Review Article

Metabolic reprogramming and cancer precision medicine: a narrative review

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Objective: This review focuses on how to target cancer metabolic reprogramming to accurately manage cancer, considering factors affecting metabolic heterogeneity. A deeper understanding of cancer metabolic reprogramming could provide new way for precision medicine.

Background: Metabolic reprogramming is a highlighted cancer hallmark in tumorigenesis and tumor response. Tumors alter metabolic pathways to fulfill their bioenergetic and biosynthetic demands for rapid growth and adaptation to microenvironment. Accordingly, numerous advances of reprogrammed activities in aerobic glycolysis, glutamine catabolism, macromolecular synthesis, and redox homeostasis can be exploited to diagnose, monitor, and treat cancer.

Methods: This review summarize major characteristics and updates of cancer metabolism, focusing on how to target cancer metabolic reprogramming for cancer precision medicine. Specifically, we discussed the key updates of cancer metabolic reprogramming, metabolic targets for cancer therapy, precision nutrition and cancer treatment, and metabolic imaging for cancer management.

Conclusions: Tumor metabolic heterogeneity and vulnerabilities exist across tumor types, which brings in challenges to precisely target cancer metabolism for diagnosis and treatment. Further research and deeper understanding on the metabolic network and dynamic regulation are required to enhance the implication of cancer metabolism. These insights have the potential to provide new effective therapeutic and monitoring approaches for cancer precision medicine.

Keywords: Metabolic reprogramming; precision medicine; cancer management

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Introduction

Precision medicine in cancer aims to improve outcome of cancer patients by using customized strategy to prevent, diagnose and treat cancer according to tumor molecular features. As the metabolic reprogramming empowers cancer cells flexibility to adapt stress and microenvironment, metabolic reprogramming is critical for tumorigenesis, cancer progression, tumor responses upon treatment, and therapy resistance. Therefore, targeting cancer metabolism can provide effective approaches for cancer precision management. Increasing research in cancer metabolism investigate how reprogrammed metabolism works and drives rapid cell proliferation, or which reprogrammed activities are relevant to resistance of treatment. Deep understanding of these molecular insights about cancer metabolism is the foundation for design of effective cancer management and therapeutic strategies for different cancer

types.

Tumor metabolism is a complex progress dynamically affected by intrinsic and extrinsic factors, which results in high metabolic heterogeneity of cancer. Cancer cell intrinsic effects of oncogene include perturbed signaling, genetic mutations, gene expressions and so on. While extrinsic factors depend on the tumor microenvironment (TME) and systematical metabolism of the patient (1). There are key characteristics of cancer cells, for example, enhanced aerobic glycolysis, mutations in the tricarboxylic acid (TCA) cycle metabolic enzymes, and dependence on lipid and glutamine metabolism. Moreover, cancer cells switch metabolic pathways to avoid cell death upon anti-cancer drugs. Therefore, targeting metabolic plasticity and flexibility is expected to decrease anti-cancer drug resistance (2). Collectively, cancer metabolic heterogeneity and flexibility bring in big challenges for cancer treatment. And targeting cancer metabolic reprogramming is critical for cancer precise treatment and management.

We present the following article in accordance with the Narrative Review reporting checklist (available at: https://dx.doi.org/10.21037/pcm-21-27).

Methods

Here, this review aims to summarize major characteristics and updates of cancer metabolism, focusing on how to target cancer metabolic reprogramming for cancer precision medicine (*Figure 1*). Specifically, we discussed the key updates of cancer metabolic reprogramming, metabolic targets for cancer therapy (*Figure 2*), precision nutrition and cancer treatment (*Figure 3*), and metabolic imaging for cancer management.

Cancer metabolic reprogramming

Warburg effect and cancer diagnosis

Hyperactive glycolysis is the common and important feature of many cancers. Normal cells oxidize glucose to CO_2 through mitochondrial oxidative phosphorylation to efficiently produce adenosine triphosphate (ATP) when oxygen is enough, and use glucose to produce lactic acid through fermentation (3) under hypoxia condition, which is a fast metabolic pathway but low-efficient in producing ATP. Nevertheless, cancer cells prefer to a glycolytic form for fulfill their bioenergetic and biosynthetic needs of rapid energy generation even if oxygen is available, which is known as Warburg Effect (4). In addition to ATP generation, multiple intermediate products of glucose metabolism feed into biosynthetic pathways to produce lipids, nucleotides and synthesis of macromolecules to support tumor growth (5). Moreover, emerging evidence shows that lactic acid is a regulator participating in tumor progression (6). Abundant lactic acid generated from glycolysis not only fuels tumor (7,8), but also creates an immune suppressive microenvironment to promote tumor progression. Lactic acid limits retinoic acid-inducible gene I (RIG-I)-like receptor (RLR)-mediated type I interferon (IFN) production to suppress innate immunity (9) and contributes to the intra/extracellular pH within TME to polarize tumor associated macrophages (10). The acidic extracellular pH can also promote the secretion of lysosomal enzymes, and induces the expression of pro-metastatic factors via intracellular signaling (6).The Warburg effect phenotype is commonly observed in many aggressive cancers (11,12). Base on the high glucose uptake and glycolysis of cancer cells, ^{18}fluoro-2-deoxy-d-glucose (^{18}F-FDG) positron emission tomography (PET) scan has been widely used in clinic as a diagnostic marker of tumor detection, stage, and prognostic evaluation (13). However, the limitation of ^{18}F-FDG-PET in detecting prostate cancer and brain tumor, demonstrates that metabolic reprogramming other than glycolysis exists in cancers.

