Metabolic Strategies for Inhibiting Cancer Development

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ABSTRACT

The tumor microenvironment is a complex mix of cancerous and noncancerous cells (especially immune cells and fibroblasts) with distinct metabolisms. These cells interact with each other and are influenced by the metabolic disorders of the host. In this review, we discuss how metabolic pathways that sustain biosynthesis in cancer cells could be targeted to increase the effectiveness of cancer therapies by limiting the nutrient uptake of the cell, inactivating metabolic enzymes (key regulatory ones or those linked to cell cycle progression), and inhibiting ATP production to induce cell death. Furthermore, we describe how the microenvironment could be targeted to activate the immune response by redirecting nutrients toward cytotoxic immune cells or inhibiting the release of waste products by cancer cells that stimulate immunosuppressive cells. We also examine metabolic disorders in the host that could be targeted to inhibit cancer development. To create future personalized therapies for targeting each cancer tumor, novel techniques must be developed, such as new tracers for positron emission tomography/computed tomography scan and immunohistochemical markers to characterize the metabolic phenotype of cancer cells and their microenvironment. Pending personalized strategies that specifically target all metabolic components of cancer development in a patient, simple metabolic interventions could be tested in clinical trials in combination with standard cancer therapies, such as short cycles of fasting or the administration of sodium citrate or weakly toxic compounds (such as curcumin, metformin, lipoic acid) that target autophagy and biosynthetic or signaling pathways. *Adv Nutr* 2021;12:1461–1480.

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Introduction

The incidence of various cancers [colorectal cancer (CRC), hepatocellular carcinoma (HCC), etc.] is strongly correlated with metabolic disorders such as diabetes, fatty liver disease, and obesity; hence, counteracting these conditions is mandatory for the prevention of cancer and the optimization of treatment (1). The metabolism of cancer cells differs from that of normal cells due to epigenetic defects, gene mutations, and metabolic reprogramming, resulting in the upregulation of oncogenic proteins and signaling pathways, and the inactivation of key suppressors such as tumor protein 53 (TP53) (2, 3). Current anti-cancer treatments (chemotherapy, immunotherapy, and targeted therapies) that target a specific aspect of cancer cell development, such as uncontrolled replication or deregulated molecular pathways,

frequently show poor or transient efficacy, thus emphasizing the need for new strategies. Current research is focused on the interaction between the intrinsic metabolism of cancer cells, the tumor microenvironment (TME), and the host to develop strategies needed to improve standard therapies. This review aims to clarify current issues (summarized in **Figure 1**), presenting their rationales, proof of concepts, limits, and drawbacks.

Current Status of Knowledge

Cancer cell metabolism

The Warburg effect.

Cancer cells display enhanced glucose uptake and convert a significant amount of glucose into lactic acid, even in

the presence of oxygen. In this so-called "Warburg effect" (4), a substantial part of glycolysis intermediates sustains biosynthesis processes. Inappropriate expression of pyruvate kinase (PK) in its PK muscle embryonic isozyme 2 (PKM2) embryonic dimeric form (less active than the adult tetrameric form) creates a bottleneck at the end of glycolysis, thus promoting the accumulation of glycolytic intermediates upstream. Therefore, the main branched pathways of glycolysis are promoted, in particular, the hexosamine biosynthetic pathway (HBP), the pentose phosphate pathway (PPP), the glycerol pathway, and the serine-glycine-folate-methionine pathway (SGFMP) (5) (**Figure 2**). Of note, the oxidative PPP generates reduced $NAD(P)H H^+$, which is required for redox balance, nucleotides, and fatty acid (FA) synthesis (FAS) (6).

Abnormal glucose consumption by cancer cells also sustains fast ATP production. Glycolysis is regulated by phosphofructokinase-1 (PFK1), the activity of which is stimulated by low cytosolic concentrations of ATP, citrate, and basic intracellular pH induced by decreased mitochondrial functioning (7). The extracellular acid pH favors cancer invasiveness and resistance to chemotherapy (CT) (7).

From a molecular point of view, the Warburg effect is related to pyruvate dehydrogenase (PDH) inhibition by pyruvate dehydrogenase kinase 1 (PDK1), a process promoted by hypoxia-inducible factor 1 alpha (HIF-1α) and protein kinase B (PKB or AKT) (2). Several oncogenes, in particular the myelocytomatosis viral oncogene (*MYC*) and the Kristen rat sarcoma viral oncogene homolog (*RAS*), promote HIF-1α and the Warburg effect, a reductive metabolism also sustained by signaling pathways such as phosphoinositide-3-kinase–PKB/Akt (PI3K-PKB/Akt), and mammalian target of rapamycin (mTOR) (8–11). Concomitantly, key suppressors,

such as *TP53*, inhibiting glycolysis, and phosphatase and tensin homolog (*PTEN*), inhibiting PI3K/AKT/mTOR, are inactivated (8–11). Key oncogenic drivers involved in cancer cell metabolism reprogramming are listed in **Table 1**.

Importantly, lactate excreted in the TME by monocarboxylate transporter (MCT) 4 (MCT4) promotes invasiveness and angiogenesis and suppresses the immune response (12, 13). Aerobic glycolysis is associated with concomitant mitochondria downregulation, a process that limits the production of reactive oxygen species (ROS) and allows active cell proliferation (14).

