models. This intervention leads to the suppression of tumor growth in models characterized by the presence of tumor infiltrating $CD8^+$ T cells, NK cells and Treg cells (51). Notably, as cancer cells exhibit a greater dependence on glutamine than immune cells, and V-9302 does not impair the viability and activation of $CD8^+$ T cells (52), pharmacological inhibitors targeting SLC1A5 hold significant therapeutic potential (52-54). This suggests a promising avenue for developing treatments that selectively target cancer cells while preserving the function of immune cells in the tumor microenvironment. For instance, glutamate blockade using glutamate antagonist JHU083 simultaneously suppressed oxidative phosphorylation and glycolytic metabolism of cancer cells, so it can lead to modulate TME including hypoxia, acidosis, and nutrient depletion. Therefore, antitumor immune response is increasing by highly activated phenotype and increased survival of effector T cells. Together, it can overcome tumor immune evasion via changing the TME (55). In addition, it suppresses MDSCs by decreasing cell survival and expression of CSF3 in tumor, so it can enhance function of effector T cells. Moreover, Glutamate blockade enhances the ICI efficacy as well as overcoming the ICI resistance (e.g. anti-PD-1 and/or anti-CTLA-4) (56). More clinical relevance triple negative tumor However, in triple negative breast cancer patients, increased glutamine metabolism inhibits effect T cell cytotoxicity and cell survival. Using V-9302 which is inhibitor of glutamine transporter suppressed glutamine uptake in tumor cells but not $CD8^+$ T cells to improve effector function by glutathione synthesis. For targeting glutamine, selective targeting may require

for TNBC therapeutic treatment strategy (57).

One good examples of promising target for metabolism are fatty acid metabolism. Even if lipid and cholesterol accumulation has been shown to correlate with cancer aggressiveness (58), it is promising target for therapy because effect of inhibitor is opposing in immune cells. Under physiological conditions, immune cells exhibiting anti-tumor functionality, such as effector $CD8^+$ T cells, NK cells, and M1 macrophages, primarily rely on glycolysis to facilitate their maturation and function. Conversely, immune-regulatory cells, including Tregs, M2 macrophages, and MDSCs, predominantly utilize fatty acid oxidation (FAO) pathways to exert tumor immune-suppressive effects. For example, within TAMs, heightened lipid accumulation and increased FAO contribute to their polarization toward the M2 phenotype. This polarization inhibits anti-tumor T cell responses and reinforces the immunosuppressive capabilities of T cells (59, 60). Similarly, elevated uptake of oxidized lipids and heightened lipid peroxidation within $CD8^+$ TILs lead to their immune dysfunction. However, resolving lipid peroxidation restores the functionalities of $CD8^+$ TILs *in vivo*.

For inhibiting lipid metabolism, we can use several different strategies depends on source of lipid. Commonly, exogenous lipids are uptaken by CD36. Anti-CD36 or SSO treatment regulate survivin expression and it associated with poor prognosis. Moreover, CD36 associate with tumor metastasis. Given the pivotal roles played by endogenous fatty acid synthesis in cancer progression, FASN emerges as an appealing target for cancer therapy. Small molecule inhibitors like cerulenin and C75, known for their potency in inhibiting FASN, have demonstrated the ability to delay disease progression in models of ovarian and breast cancers. However, despite these promising therapeutic effects, targeting FASN can perturb multiple layers of lipid metabolism and homeostasis, potentially leading to undesired side effects such as weight loss—potentially attributed to cross-activation of lipolysis and β-oxidation. Alternative, milder approaches, including dietary interventions, might offer a balanced solution. For instance, catechin, a natural flavonoid and antioxidant, exhibits FASN inhibitory properties without stimulating β-oxidation or inducing weight loss in mice.

In an *ex vivo* coculture assay involving murine cancer cells and tumor-infiltrating lymphocytes, our investigation revealed that all seven statin drugs exhibited inhibitory effects on tumor cell proliferation. Specifically, simvastatin and lovastatin demonstrated an additional enhancement in T-cell-mediated killing of tumor cells. High fat diet-induced obesity accelerates tumor growth by leading $CD8^+$ T cell exhaustion and reduction of IFN-γ, TNF-α and Granzymes (61). Take together, lipid metabolism could be the best options for the more succeed to boost immune cells for treating cancer. Notably, as dietary manipulation gains traction as an attractive strategy to complement traditional cancer therapies, further research is essential to fully elucidate the potential therapeutic effects of some natural products as FASN inhibitor.