Mitochondrial metabolism and updates of Warburg effect

As an update of Warburg Effect that cancer cells prefer glycolysis while decrease mitochondrial oxidative phosphorylation, mitochondrial metabolism is found to be hyperactive and necessary for tumor growth in recent years (14). Mitochondria are well known as the principal organelles to produce ATP for the energy needs of cells. Carbon sources, such as pyruvate, glutamine, and fatty acids, generate NADH and FADH2 through the TCA cycle in mitochondrial matrix and transfer their electrons to the electron transport chain (ETC) which embedded in the inner mitochondrial membrane (15). Therefore, mitochondria are essential in biosynthetic and bioenergetic signaling and play a critical role in cell differentiation, proliferation, and death (16). Warburg effect firstly described mitochondria in malignant cancer cells is structurally and functionally different from normal cells (17), which promotes the dependence on glycolysis in cancer cells. However, rising evidence show a normal function of mitochondria in cancer. Recent

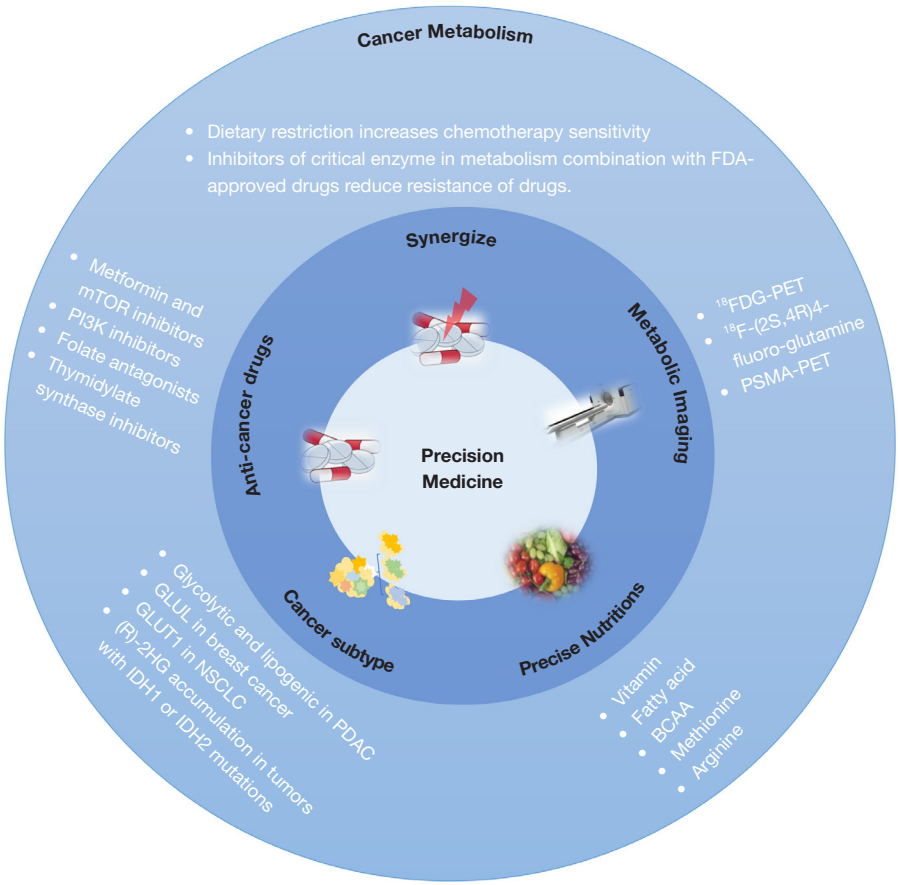

Figure 1 Cancer metabolism and precision medicine. To cancer therapy, targeting metabolic reprogramming provides three major approaches to help fight against cancer. For example, metabolic anti-cancer drugs to target key enzymes or regulators of hyperactivated metabolic pathways. And metabolic modulators can synthesize chemotherapy, radiotherapy and immunotherapy. Besides, various dietary interventions can suppress cancer progression. Metabolic imaging can not only help to diagnose but also monitor cancer development, and deep understanding of these molecular insights about cancer metabolism is the foundation for design of effective cancer management and therapeutic strategies for different cancer types, such as TNBCs can be classified into the lipogenic subtype with upregulated lipid metabolism, the glycolytic subtype with upregulated carbohydrate and nucleotide metabolism, and mixed subtype. mTOR, Mammalian target of rapamycin; PI3K, phosphoinositide 3-kinase; ^{18}F-FDG, ^{18}fluoro-2-deoxy-d-glucose; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; BCAA, branched-chain amino acid; PDAC, pancreatic ductal adenocarcinoma; GLUD, glutamate dehydrogenase; NSCLC, non-small cell lung cancer; TNBC, triple-negative breast cancer.

studies reveal that mitochondrial metabolism supports tumor anabolism by providing key metabolites for macromolecule synthesis and generating oncometabolites to maintain the cancer phenotype. Multiple substrates feed into the biosynthetic pathways in mitochondrial, providing cancer cells with metabolic flexibility to support tumor growth under various conditions (14). And mitochondrial biogenesis and glycolysis in the p53 knockout mouse were significant upregulation at the same time. Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function for survival (18). Moreover, targeting mitochondrial ETC can synergy the anti-cancer efficacy of immuno-, antiangiogenic, or oncogene targeted therapies. Mechanistically, tumor growth requires the ETC to oxidize ubiquinol, which is an essential activity of mitochondrial complex III that allows complex I, II, and dihydroorotate dehydrogenase (DHODH) to function. Therefore, ETC is essential to drive the oxidative TCA cycle and DHODH activity in cancer (19).