In summary, the Warburg effect is associated with resistance to apoptosis, CT, and radiotherapy (RT). A high uptake of 18F-fluoro-2-deoxyglucose (18F-FDG) in positron emission tomography/computed tomography scanning reflects an increase in glucose consumption in the tumor, and correlates with higher resistance to treatment and poor survival (15). Therefore, the high reliance on glycolysis can constitute a vulnerability in many aggressive cancer cells, which is especially important to target.

Glutaminolysis.
Glutamine metabolism provides the molecules and amine groups for nucleotide synthesis, in particular during the S phase progression (16), and reloads the tricarboxylic acid (TCA) cycle into α-ketoglutarate (AKG), a molecule derived from glutamate. Glutamine can also sustain lipid synthesis, by supporting citrate formation either by the TCA cycle or by a pathway involving the carboxylation of AKG and a reverse isocitrate dehydrogenase (IDH) reaction (9). Therefore, glutaminase 1, regulating the conversion of glutamine to glutamate, appears to be a key target for specific inhibition.

ATP citrate lyase links glycolysis with de novo lipid synthesis.
ATP citrate lyase (ACLY) has a pivotal role in cancer cell metabolism because its activity links glycolysis and/or glutaminolysis with lipid and sterol synthesis, protein acetylation, isoprenylation, and glycosylation of proteins (17). ACLY converts citrate into acetyl-CoA and oxaloacetate (OAA). Acetyl-CoA sustains histone acetylation allowing transcription (18) and/or the de novo FAS required for membrane replication and the modification of proteins. Acetyl-CoA carboxylase (ACC) catalyzes and regulates the first step of FAS, a pathway sustained by fatty acid synthase (FASN) and leading to palmitate (19). Although palmitate, the most common FA in the human body (20–30% of total FAs), can be provided by the diet, most cancer cells synthesize de novo palmitate and FA independently of nutrient availability (19).

OAA can undergo a transamination reaction to form aspartate, a molecule required for nucleotide and polyamine synthesis. OAA metabolism also sustains the regeneration of pyruvate by the malic enzyme (ME) reaction. This reaction regenerates $NADPH H^+$, a cofactor required for FAS and nucleotide synthesis, and the regeneration of reduced glutathione, an antioxidant molecule. Pyruvate
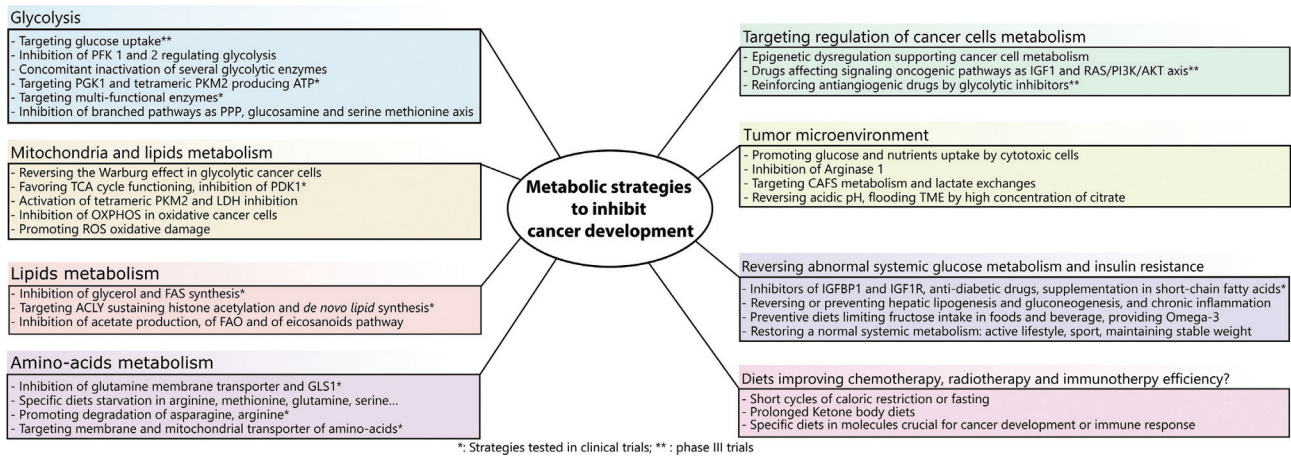
FIGURE 1 Key figure summarizing the different metabolic strategies which enable inhibition of cancer development.

can sustain lactate production, the TCA cycle, or gluconeogenesis. Opened by pyruvate carboxylase (PC), this later pathway is truncated in cancer cells because fructose-1,6-bisphosphatase (FBPase; regulating the exit) is inactivated, in particular, because of a low citrate concentration, a physiological activator of FBPase (20). Thus, in cells lacking glucose, PC redirects the carbon flux from the glutaminolysis and/or β-oxidation of FAs (FAO) toward gluconeogenesis sustaining nucleotide synthesis.

Cancer cell metabolism is not inherently glycolytic.
Several studies have demonstrated that numerous cancer cells may rely on predominant oxidative or intermediate metabolism (21–23). In particular, the lactate that is released by cancer cells expressing MCT4 can be assimilated by cells expressing MCT1. In these cells, lactate is recycled as fuel for mitochondrial oxidation after conversion into pyruvate by reversed lactate dehydrogenase-5 (LDH-5) functioning (22, 24). This mode of ATP production can efficiently support the metabolism of oxidative cancer cells and immune-suppressive cells, a glucose-sparing process for cancer cells relying on dominantly glycolytic metabolism (25).