Supplementations of metabolites

Glucose and amino acids are metabolized by tumor cells, so their availability to immune cells is limited in TME. For this reason, metabolic adaptation is needed for appropriating immune cell function. For examples, glucose restricted $CD8^+$ T cells dampened function, but acetated rescues effector function of these $CD8^+$ T cells. Mechanistically, acetate enhancer IFN-γ production of T cells by promoting histone acetylation and chromatin accessibility. In contrast ACSS deficient T cells impairs IFN-γ production and fail to tumor clearance (62). Other examples show supplementation of L-arginine promotes differentiation of central memory like T cell and survival. Furthermore, L-arginine promoted the development of central memory-like T (Tcm) cells, exhibiting enhanced anti-tumor activity in a mouse model (33).

The other metabolites asparagine supplementation has been demonstrated promotion of T cell activation via Lck activation (63). Furthermore, in glucose-restricted conditions, inosine plays a significant role in central carbon metabolism, sustaining energy production and the generation of biosynthetic precursors, enhancing antitumor immunity (64). The exploration of nutrient supplementation to improve Adoptive Cell Therapy (ACT) holds considerable promise in terms of feasibility and the potential to prevent side effects. The *ex vivo* treatment approach offers a means of metabolic optimization for T cells without disrupting the metabolic homeostasis of other tissues. This nuanced strategy represents a noteworthy avenue for enhancing the efficacy of T cell-based immunotherapies.

COMBINATION THERAPY WITH METABOLISM-BASED INHIBITORS AND ICI THERAPY

Undoubtedly, the success of immunotherapy including checkpoint blockade and CAR-T therapy has revolutionized the treatment of cancer. While these successes have been remarkable, there is a clear imperative to further advance immunotherapy by deepening its impact on tumors deemed sensitive and broadening its effectiveness to tumors with limited responsiveness. Given our current knowledge of metabolic inhibitor in cancer treatment, targeting metabolism provides benefit to enhance immunotherapy by modulating TME (65). It still needs to explore the distinct metabolic programs that both immune cell and tumor cell required, then we can suggest the promising combination therapeutic strategies for overcoming current therapy. Therefore, integrating metabolic therapy into the treatment paradigm holds immense promise to accelerate these goals. The addition of pemetrexed to immunotherapy for non-small cell lung cancer (NSCLC) serves as an initial step in this direction. Targeting metabolism has the potential to augment immunotherapy efficacy in NSCLC, melanoma, renal cell carcinoma, and other cancers where checkpoint blockade has gained approval. Furthermore, for cancers like prostate, breast, and pancreatic cancers, where immunotherapy has shown limited efficacy, metabolic therapy can potentially reshape the

tumor microenvironment, increase immune infiltration, and transform these resistant tumors into susceptible ones. The potential of metabolic therapy extends to facilitating the expansion of CAR-T therapy into solid tumors. Additionally, by enhancing the persistence of adoptively transferred cells, metabolic therapy has the potential to improve the overall efficacy of CAR-T therapy, marking a significant stride toward comprehensive and effective cancer immunotherapy.

There is evidence that targeting glucose metabolism may have benefit for synergistic effect with ICI therapy. Glucose transporter, Glut14 (also called SLC2A14), in T cells are highly expression in PD-1 blockade responder population by scRNAseq analysis. In addition, Glut-14 expression in circulating T cell population is elevated in responder patient by flow cytometry analysis (66). Therefore, targeting glucose uptake may enhance the ICI immunotherapy. The other example is Dimethyl fumarate (DMF), which is FDA approved glycolysis inhibitor, enhance anti-tumor response against 4T1 tumor and it shows synergistic effect in combination therapy with anti-PD-1 therapy. Notably, impact of lactate metabolism on the effectiveness of ICI therapy is substantial. Monocarboxylate transporter 1 (MCT1), prominently found in Treg cells within the TME, facilitates lactate uptake and triggers PD-1 expression. Inhibiting MCT1 in Treg cells notably improves the antitumor efficacy of anti-PD-1 therapy. In addition, Treg-specific deletion of the lactate transporter which is SLC16A1 results in not only decreased tumor growth but also in synergistic effect with ICI therapy. LDHA is also one way to target lactate pathway. It also plays a crucial role in modulating response to ICIs in colorectal cancer. Selectively targeting LDHA proves beneficial in improving ICI efficacy and reversing T cell exhaustion. Current literature underscores that glycolysis not only increases PD-L1 expression in immune cells but also in tumor cells, correlating with a more favorable response to immunotherapy. Targeting glycolysis emerges as a strategic approach to enhance immunotherapy effectiveness.