Targeting mitochondrial reprogramming offers

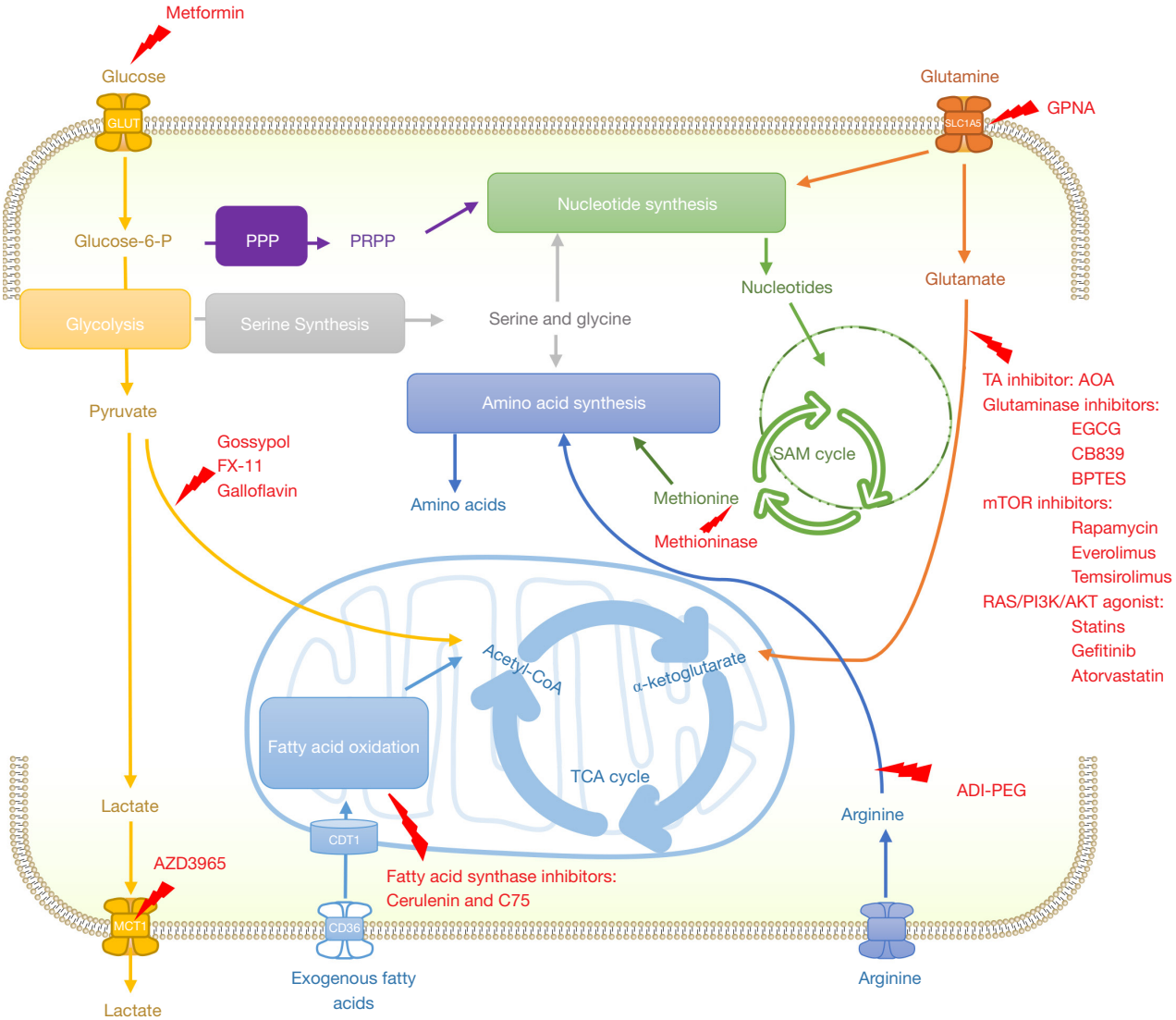

Figure 2 Metabolic anti-cancer drugs. The key updates of cancer metabolic reprogramming, metabolic targets for cancer therapy. Metabolic anti-cancer drugs which target key enzymes or regulators of hyperactivated metabolic pathways. For example, glutamate metabolism is a promising anticancer therapeutic target with glutaminase inhibitors, BPTES and CB839, show great anticancer effect in several tumor models. Fatty acid synthase inhibitors, mTOR inhibitors and RAS/PI3K/AKT agonists also show significantly efficiency for anti-cancers. PPP, pentose phosphate pathway; PRPP, 5-phosphoribosyl-1-pyrophosphate; GPNA, L-γ-glutamyl-p-nitroanilide; SAM, S-adenosyl-methionine; mTOR, mammalian target of rapamycin; RAS, from "rat sarcoma virus", small GTPase ; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; TCA, tricarboxylic acid.

important therapeutic targets for cancer patients. For instance, increased oxidative phosphorylation drives resistance to BCL-2 inhibition, Venetoclax, a FDA-approved BCL-2 inhibitor for chronic lymphocytic leukemia (CLL) (20) and acute myeloid leukemia (AML) (21). And inhibitors of the ETC complex III (antimycin A) and complex V (oligomycin), can promote Venetoclax sensitivity in CLL patient samples (22), supporting implementation of combinatorial therapy with metabolic modulators to address Venetoclax resistance (22). Moreover, targeting multiple tyrosine kinases in mitochondrial ETC complexes, Sorafenib induced intra-tumoral hypoxia and reactive oxygen species (ROS) production in sorafenib-resistant cells, by upregulated