Furthermore, cells growing in a lipid-rich environment (such as ovarian cancer cells, triple-negative breast cancer cells) can be supported by active FAO (26, 27). Cancer stem cells frequently show both glycolytic and mitochondrial functioning (28), increasing their survival and maintaining their stemness properties by the upregulation of FAO (29).

Targeting cancer cell metabolism
The inhibition of metabolic pathways is a promising strategy to inhibit growth of cancer cells and enhance the efficacy of current therapy.

Inhibition of aerobic glycolysis.
Glucose uptake can be targeted by inhibitors of glucose transporter 1 (GLUT1) (30) or hexokinase 2 (HK2) (31,

32). Theoretically, the inactivation of 1 of the 10 glycolytic enzymes may disrupt glycolysis [for lists of inhibitors, see Akins et al. (33), Abdel-Wahab et al. (34), and **Table 2**]. Targeting PFK1, the key regulatory enzyme of glycolysis, as well as GAPDH, a limiting enzyme at the end of glycolysis (because its functioning requires NAD^+), provides a rational strategy to limit glycolytic flow. Similar considerations apply to the inhibition of the 2 enzymes sustaining ATP production [phosphoglycerate kinase 1 (PGK1) and tetrameric PKM2], since their blockade may cause an energy crisis leading to cell death in clones that are strongly reliant on glycolysis (35). The inhibition of branched pathways can be attempted to counterbalance the nucleotide and polyamine biosynthesis required for cell growth: *1*) HBP sustaining protein glycosylation (required for transcription, epigenetics, signaling, and bioenergetics) can be inhibited by quercetin, a natural flavonoid (36); *2*) oxidative PPP can be targeted by glucose 6-phosphate dehydrogenase (G6P) inhibition, and nonoxidative PPP by transketolase 1 (TKL1) inactivation (37); *3*) SGFMP can be targeted by the concomitant inactivation of PGK1 and phosphoglycerate dehydrogenase (PHGDH) regulating this pathway (38). Targeting the entrance and exit of aerobic glycolysis is particularly effective as shown by the concomitant inhibition of glucose-6-phosphate isomerase (GPI), LDH-5, and lactate export regulated by MCT1/4 (39). Pan glycolytic inhibitors could be particularly effective as the alkaline agent 3-bromopyruvate (3-BP), targeting several enzymes such as HK2 and PKM2 (40). However, to date, its toxicity has not been determined in phase 1 studies.