Even though amount of evidence suggest that IDO1- or TDO2-expressing tumor cells can escape immunosurveillance via Trp starvation, and AhR is involved in tumor immune evasion, there have not been observed for epacadostat in combination with pembrolizumab (targeting PD-1), efficacy was globally lacking from multiple clinical trials evaluating IDO1 inhibition with anti-PD-1/L1-based ICI. We need to examine more related to Trp metabolism and it may understand the mechanism of MOA of combination therapy. Therefore, it is still unclear how to target Trp metabolism for enhancing effect of ICI therapy.

Inhibitor of glutamine uptake (Benzylserine) and glutamine analogues (DON) show systemic toxicity, but prodrug version may be less toxic. Telaglenastat which is also called CB-839 is potent oral inhibitor of GLS has demonstrated favorable PK, PDs and safety in early clinical study and combination with ICI (anti-PD1 or anti-CTLA4 antibodies) increased effector T cells accumulation and improved the antitumor activity of these checkpoint inhibitors in mouse melanoma model (67). Moreover, responsiveness to these treatments was also accompanied by an increase of interferon gamma (IFNγ)-associated gene expression in the tumors. Together, these results provide a strong rationale for combining CB-839 with immune therapies to improve efficacy of these treatments against melanoma.

Targeting lipid transport receptors could improve rate of ICI response. PD-1 expression on $CD8^+$ T cells is upregulated by cholesterol in TME and it leads to $CD8^+$ T cell dysfunction (68). For restoring function of $CD8^+$ T cell by reducing cholesterol may induce synergistic effect with ICI therapy. Additionally, targeting CD36 on Treg was found to enhance the efficacy of αPD-1 therapy (36). Moreover, other lipid transporters, FABP4/5, support ICI therapeutic effect. FABP4/5 expression reduced by PD-L1 blockade in tumor cells but increased FABP4/5 expression in Trm cells. Mechanistically, it is providing adequate lipid uptake in Trm cells and contributing to antitumor immune response (69). Targeting lipid peroxidation-related enzymes represents a potential strategy to enhance ICI therapy. Excessive lipid accumulation can induce lipid peroxidation, leading to ferroptosis. Glutathione peroxidase 4 (GPX4) plays a crucial role in rescuing cells from ferroptosis by degrading lipid peroxides. While there is no direct evidence of crosstalk between GPX4 and immune checkpoints, numerous studies indicate that targeting ferroptosis in conjunction with ICI therapy can yield improved antitumor effects. PPARγ agonists, including rosiglitazone and bezafibrate, known for their ability to reduce fatty acid storage, have demonstrated enhanced efficacy in inhibiting tumor growth and extending survival time. These effects are particularly pronounced in melanoma and lung cancer when these agonists are employed in combination with immunotherapeutic approaches, such as anti-PD-1 and cancer cell vaccines. Lipid signaling pathway is also one promising candidates for targeting. For instance, pharmacological and genetic inhibition of ACLY effectively surmounts cancer resistance to anti-PD-L1 therapy through a cGAS-dependent mechanism. Additionally, dietary PUFA supplementation mirrors the heightened efficacy of PD-L1 blockade achieved by ACLY inhibition. These discoveries unveil the immunomodulatory role of ACLY, offering insights into combinatorial strategies that can be employed to overcome immunotherapy resistance in tumors. Furthermore, deficient SCAP in Tregs also has a synergistic effect with anti-PD1 therapy (70).