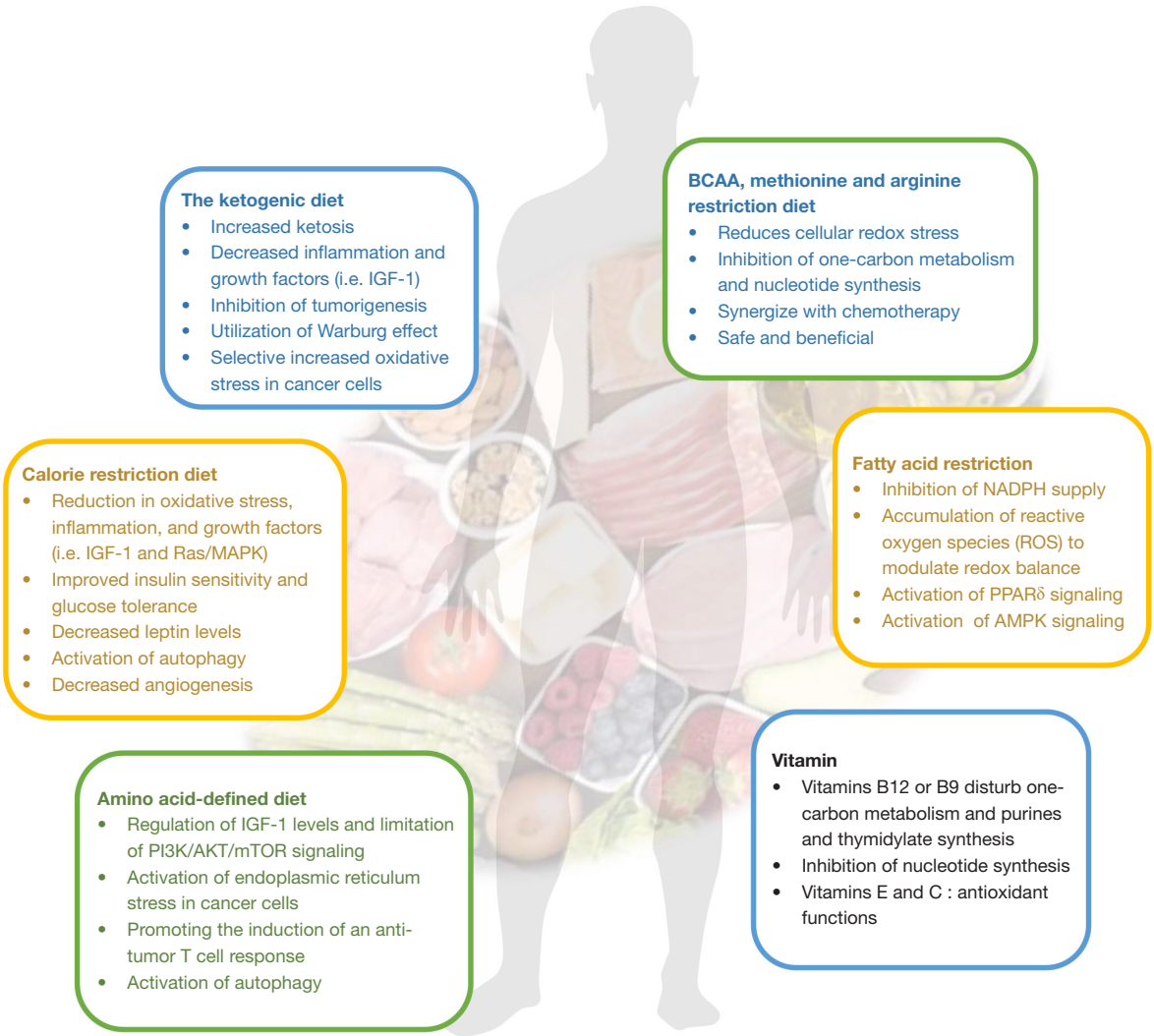

Figure 3 Precision nutrition to fight against cancer. Precision nutrition including vitamin, fatty acid, BCAA, methionine and arginine, these can provide novel strategy to suppress cancer progression such as the CR, the KD, the amino acid-defined diet and so on. Reported benefits are list above and these dietary interventions may provide novel strategy to influence tumor progression. BCAA, branched-chain amino acid; NADPH, nicotinamide adenine dinucleotide phosphate; ROS, reactive oxygen species; PPARδ, peroxisome proliferator-activated receptor delta; AMPK, AMP-activated protein kinase; mTOR, mammalian target of rapamycin; IGF-1, insulin-like growth factor-1; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; CR, calorie restriction; KD, ketogenic diet.

UBQLN1 induced peroxisome proliferator-activated receptor γ coactivator 1β (PGC1β) degradation (23). Furthermore, targeting complex I of ETC, IACS-010759 significantly inhibits tumor growth in ibrutinib-resistant patient-derived cancer models (24). These studies provide a clinically viable approach of subverting therapeutic resistance by targeting cancer mitochondrial oxidative phosphorylation.

Oxidative stress in cancer

Tumor cells continually accommodate to oxidative stress by NADPH production in different ways during tumorigenesis, such as stimulated AMP-activated protein kinase (AMPK) , the pentose phosphate pathway (PPP), and reductive glutamine and folate metabolism (25). Notably, ROS usually work in distinctive ways in tumor initiation, progression, and metastasis (25). On one hand, increased

can only get from diet. BCAA play vital roles in protein synthesis, nutrition metabolism, gut and immune in humans (43). Notably, BCAA metabolism plays critical roles in cancers with hyperactivating RAS signaling. Elevation of circulating BCAA is an early event in human pancreatic adenocarcinoma development (44), majority of which harboring KRAS mutations. Further research revealed that BCAA transaminase 2 (BCAT2)-mediated BCAA catabolism promotes KRAS-driven pancreatic ductal adenocarcinoma (PDAC) development (45). KRAS can inhibit BCAT2 ubiquitylation and degradation to stabilize BCAT2, through mediation of TRIM21 E3 ligase by suppressing SYK induced Y228 phosphorylation. In consistent, BCAT2 is significantly upregulated in human PDAC samples and enhances BCAA uptake in PDAC cells to promote cancer cell growth and survival (45). In addition, another BCAA metabolic enzyme, BCAT1, have emerged as useful prognostic cancer markers. BCAT1 expression commonly correlates with more aggressive cancer growth and progression (46). BCAAs also support cancer growth as a fuel in melanoma, nasopharyngeal carcinoma, and breast cancer. Therefore, targeting BCAT2 or lowering dietary BCAA therefore have promising anti-cancer effect, especially for KRAS-driven cancers like PDAC (45).

One-carbon metabolism

One-carbon (1C) metabolism comprises a series of interlinking metabolic pathways that include the methionine and folate cycles that are central to cellular function, providing 1C units (methyl groups) for the synthesis of DNA, polyamines, AAs , creatine, and phospholipids (47). One-carbon metabolism can also produce glutathione to keep the redox homeostasis in the TME and provides substrates for the methylation reaction (48).