Most notably, several enzymes such as PKM2, GAPDH [and also 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3) promoting PFK1 activity] display nonglycolytic functions, promoting cell cycle progression by periodical translocation (directly or through their products) into the nucleus [for review, see Icard et al. (41)]. Hence, pharmacological inhibition of these multifunctional enzymes can be particularly effective in
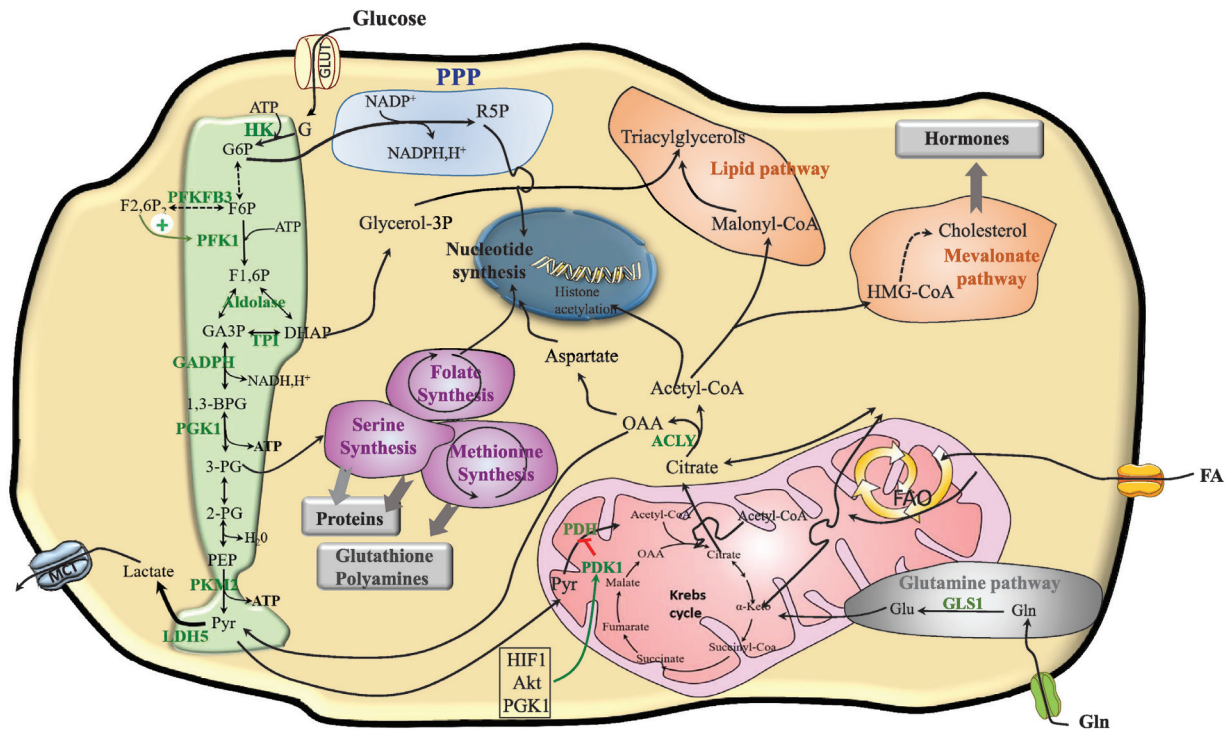
FIGURE 2 The metabolism of cancer cells relying on the Warburg effect. Cancer cell metabolism is supported by glycolysis, glutaminolysis, and/or FAO. Glycolysis is enhanced: PFK1 is promoted by F2,6P produced by PFKFB3. Dimeric embryonic PKM2 creates a bottleneck at the end of glycolysis promoting branched pathway activities: PPP provides R5P for nucleotide synthesis, the DHAP pathway provides G3P for triglyceride synthesis, and SGFMP sustains protein and glutathione synthesis, as well as one-carbon metabolism required for methylation processes (in particular of epigenome and genome), and for polyamine formation. The Warburg effect is related to PDH inhibition by PDK1, a process stimulated by HIF1 and AKT. Lactate produced by LDH5 is expulsed by MCT4. Due to PDH inactivation, acetyl-CoA is produced by FAO or derives from oxidation of AKGα, which enters the Krebs cycle (also named the TCA cycle). Cytosolic citrate derives from mitochondrial export or from carboxylation of AKG deriving from glutaminolysis. ACLY transforms citrate into OAA and acetyl-CoA. Acetyl-CoA sustains lipid synthesis and histone acetylation while OAA sustains aspartate synthesis or pyruvate and lactate formation. Glycolysis is green, PPP is blue, amino acid synthesis is purple, lipid and hormone pathways are orange, and the glutamine pathway is gray. ACLY, ATP citrate lyase; AKG, α-ketoglutarate; Akt, protein kinase B; DHAP, dihydroxyacetone phosphate; FA, fatty acids; FAO, fatty acid β-oxidation; F6P, fructose 6-phosphate; F1,6P, fructose-1,6-bisphosphate; F2,6BP, fructose-2,6-biphosphate; G, glucose; G6P, glucose 6-phosphate; GA3P, glyceraldehyde 3-phosphate; GLS1, glutaminase 1; GLUT1, membrane glucose transporter 1; Glycerol-3P, glycerol-3-phosphate; HIF1α, hypoxia inducible factor 1 alpha; HK, hexokinase; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; LDH5, lactate dehydrogenase 5; MCT, monocarboxylate transporter; NADPH,H$^+$, nicotinamide adenine dinucleotide phosphate; OAA, oxaloacetate; PDH, pyruvate dehydrogenase; PDK1, pyruvate dehydrogenase kinase 1; PEP, phosphoenolpyruvate; PFK1, phosphofructokinase 1; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PGK1, phosphoglycerate kinase 1; PK, pyruvate kinase; PKM2, embryonic pyruvate kinase; PPP, pentose phosphate pathway; R5P, ribose 5-phosphate; SGFMP, serine-glycine-folate-methionine pathway; TCA, tricarboxylic acid; TPI, triosephosphate isomerase; 2-PG, 2 phosphoglycerate; 3-PG, 3 phosphoglycerate; 1,3-BPG, 1,3-bisphosphogylcerate.

reinforcing cyclin-dependent kinase (CDK) inhibitors. For example, GAPDH sustains entrance in mitosis (42), and therefore its inactivation could reinforce inhibitors of CDK1, aurora kinase, and polo-like kinase 1, regulating cell cycle progression toward mitosis. The efficiency of anti-angiogenic drugs could also be increased by glycolysis inhibitors. Indeed, the benefit of anti-angiogenic therapy is generally short-term in both preclinical models and clinical trials, because these agents induce chronic hypoxia in tissues, which favors the emergence of high glucose-dependent phenotypes through HIF-1 activation and/or possibly the selection of pre-existing resistant cancer clones (43).

Modulation of mitochondrial functioning and autophagy. Promoting mitochondrial activity can reverse the Warburg effect, counteracting tumor progression (44). This can be obtained by redirecting the glycolytic carbon flux toward mitochondria through the promotion of PKM2 tetrameric functioning (45) and/or PDH activity either by lipoic acid (46) or dichloroacetate [a molecule reversing the inhibition of PDK1 (47)]. The inhibition of lactate production, export, or recycling can also favor the reactivation of mitochondrial functioning (39).