Metformin which can regulate lipid metabolism can inhibit oxygen consumption in tumor cells to reduce intra-tumoral hypoxia. A combination of metformin with PD-1 antibody improves T-cell function and tumor clearance in mice with melanoma (71). Favorable treatment outcomes were also observed in melanoma patients receiving metformin in combination with ICIs (72). Similarly, patients with non-small cell lung cancer receiving concurrent metformin and ICIs showed higher response rate and overall survival (73). In murine models, the daily oral administration of simvastatin or lovastatin demon-

strated an enhancement in tumor control and prolonged survival when combined with PD-1 blockade. Notably, this combined treatment resulted in the rejection of MOC1 tumors in 30% of mice treated with lovastatin plus anti-PD-1 (74). Fenofibrate (FF), a PPAR-α agonist known for enhancing fatty acid (FA) catabolism, induces increased PD-1 expression in $CD8^+$ tumor-infiltrating lymphocytes (TILs) and preserves their effector function (75). Bezafibrate, an agonist of PGC-1α/PPAR complexes, promotes the FAO pathway by upregulating the expression of CPT1, a crucial enzyme in mitochondrial fatty acid metabolism. The combination of bezafibrate and PD-1 blockade activates mitochondrial biogenesis and FAO in $CD8^+$ T cells, leading to enhanced survival and proliferation of tumor-reactive cytotoxic T lymphocytes (CTLs). This synergistic approach improves the efficacy of PD-1 blockade, particularly against unresponsive tumors exhibiting systemic immunosuppressive properties (76-78). Furthermore, avasimibe, a compound targeting ACAT, when used in combination with anti-PD-1 treatment, demonstrates superior efficacy compared to monotherapies in controlling tumor growth (79).

CONCLUDING REMARKS

Immunotherapy has undeniably revolutionized cancer treatment, yet formidable challenges persist. While the appreciation for the importance of tumor bioenergetics and its impact on immunity has reached new heights, numerous critical questions linger regarding the intricate interplay between tumor metabolism and immunotherapy. Despite significant strides in understanding immune cell metabolism and cancer metabolism over the past decade, we stand at the threshold of translating this knowledge into therapeutically meaningful interventions. The differential metabolic requirements of diverse immune cells within the cancer response present a unique opportunity for selectively regulating immune cell functions. Integrating metabolic inhibitors with immunotherapy heralds novel approaches to cancer treatment, offering opportunities to reshape the TME in favor of robust immune responses. Thus, the emphasis on combination therapy has surged as a promising avenue for surmounting hurdles presented by the TME, thereby enhancing the efficacy of cancer immunotherapy. However, challenges are remining, and our current understanding raises critical questions that demand further exploration. Deeper insights into the timing of major metabolic switches during immune cell activation and differentiation are essential. Beyond pharmacological agents, there is an urgent need to employ a broader array of genetic modifications, including transgenic mouse models targeting diverse metabolic regulators, to precisely delineate their immune-modulating effects. The adaptation of antitumor immune cells, such as tumor-infiltrating lymphocytes, and tumor-promoting cells like MDSCs to metabolic constraints within the TME remains poorly understood. Additionally, unraveling how metabolic pathways support the proliferative capacity and function of memory T cells within the TME is crucial for harnessing superior antitumor immunity.

More research is imperative to define the relative contributions of tumor regression and immune promotion by metabolic targeting. Strategic targeting of metabolic vulnerabilities in cancer cells, coupled with reinforcing the antitumor fitness or function of immune cells, holds immense potential. This approach may extend the success of immunotherapy to a broader spectrum of cancer types, benefiting a larger proportion of patients in clinical settings. In conclusion, as we navigate the intricate landscape of immunotherapy and tumor metabolism, a concerted effort is needed to address these research gaps. A collective commitment to unraveling these complexities will not only deepen our understanding but also pave the way for innovative therapeutic strategies, ultimately advancing the field and benefiting cancer patients worldwide.

ACKNOWLEDGEMENTS

This work was supported by the Ewha Womans University Research Grant of 2023 (1-2023-0406-001-1) and by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (RS-2024-00336028).

CONFLICTS OF INTEREST

The author has no conflicting interests.

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