Agents targeting folate metabolism have been widely used in cancer chemotherapy, including two major drug groups: folate antagonists (e.g., methotrexate) and thymidylate synthase inhibitors (e.g., 5-fluorouracil). But in view of the important function of folate to normal cells, the administration of these drugs in cancer chemotherapy can induce a state of acute folate depletion with sometimes life-threatening toxic sequelae (49). Mitochondrial serine catabolism is considered the sole contributor of folate-mediated 1C units in proliferating cancer cells. A recent study report that under physiological folate levels in cell, cytosolic serine-hydroxymethyltransferase (SHMT1) is the predominant source of 1C units in a variety of cancers, while mitochondrial 1C flux is overly repressed (50). Moreover, tumor-specific reliance on cytosolic 1C flux is associated with poor capacity to retain intracellular folates, which is determined by the expression of SLC19A1. This study revealed major diversity in cancer cell utilization of the cytosolic versus mitochondrial folate cycle across tumors and SLC19A1 expression as a marker for increased reliance on SHMT1 (50), providing a possible way to optimize folate drugs for future precise use in cancer.

Methionine is a critical component of one-carbon metabolic network and the primary source for S-adenosyl-methionine (SAM), which is a methyl-donor for histone and DNA methylation. Notably, targeting methionine metabolism influences cancer therapy response. Dietary methionine restriction sensitizes PDX models of colorectal cancer to chemotherapy with 5-FU, and sensitizes mouse models of RAS driven autochthonous sarcoma to radiation (51). Moreover, pharmaceutical inhibition of MAT2A, key enzyme of methionine metabolism, blocks the growth of MTAP-deleted cancer cells by reducing PRMT5-dependent mRNA splicing and inducing DNA damage (52). But not all cancer cells are sensitive to methionine restriction or inhibition of methionine metabolism. MAT2A inhibitors that substantially reduce levels of S-adenosylmethionine (SAM), AGI-24152 and AG-270 significantly reduce proliferation of cancer cells and tumors that lack MTAP (52). And hepatocyte nuclear factor 4α (HNF4α) dictates the sensitivity of liver cancer to methionine restriction. Hepatic sulfur amino acid (SAA) metabolism is under transcriptional control of HNF4α. Knocking down HNF4α or SAA enzymes in HNF4α-positive epithelial liver cancer lines impairs SAA metabolism, increases resistance to methionine restriction or sorafenib, promotes epithelial-mesenchymal transition, and induces cell migration (53).

Serine is an important one-carbon donor to the folate cycle and many cancer cells highly rely on serine for nucleotide synthesis, methylation reactions and the generation of NADPH for antioxidant defence (54). MYCN overexpression in neuroblastoma cells activates the serine-glycine-one-carbon biosynthetic pathway and rely on this way for supplying glucose-derived carbon. Blocking the signaling in MYCN-amplified cell lines with small molecule inhibitors induces metabolic stress and autophagy, which may be exploited as a selective target (55). Moreover, 3-phosphoglycerate dehydrogenase (PHGDH) is recognized as the rate-limiting step during glucose-derived serine synthesis and plays a critical role in brain metastasis

myeloid cell-derived ROS and TNF-α mediated signaling can lead to epithelial mutagenesis and carcinogenesis (26). ROS can affect GAPDH, PKM2, and G6PD activities by coordination with Cys residues oxidation in the ETC within complexes I, III, and IV, resulting in cancer metabolic adaptation (27). On the other hand, oxidative stress modulates gene expression of downstream targets involved in DNA repair, cell proliferation and antioxidants (28). Oxidative stress limits distant metastasis by melanoma cells *in vivo* (29). Melanoma cells in the blood and visceral organs experienced higher oxidative stress than subcutaneous tumors. Successfully metastasizing melanomas underwent reversible metabolic changes during metastasis that increased their capacity to withstand oxidative stress, including increased dependence on NADPH-generating enzymes in the folate pathway. Antioxidants thereby promoted distant metastasis in mice (29). Moreover, high-OXPHOS tumor exhibit chemosensitivity through increased oxidative stress and PML (30). High-grade serous ovarian cancers (HGSOCs) show that chronic oxidative stress promotes aggregation of PML-nuclear bodies and activation of the transcriptional co-activator PGC-1α which increases synthesis of ETC complexes in high-OXPHOS tumors. OXPHOS metabolic heterogeneity in high-OXPHOS tumors, promotes aggregation of PML-nuclear bodies that activate PGC-1α, ETC synthesis, and mitochondrial respiration (30). Therefore, antioxidants need to be used with caution in cancer, depending on the oxidative stress status of cancer.

Many transcription factors (TFs), including nuclear factor erythroid 2-related factor 2 (Nrf2), hypoxia inducible factor 1 α (HIF-1α), activator protein 1 (AP-1), heat shock factor 1 (HSF1), nuclear factor κB (NF-κB) and tumor protein p53 can be activated by ROS and regulate the redox status as feedback (31). Nrf2, a vital regulator in cell signaling transduction, is a highlighted stress-responsive TF and was considered as an antioxidative TF. Nrf2 also regulates metabolic flexibility of cancer cells upon different ROS levels. Nrf2 regulated antioxidant defense is required by activation of the AMPK-HIF-1α signaling in high ROS condition, while Nrf2 was not required in low ROS condition (32). In addition, HIF-1α increases expression of GSH-based antioxidant genes under hypoxic conditions. And chemotherapy including paclitaxel, gemcitabine and carboplatin triggers HIF-1–dependent glutathione synthesis, which induces the enrichment of breast cancer stem cells (33). Collectively, HIF1a-Nrf2 signaling plays critical role in regulating cancer cell adaptation to oxidative stress.