However, promoting oxidative functioning can be deleterious, particularly if it stimulates: *1*) the activity of mutated

TABLE 1 Key oncogenic drivers and signaling pathways involved in cancer cell metabolism[1]

Pathway (reference)	Anomaly	Target	Effect
PI3K-AKT-mTOR (48–50)	Activation	↑PDK1 ↑GLUT1 (51) ↑HK2 (51) ↑SREBP Induction of HIF-1	Stimulation of glucose transport and glycolysis Increased FAS Suppression of autophagy with increased net protein synthesis
RAS-RAF-MEK-MAPK (52)	Activation	Induction of HIF-1	Increased glucose transport Inhibition of OXPHOS Increased FAS
PTEN (51)	Loss	Activation of AKT	Stimulation of glucose transport and glycolysis Increased FAS
HIF-1 (49, 53, 54)	Increase	↑GLUT1 (51) ↑HK2 (51) ↑PDK1 ↑SREBP ↑SHMT2	Increased glucose transport Inhibition of OXPHOS Increased FAS Serine-glycine conversion and increased one-carbon metabolism
c-MYC (55, 56)	Amplification	↑GLUT1 (51) ↑LDH-A ↑SHMT2 ↑HK2 (51) ↑PFK1 ↑MCT4 ↑OXPHOS	Stimulation of glucose transport and glycolysis Increased lactate synthesis and extrusion Increased GLUT1 (51) glutaminolysis Increased FAO Serine-glycine conversion and increased one-carbon metabolism
p53 (57–59)	Loss/inactivation	↓TIGAR (51) ↑PGM ↓OXPHOS ↑G6PD ↑SREBP	Stimulation of glucose transport and glycolysis Increased PPP Increased FAS
LKB1/AMPK (60, 61)	Loss/inactivation	Activation of mTOR and HIF1 Inhibition of p53 ↓OXPHOS ↑SREBP	Stimulation of glycolysis Increased oxidative stress during glucose deprival Increased FAS
STAT3 (62)	Activating mutation	Induction of HIF-1 ↑PDK1 ↓OXPHOS	Increased glucose transport Inhibition of OXPHOS Increased FAS

[1] AKT, protein kinase B; AMPK, AMP-activated protein kinase; c-MYC, c-myelomatosis viral oncogene; FAO, fatty acid oxidation; FAS, fatty acid synthesis; GLUT1, glucose transporter 1; G6PD, glucose-6-phosphate 1-dehydrogenase; HIF-1, hypoxia-inducible factor; HK2, hexokinase 2; LDH-A, lactate dehydrogenase A; LKB1, liver kinase B1; MAPK, mytogen-activated protein kinase; MCT4, monocarboxylate transporter 4; MEK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; OXPHOS, oxidative phosphorylation; PDK1, pyruvate dehydrogenase kinase 1; PFK1, phosphofructokinase 1; PGM, phosphoglycerate mutase; PI3K, phosphatidylinositol-3-kinase; PPP, pentose phosphate pathway; PTEN, phosphatase and tensin homolog; RAF, rapidly accelerated fibrosarcoma; RAS, Kristen rat sarcoma viral oncogene homolog; SHMT2, serine hydroxymethyltransferase; SREBP, sterol regulatory element-binding protein; STAT3, signal transducer and activator of transcription 3; TIGAR, tumor protein 53–induced glycolysis and apoptosis regulator.

enzymes in the TCA cycle, with overproduction of molecules acting as oncometabolites (such as succinate and fumarate), which alter the methylation of the genome and promote resistance to CT (63), and *2)* the mobility of some cellular subclones as shown in breast cancer models (64, 65), probably by increasing ROS production because high concentrations of ROS play a major role in the metastatic process (66). Importantly, metformin could limit ROS production by inhibiting the complex I of oxidative phosphorylation (OXPHOS) (67), a major source of ROS, with complex III.

However, the benefit of metformin is controversial [as shown in renal cancer (68)], probably because this molecule can activate the key sensor of energy, AMP-activated protein kinase (AMPK), which might favor cell survival in some contexts (69). Indeed, AMPK promotes ATP generation by several processes favoring survival, such as *1)* FAO activation (70), *2)* mitochondrial biogenesis through activation of

the peroxisome proliferator-activated receptor γ coactivator (PGC)-1α (71), *3)* and autophagy, providing molecules for catabolic pathways and thus an energy supply to endure metabolic and cytotoxic stress (72). Autophagy is a cellular process that recycles damaged organelles, superfluous proteins, and lipids. Initially regarded as a cancer-suppressive mechanism, autophagy is now most often considered to be a survival process, which allows cancer cells, especially "autophagy-dependent" cells such as *RAS*-induced lung cancer cells (73), to overcome stressful conditions such as exposure to CT (74, 75).

The complex mechanisms supporting autophagy include preserving the quality and abundance of mitochondria. Autophagy is regulated by the mammalian ortholog of the yeast autophagy-related gene 6 (*ATG6/BECN1*) and *TP53*, which enhances mitochondrial function and ATP production (75). Combining autophagy inhibitors (such as

TABLE 2 List of metabolic inhibitors tested in preclinical models[1]

Main targeted pathways	Metabolic inhibitors tested in vitro (reference)	Metabolic inhibitors tested in vivo	Experimental tumor type
Glycolysis			
GLUTs	Fasentin (76)	Ritonavir (78)	Breast cancer
	STF-31 (77)	Silybin (79)	Bladder cancer
		Phloretin (80)	Breast cancer
		WZB-117 (81)	NSCLC
HK2	Astragalin (82)	Lonidamine (84)	Prostate and ovarian cancers
	Resveratrol (83)	2-Deoxyglucose (85)	Breast and prostate cancers
		Genistein (86)	HCC
		Benserazide (87)	CRC
PFK1	Oxamate (88)	Sulforaphane (89)	Triple-negative breast cancer
PFK2/PFKFB3		Citrate (90)	Pancreatic cancer
GAPDH		PFK158, 3PO (91)	Ovarian and cervical cancers
PKM2		3-Bromopyruvate (92)	Gastric cancer
LDH-A		Apigenin (93)	HCC
		FX11 (94)	Esophageal cancer
IGF signaling			
IGF-1R/IR	NVP-AEW541 (95)	BMS-754807 (98)	Pancreatic cancer
	BMS-536924 (96)	GSK1904529A (99) GSK1838705A	Osteosarcoma
	AG-1024 (97)	(100)	Glioma Rhabdomyosarcoma
		Picropodophyllin (101)	Glioma
		PQ 401 (102)	
Mitochondrial functioning			
PDK1	—	Dichloroacetate (103)	NSCLC
PDH	—	Lipoic acid (PDH activator) (104)	Breast cancer
OXPHOS inhibition	Niclosamide (105)	Gamatrinib (106)	Prostate cancer
Complex I	Menadione (107)	Metformin (108)	CRC
		Phenformin (109)	Ovarian cancer
Complex II (or SDH)	3-Bromopyruvate (110)	—	—
Complex III	—	Antimycin A (111)	Lung cancer
Complex V	Oligomycin (112)	Bedaquiline (113)	Lung cancer
Mitochondrial biogenesis	Doxycycline Tetracycline (114, 115)	Azithromycin (116)	CRC
Lactate exchanges			
MCT1	—	AZD-3965 (117)	Burkitt's lymphoma
Amino-acid metabolism			
ASCT2 (SLC1A5)	Benzylserine (118)	V-9302 (119)	CRC
		GPNA (120)	NSCLC
GLS1	Acivicin (121)	CB-839 (123)	NSCLC
	Zaprinast (122)		
IDH	—	Ivosidenib (IDH1) (124)	AML
		Enasidenib (IDH2) (125)	AML
Lipid metabolism			
CPT1	Etoximir (126)	Avocatin B (127)	AML
ACLY	Cucurbitacin B (128)	Hydroxycitrate (129)	NSCLC
			Bladder cancer and melanoma
FAS inhibition	Orlistat (130)	Epigallocatechin-3-gallate (131)	Breast cancer
		Cerulenin (132)	CRC
Mevalonate and cholesterol	—	Statins (133)	Ovarian cancer
Redox homeostasis			
Antioxidants inhibition	Auranofin (134)	Disulfiram (135)	Testicular cancer
		Arsenic trioxide (136)	HCC
		Gossypol (137)	HNC
Glutathione biosynthesis	Imexon (138)	Buthionine sulfoximine (139)	Lung cancer

[1] ACLY, ATP citrate lyase; AML, acute myeloid leukemia; CRC, colorectal cancer; FAS, fatty acid synthesis; GLS1, glutaminase 1; GLUT, glucose transporter; GPNA, L-γ-glutamyl-p-nitroanilide; HCC, hepatocellular carcinoma; HK2, hexokinase 2; HNC, head and neck carcinoma; IDH, isocitrate dehydrogenase; IGF, insulin-like growth factor; LDH-A, lactate dehydrogenase A; MCT1, monocarboxylate transporter 1; NSCLC, non–small cell lung carcinoma; OXPHOS, oxidative phosphorylation; PDH, pyruvate dehydrogenase; PDK1, pyruvate dehydrogenase kinase 1; PFK, phosphofructokinase; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3; PFK158, 1-(4-pyridinyl)-3-(2-quinolinyl)-2-propen-1-one; SDH, succinate dehydrogenase; V-9302, 2-amino-4-bis(aryloxybenzyl)aminobutanoic acid; 3PO, 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-one.

chloroquine) with glycolysis and/or OXPHOS inhibitors (such as metformin or curcumin) can result in anti-cancer activity as shown in studies in vitro and in vivo, probably by depriving cancer cells of energy (140). Curcumin has demonstrated multiple anti-cancer mechanisms, and in association with metformin can result in a synergistic effect by suppressing signaling pathways that promote glycolysis such as PI3K/AKT/mTOR and epidermal growth factor receptor/signal transducer and activator of transcription 3 (EGFR/STAT3) (141, 142). Metformin is currently being tested in trials with chloroquine in solid cancers with *IDH* mutated genes (high-grade chondrosarcoma, glioma, and intrahepatic cholangiocarcinoma) (143). Metformin is also currently being tested with *EGFR* tyrosine kinase inhibitors in advanced or metastatic non–small cell lung cancer (NSCLC) with *EGFR* mutations (NCT01864681).

Inhibition of amino acid and FA metabolism (uptake and transformation).

L-Asparaginase dramatically improved the treatment of acute lymphoblastic leukemia by transforming L-asparagine (an essential molecule for these cells) into aspartate and ammonia ($NH4^+$) (144, 145). Thus, dietary deprivation of specific amino acids, and inhibition of membrane transporters, can be efficient in counteracting cancer cell growth.

For example, glutamine starvation can inhibit the proliferation of cancer cells, especially those that are highly consuming of this amino acid. Platinum-resistant ovarian and lung cancer cells (146–149) appear particularly sensitive to glutamine deprivation, a strategy restoring the cisplatin response (146). In ovarian cancer cells, MYC promotes glutamine addiction by increasing glutamine uptake and GLS1 expression and also promotes cisplatin resistance (147, 148). Thus, targeting the main plasma membrane transporter of glutamine [alanine serine cysteine preferring transporter 2 (ASCT2) also known as SLC1A5] and GLS1 could be an important strategy to inhibit platinum-resistant cancer cells (147–149). Importantly, in several models of tumor-bearing mice (colon, lymphoma, and melanoma xenograft cancers), GLS1 inhibition by 6-diazo-5-oxo-L-norleucine (DON) reduced tumor growth and activated cytotoxic effector T cells (150). DON inactivated oxidative and glycolytic metabolism of cancer cells while it promoted oxidative metabolism and the activation of effector T cells (150).