Glutaminolysis and cancer

As the most abundant circulating amino acid (AA) in blood, glutamine plays vital roles in cancer metabolism including synthesis of metabolites that maintain mitochondrial metabolism, balances the redox homeostasis and activation of cell signaling (34). Glutamine is converted to glutamate by glutaminase (GLS). Glutamate is deaminated to α-ketoglutarate (α-KG) by catalyzing of glutamate dehydrogenase (GLUD) or transaminases. α-KG further enter into TCA cycle to produce energy (35). In cancer, glutamine can not only fulfill the TCA cycle to provide energy and intermediate metabolites for fast proliferating cancer cells, but also serve as a signaling molecule to stimulate the mechanistic target of rapamycin complex 1 (mTORC1) pathway and promote cell growth (36). For instance, cancer cells with mutant KRAS can promote glutaminolysis and activate Nrf2 antioxidant signaling to increase tumor progression (37). Accordingly, mitochondria derived ROS are essential for KRAS-induced cell proliferation and tumorigenesis by regulation of the ERK1/2 MAPK pathway in mouse model of lung cancer (38). A recent study suggested that inhibition of glutaminolysis can increase gemcitabine sensitivity in gemcitabine-resistant pancreatic cancer cells (39). And a shift in glutamine nitrogen metabolism contributes to the malignant progression of cancer (40). Therefore, many inhibitors of key enzymes in glycolysis and glutaminolysis pathways has been proven beneficial to in suppression tumor growth in clinical trials (41). Importantly, the SLC1A5 (also known as ASCT2) variant has recently been identified as a mitochondrial glutamine transporter, with a specific mitochondrial targeting sequence induced by HIF-2α. The SLC1A5 variant mediates glutaminolysis and redox regulation in cancer cells. In consistent, SLC1A5 variant knockdown strongly suppressed cancer cell growth in pancreatic cancer (42). Collectively, targeting glutamine metabolism and mitochondrial glutamine transporters may become a new therapeutic strategy for controlling tumor growth.

Branched-chain amino acid (BCAA)

BCAA includes three essential AAs , leucine, isoleucine, and valine, which are not synthesized in humans and

of multiple cancer types. Increased serine synthesis promotes nucleotide production and growth in cancer cells. Therefore, PHGDH inhibitors are potential drugs to treat brain metastasis, which have achieved good efficacy in preclinical models (56). Lastly, MDM2 overexpression mediates serine metabolism to sustain nucleotide synthesis and tumor growth in p53 wild-type liposarcomas. Targeting MDM2 functions in serine metabolism shows a potential therapeutic strategy for liposarcomas (57). All together, altered one-carbon metabolism is essential for cancer cell growth, which provides potential therapeutic targets for cancer treatment.

Immune metabolism and cancer therapy

Metabolism of immune cells can not only influence their differentiation and function, but also regulate cancer progression and cancer therapy response. Almost every immune cell type actively participates in regulation of cancer progression (58-60). On one hand, there is complex tumor-immune crosstalk that can modulate metabolic conditions in the TME (61). For example, the competitive environment of the TME promote TILs to enter an exhausted state. Exhausted $CD8^+$ T (Tex) cells weaken effector function and metabolic dysregulation are up-regulated during chronic infection or cancer (62). Besides, glutamine blockade can promote both increased $CD8^+$ TIL effector function and tumor suppression. Therefore, glutamine antagonism is exploited as a "metabolic checkpoint" to enhances antitumor immune response (63). On the other hand, immune metabolism and improve the efficacy of target immune checkpoint therapy, which has achieved striking clinical breakthrough in cancer immunotherapy in recent years (64-66). NAD^+ replenishment increase the sensitivity of anti-PD-L1 antibody in immunotherapy-resistant tumors (67). Similarly, blocking retinoic acid production can synergize with anti-PD-1 therapy (68). Taken together, immune metabolism is tightly associated with cancer progression and cancer therapy response. Immune checkpoint blockade combination with regulation of metabolic modulators could be effective therapeutic strategy to increase immunotherapy.

Precision nutrition for cancer therapy

Tumor growth and proliferation rely on the nutrients from environment. Therefore, dietary interventions may provide novel strategy to influence tumor progression (*Figure 3*).

Calorie restriction (CR)

CR is a robust environmental intervention known to increase healthy life, prolong lifespan and decrease cancer incidence in mammalians (69). CR inhibits cancer through multiple molecular signaling pathway, mainly including hyperactivation of sirtuins, suppressing LKB1/AMPK and IGF1/PI3K/AKT/mTOR signaling transduction (69). Short-term fasting can also improve anticancer chemotherapy via T cells and autophagy (70). But fasting is difficult for patients, requiring pharmacological agents mimicking caloric restriction. While role of sirtuins vary among different cancer types, metformin and mTOR inhibitors have demonstrated the anti-cancer effect by suppressing the IGF1/PI3K/AKT/mTOR pathway. Caloric restriction mimetics (CRMs) also mimic the biochemical effects of nutrient deprivation by reducing lysine acetylation of cellular proteins, thus triggering autophagy. Short-term fasting or treatment with several chemically unrelated autophagy-inducing CRMs, including hydroxycitrate and spermidine, improved the inhibition of tumor growth by chemotherapy *in vivo*. Notably, this effect was only observed for autophagy-competent tumors, depended on the presence of T lymphocytes, and was accompanied by the depletion of regulatory T cells from the tumor bed (70). In addition, cancer cells with mutations in the PI3K signaling pathway are resistant to the growth inhibitory effects of caloric restriction, and genetically engineering an activating PI3K pathway mutation into cancer cells confer resistance to caloric restriction (71,72).

Fasting-mimicking diet (FMD)

FMD is a straightforward approach in various dietary interventions for cancer therapy, including acute intermittent fasting or short-term fasting. FMD can widely alter growth factors and metabolite levels to improve anti-tumor effect of cancer therapies to keep environments that can reduce the capability of cancer cells to adapt and survive. For example, FMD can increase the anti-tumor effect of tamoxifen and fulvestrant in $HR^+/HER2^-$ breast cancer *in vitro* and *in vivo* (73). FMD can also selectivity reverses vitamin C-induced heme-oxygenase-1 and ferritin activation in KRAS-mutant cancer cells. And the combination of FMD and vitamin C represents a promising therapeutic strategy with low toxicity in KRAS mutated

tumors (74,75). Moreover, fasting or FMD can increase resistance to chemotherapy in normal tissue but not cancer cells. In other words, FMD prevent damage and potentially side effects to normal tissues during clinical treatments (76). Therefore, FMD can synergize with cytotoxic chemotherapy or other antitumor therapies to protect normal tissues from chemotherapy-induced toxicity (77). However, a clinical trial showed the overall no beneficial effect of FMD during chemotherapy in breast cancer patients (77). More research is needed to evaluate the effect of FMD during cancer treatment *in vivo* and to find FMD-based therapeutic combinations.

The ketogenic diet (KD)

The KD, a low-carbohydrate with adequate calories diet, restricts both carbohydrates and protein intake to decrease blood glucose and reduce serum levels of insulin and insulin-like growth factor (IGF)-1, leading to change of glycolysis in tumor and decrease of tumor growth (76,78). Fatty acids from KD can be converted to β-hydroxybutyrate, acetoacetate and other ketones in the liver by β-oxidation. The ketone bodies then circulate in the bloodstream and be transported to acetyl-CoA to participate in the TCA cycle (79). Therefore, KD can provide enough energy for life activities while reduce blood glucose and insulin signaling. As a result, KD show great importance in affecting the efficacy of PI3K inhibitors. PI3K inhibitors suppress glucose uptake, resulting in elevated blood glucose and pancreatic insulin release after drug treatment. The increased levels of insulin in blood reactivates PI3K signaling and increases glucose uptake in the tumor, limits the efficacy of PI3K inhibitors on tumor growth by inhibition of the insulin-PI3K-AKT-mTOR signaling pathways (71,80). Additionally, tumor genetic background can also regulate tumor response to the KD, for example, KD enhances the growth of $BRAF^{V600E}$ melanoma (81,82).

Amino acid-defined diet

AAs play a critical role in tumor survival and growth, including providing carbon sources for the TCA, nitrogen sources for base synthesis, and regulation of redox balance. Targeting amino acid metabolism by depleting circulating blood AAs in dietary has become one of the focuses of modern tumor therapy. For instance, dietary serine and glycine starvation was confirmed to suppress tumor growth in intestinal cancer and lymphoma mouse model (83). Whereas, reducing essential AAs also can disturb the living state of normal tissues, this potential strategy is more suitable for auxotrophic tumors, which relying on the external supply of AAs without the synthesizing of one specific nonessential AA (84).

BCAA includes three essential amino acids, leucine, isoleucine, and valine. BCAA metabolism is mainly carried out in muscle tissue, it is an important nutrient source and catabolized as substrates by highly reversible enzymes (43). Dietary restriction of BCAA inhibits the resistance of insulin in obese mice treated with high fat/high sugar (85), and limit the development and progression of some tumors (46), like liver cancer development (86) and KRAS-driven PDAC (45).

Methionine deprivation can reduce cellular redox stress (87), inhibit one-carbon metabolism and nucleotide synthesis (51). Dietary methionine restriction to enhance anti-tumor effect was demonstrated in various cancer cells and mouse models (88). Methionine-restricted diet also can synergize with various chemotherapies and radiotherapy (89,90). Moreover, synergies between methionine restriction and 5-fluorouracil, the inhibitor of one-carbon metabolism is demonstrated in many studies (91,92). Notably, methionine restriction is not beneficial for all cancer. And tumors that lack MTAP (52) and HNF4α (53) dictates the sensitivity of liver cancer to methionine restriction. In these studies, methionine restriction is a safe and beneficial way to fight with cancer.

Arginine is a nonessential AA required for protein synthesis, participating in nitric oxide production and the synthesis of nucleotides, polyamine, creatine, proline, glutamate, or urea. Arginine limitation is advantageous to tumor cells, allowing cytosolic aspartate used for pyrimidine production to take part in RNA and DNA synthesis (93). For example, arginine deficiency therapy is worked well in small-cell lung cancers driven by MYC (94). Arginine restriction by ADI-PEG20 treatment has been proved to synergize with chemotherapy in sarcoma (95). Therefore, tumor cells with metabolic defect become dependent on an exogenous arginine supply, a vulnerability that can be exploited for therapy.

Fatty acid restriction

Aberrant lipid metabolism occurs in many human cancers. Fatty acid oxidation (FAO) has been reported to be preferred and activated in breast cancer (96,97), such as in

MYC-overexpressing triple-negative breast cancer (98), and CPT1C overexpression cancers (99). NADPH is a key metabolite in redox balance and FAO can produce NADPH to keep cancer cells survival under metabolic stress. Inhibition of FAO can accumulate ROS and reduce tumor growth in glioma cells (100). And tumor cells can keep their rapid proliferation state with NADPH supply through AMPK signaling (101). Therefore, high-fat diet (HFD) can increase the risks of adenomas and carcinomas in the intestine. And HFD increase aberrant proliferation in xenograft by activation of PPARδ (102). Consistently, a low-fat diet (LFD) is reported can prolong the survival of obese leukemia-bearing mice by inhibition of FAO in mouse model (103). Restriction of nutritional fatty acids may be a potential therapy to starve some cancers (104).

Vitamin

Vitamin deficiencies have been linked to the development of certain cancers (105). For example, vitamin B12 or B9 restriction can disturb one-carbon metabolism and purines and thymidylate synthesis (88). Limitation of vitamins B12 or B9 can impede cancer progression (106). Vitamins B9 also named folate is an essential vitamin for nucleotide synthesis and is essential for cell proliferation, especially for rapidly proliferating intestinal epithelial cells, hematopoietic cells and tumor cells. Combination with dietary uridine supplementation, folate restriction decrease the growth of intestinal tumors in $Apc^{min/+}$ mice (107). In addition, vitamins E and C as dietary supplements can suppress cancer development due to their antioxidant functions (108,109). Intravenous vitamin C selectively kills KRAS and BRAF mutant colorectal cancer cells by targeting GAPDH (108), providing a mechanistic rationale for exploring the therapeutic use of vitamin C for CRCs with KRAS or BRAF mutations (108). High-dose vitamin C also enhances cancer immunotherapy (110). Vitamin C not only enhances the cytotoxic activity of adoptively transferred CD8 T cells but also cooperates with immune checkpoint therapy in several cancer types (110).