Arginine deprivation arrests the growth of various cancer cells (such as sarcomas and HCC, malignant melanoma and pleural mesothelioma, prostate and renal cancer cells, and cisplatin-resistant ovarian cancer), because these cancer cells do not synthesize sufficient arginine (108, 151). This results from the epigenetic silencing of the gene promoter of argininosuccinate synthetase (ASS1), the rate-limiting enzyme of arginine synthesis; therefore, these cancer cells become auxotrophic to arginine (151). Consequently, an arginine deprivation diet [as realized by arginine deiminase (ADI-PEG20) administration] can inhibit the growth of cancer cells with ASS1 deficiency, as shown by preclinical studies—in particular, in sarcomas (152).

Methionine starvation can promote the therapeutic response of CT-resistant *RAS* CRC cancer xenografts and RT-resistant mutated *KRAS* (Kristen rat sarcoma viral oncogene homolog) soft tissue sarcoma with *TP53* deficiency (153). However, methionine starvation diets may have a dual effect, promoting liver cancer in some experimental studies (154). Therefore, diet strategies targeting amino acids must be conducted with a clear understanding of the specific metabolism of the various cancer tumors.

Inhibiting membrane transporters might also be an efficient strategy in altering the proliferation of cancer cells and/or stimulating the immune response. For example, L-cysteine is imported into cancer cells and myeloid-derived suppressor cells (MDSCs) by the L-cystine (L-CSSC) transporter, a carrier not expressed in CD8$^+$ T cells (155). Therefore, inhibition of this transporter can suppress cancer cell growth and promote a cytotoxic immune response (156).

Counteracting anaplerosis, the process of reloading the TCA cycle with intermediates (OAA, AKG, and fumarate) that have been extracted for biosynthesis (in what are called anaplerotic reactions) can inhibit cancer cell growth. For example, the inhibition of PC (the enzyme that produces OAA) decreases the growth of breast and lung cancer cells (157, 158) while the inhibition of the mitochondrial pyruvate carrier (MPC) arrests the proliferation of various cancer cells lines (159). However, in apparent contrast, promoting the activity of MPC can decrease the growth of cancer cell lines that predominantly rely on glutamine (160, 161). Further studies must clarify the specific metabolism supporting cancer tumor development in vitro and in vivo. Of note, translocases of the outer and inner mitochondrial membrane (TOMM and TIMM, respectively) carry hundreds of proteins into the mitochondria (162). Targeting these translocases, in particular TOMM20, could be useful in reducing the growth of cancer cells, as shown by knockdown of TOMM20 in a xenograft mouse model of colon cancer (163).

Inhibition of lipid metabolism can also be an important strategy as many cancer cells activate de novo FAS (164). Thus, ACLY and FASN are key targets for specific inhibition (17, 90, 164), as well as all enzymes sustaining cholesterol and mevalonate pathways (for a list of inhibitors, see Table 2 and **Table 3**). Targeting FAO can also be an option, especially for counteracting cancer cells sustained by lipid catabolism (26, 27).

The "citrate strategy" recapitulates many advantages of metabolic interventions.

The rationale of the "citrate strategy" is based on the decrease in citrate cytosolic concentration induced by the Warburg effect (90) and/or upregulation of ACLY observed in numerous cancer cells (17). Low citrate concentrations promote PFK1 activity and FBPase inactivity since citrate physiologically regulates these key enzymes. Through fructose-1,6-bisphosphate (PFK1 product), the proliferative RAS-PI3K-AKT pathway is promoted, and therefore the Warburg effect and ACLY are concomitantly activated in a feedback loop

TABLE 3 Clinical trials with metabolic inhibitors[1]