Taken together, diet-mediated changes in whole-body metabolism and systemic nutrient availability can influence the microenvironment and macroenvironment of cancer cells. Precise dietary interventions provide new approaches to help cancer patients fight against cancer.

Metabolic imaging and precise cancer management

Glucose metabolism imaging and cancer management

Hyperactivated glycolysis exist in many solid tumors. Accordingly, ^{18}fluorodeoxyglucose (^{18}F-FDG) PET/CT to detect tumor glucose uptake and glycolysis status has been widely used in cancer management. In addition to sensitive detection of primary tumor lesions, the powerful function of ^{18}F-FDG PET/CT in detecting whole-body lymphoid nodes and distant metastasis makes it widely used in cancer stage evaluation, therapy response monitoring, prognosis prediction, and radiotherapy planning for multiple cancer types. Notably, early changes of ^{18}F-FDG-PET maximum standardized uptake value (Δ^{18}F-FDG-PET SUVmax) upon cancer treatment can not only serve as nonspecific responses biomarker to chemotherapy, but also as specific responses biomarker to targeted therapy that regulates glucose metabolism like PI3K inhibitors (111). Therefore, ^{18}F-FDG PET/CT greatly improves clinical decision-making for physicians, as well as diagnosis and treatment for cancer patients.

Glutamine imaging and brain tumor management

Despite that ^{18}F-FDG PET imaging has valuable implications in most solid tumor management, ^{18}F-FDG is ineffective in evaluating gliomas because of high background uptake in the brain (112). Glutamine addiction, known as a high rate of glutamine consumption normally exceeding cellular biosynthetic and energetic needs, significantly exists in brain tumor cells (113), and is dispensable for glioma cell growth (114). Importantly, PET imaging *in vivo* with the glutamine analogue 4-18F-(2S,4R)-fluoroglutamine (^{18}F-FGln) shows high uptake in gliomas but low background brain uptake, facilitating clear tumor delineation (112). Chemo/radiation therapy reduced ^{18}F-FGln-tumor avidity, corresponding with decreased tumor burden. ^{18}F-FGln also showed high tumor/background ratios with minimal uptake in the surrounding brain in human glioma patients with progressive disease (112). A clinical trial further assessed the clinical safety, pharmacokinetics, and tumor imaging characteristics of ^{18}F-FGln (115). FGln PET depicted tumors of different cancer types (breast, pancreas, renal, neuroendocrine,

lung, colon, lymphoma, bile duct, or glioma) in 17 of the 25 patients, predominantly clinically aggressive tumors with genetic mutations implicated in abnormal glutamine metabolism (115). These studies demonstrated that ^{18}F-FGln is avidly taken up by gliomas, and could serve as a valuable tool in the clinical management of gliomas.

Metabolic imaging for prostate cancer management

The use of ^{18}F-FDG PET imaging in prostate cancer depends on the phase of the disease (116). In general, FDG uptake level significantly overlap among normal, benign, and malignant tissues in prostate cancer (116). PET with FDG may be useful in detecting metastasis and treatment response assessment for patients with castrate-resistant metastatic prostate cancer (116). Instead, newer tracers have increased detection accuracies for prostate cancer, including prostate-specific membrane antigen (PSMA)-PET, choline-PET, and ^{18}F-NaF PET/CT (117). Specifically, choline PET/CT has high sensitivity but suffers from low sensitivity, especially at low PSA levels. Nevertheless, choline PET/CT was found to significantly improve upon conventional imaging modalities in the detection of metastatic lesions at biochemical recurrence (117). And PSMA-targeted radiotracers have preliminarily demonstrated great promise in primary and recurrent staging of prostate cancer (117).

Conclusions

Metabolic reprogramming is critical for tumorigenesis and cancer cell adaptation. But cancer metabolic reprogramming is highly heterogeneous and dynamic. Therefore, a deep understanding of cancer metabolic reprogramming is required to target cancer metabolism for precise medicine. To cancer therapy, targeting metabolic reprogramming provides three major approaches to help fight against cancer (*Figure 1*). (I) Metabolic anti-cancer drugs to target key enzymes or regulators of hyperactivated metabolic pathways (*Figure 2*). For example, glutamate metabolism is a promising anticancer therapeutic target with glutaminase inhibitors, BPTES and CB839, show great anticancer effect in several tumor models (118). (II) Metabolic modulators to synthesize chemotherapy, radiotherapy and immunotherapy. (III) Dietary interventions to suppress cancer progression (*Figure 3*). While to cancer monitoring, rewiring cancer metabolism enables metabolic imaging to detect tumor early response to different anti-cancer therapies. And accurate cancer subtyping based on metabolic pathway alterations help select beneficiaries to anti-cancer drugs. For instance, on the basis of metabolic pathways, triple negative breast cancer cells can be classified into the lipogenic subtype with upregulated lipid metabolism, the glycolytic subtype with upregulated carbohydrate and nucleotide metabolism, and mixed subtype (119). Interestingly, three subtypes show distinct sensitivities to various metabolic inhibitors, and inhibition of lactate dehydrogenase could enhance the anti-PD-1 immunotherapy response in the glycolytic subtype of TNBC (119). Therefore, integration of metabolic characteristic and metabolic imaging could guide the precise usage of anti-cancer drugs.

Despite of the achievements about targeting cancer metabolism mentioned above, cancer metabolic heterogeneity need be carefully considered when targeting cancer metabolism for clinical translation. Moreover, metabolic dynamic changes are ignorable during tumor progression, accompanying with genetical dynamic changes. Increasing studies have shown that the process of metabolic reprogramming is highly dynamic (2). Furthermore, identification of metabolic checkpoints between normal cells and cancer cells with various genetic mutations is essential for reducing toxic side effects of metabolic anti-cancer strategies. Further research and deeper understanding on the metabolic network and dynamic regulation are required to enhance the implication of cancer metabolism. These insights have the potential to provide new effective therapeutic and monitoring approaches for cancer precision medicine.

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