Metabolic target	Clinical trial	Main drug	Associated treatment	Cancer type	Results
GLUTs	NCT01009437 (phase I/II)	Ritonavir	Surgery	Breast cancer	Unpublished
	NCT00487721 (phase I/II)	Silybin-phytosome	Surgery	Prostatic cancer	16.7% AEs
HK2	(165) (phase III)	Lonidamine	CT (mitomycin-C/vindesine)	NSCLC	Higher 1-y survival with CT + lonidamide vs. CT alone (32% vs. 20%)
PFKs	(166) (phase II)	Sulforaphane	Single agent	Prostatic cancer	PSA level decreased in the sulforaphane group vs. placebo
	NCT00735332 (phase II)	TLN-232	Single agent	Melanoma	Well tolerated
GAPDH	NCT02044861 (phase I)	ACT-PFK-158	Single agent	Solid malignancies	Unpublished
IGF-1R/IR	(167) (phase III)	Linsitinib	Single agent	Adrenocortical carcinoma	No increased OS vs. placebo
	(168) (phase II)	AXL1717	Single agent	NSCLC	No difference in PFS and OS vs. docetaxel
PDK1	NCT01386632 (phase II)	Dichloroacetate	Cisplatin+RT	HNC	32.0% vs. 24.0% severe AE in arms DCA vs. placebo
PDH	(169) (phase I/II)	Devimistat	Folfrinox	Pancreatic cancer	61.0% RR in phase I; phase III ongoing
Complex I	NCT01101438 (phase III)	Metformin	Single agent	Breast cancer	Unpublished; ongoing
	NCT01864681 (phase II)		Tyrosine-kinase inhibitors	NSCLC	
			Chloroquine	*IDH* mutated solid tumors	
Complex V	(170) (phase II)	Curcumin	Folfox	CRC	Curcumin use was safe and tolerable; No difference between the 2 arms in QoL
MCT1	NCT01791595 (phase I)	AZD3965	Single agent	Solid malignancies and lymphoma	Ongoing
GLS1	NCT03965845 (phase I/II)	Telaglenastat	Palbociclib	NSCLC and CRC	Ongoing
IDH	NCT02977689 (phase II)	IDH305	Single agent	Glioma	Unpublished
	(171) (phase III)	Ivosidenib	Single agent	Cholangiocarcinoma	Improved PFS vs. placebo
L-Asparagine	(172) (phase II)	Erythrocyte encapsulated asparaginase	CT	Pancreatic cancer	Improved OS and PFS vs. CT alone; Well tolerated
Arginine	NCT01910012 (phase II)	Arginine deiminase	Single agent	AML	The duration of arginine depletion was correlated with disease control; Well tolerated
FAS	NCT03808558 (phase II)	TVB-2640	Single agent	*K-RAS* mutated NSCLC	Ongoing
HMG-CoA reductase	NCT03971019 (phase III)	Statins (simvastatin and atorvastatin)	Single agent	Operated breast cancer	Ongoing
Antioxidants	NCT03323346 (phase II)	Antabuse (disulfiram)	Copper	Breast cancer	Unpublished
Glutathione	(173) (phase I)	Buthionine sulfoximine	Melphalan	Solid malignancies	No major toxicity
	NCT00165867 (phase II)	Indisulam	Idarubicin and cytarabine	AML	35.0% RR

[1] AE, adverse event; AML, acute myeloid leukemia; CRC, colorectal cancer; CT, chemotherapy; FAS, fatty acid synthesis; GLS1, glutamine synthase 1; GLUT, glucose transporter; HK2, hexokinase 2; HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA; HNC, head and neck carcinoma; IDH, isocitrate dehydrogenase; IGF, insulin-like growth factor; MCT1, monocarboxylate transporter 1; NSCLC, non–small cell lung carcinoma; OS, overall survival; PDH, pyruvate dehydrogenase; PDK1, pyruvate dehydrogenase kinase 1; PFK, phosphofructokinase; PFS, progression-free survival; PSA, prostate-specific antigen; RR, response rate; RT, radiation therapy.

(174–176). In various cancer models, the administration of high concentrations of citrate ($\sim$50 times the physiological concentration) inhibits cancer cell proliferation by several mechanisms: the promotion of apoptosis by caspase 3 and 9 activation with the extinction of the anti-apoptotic factor Mcl-1 (177); increasing sensitivity to cisplatin (177, 178); inactivation of PFK1 with decreased ATP production (179); inhibition of the insulin-like growth factor (IGF) I (IGF-I) and its type I receptor (IGF-IR); inactivation of PI3/AKT pathway and activation of the PTEN suppressor; reversion of dedifferentiation and increased T-lymphocyte response (180–182).

Citrate is a product of very low toxicity as it is an endogenous metabolite characterized by a very short half-life and a rapid and complete metabolism (183, 184). Its only toxicity in humans and mammals is due to its chelating properties on calcium and other divalent cations. Administered in excess, citrate induces hypocalcemia, which causes muscle spasms and convulsions, and also a risk of hemorrhage (183, 184). The potentially severe and eventually lethal effects of acute hypocalcemia are usually reversed and cured by the intravenous administration of calcium chloride (184, 185). Citrate is commonly used in continuous veno-venous hemofiltration, in which clinical signs of hypocalcemia (such as tingling) are detected regularly; blood calcium concentrations are monitored and hypocalcemia is avoided by administering a calcium-containing liquid as a preventive measure (185, 186). Extrapolating the results of preclinical models using citrate as anti-cancer treatment (179–182), the active dose in humans is probably much lower than that used in continuous venous hemofiltration. However, the citrate strategy should only be tested in phase 1/2 clinical trials to determine its adverse effects and toxicity, mode and duration of administration, and its efficacy. Disturbance of the acid-base balance will also be avoided by the appropriate addition of bicarbonate (187).

Bridging cell metabolism to the TME

The emergence of immunotherapy as an efficient treatment in some cancers demonstrated the impact of targeting the TME. Tumor stroma contains a wide array of noncancerous cells, including cancer-associated fibroblasts (CAFs), adipocytes, endothelial cells, macrophages, myeloid-derived cells, natural killer (NK) cells, and other immune cells, including T and B lymphocytes. Schematically, cytotoxic immune cells comprise the following: $CD8^+$ T, T-helper (Th) 1 and Th17 subpopulations of $CD4^+$ T lymphocytes ($CD4^+$Th1/Th17), dendritic cells (DCs), NK cells, and proinflammatory tumor-associated macrophage (TAM) 1 (TAM1). Immunosuppressive cells comprise regulatory T cells (Tregs; a subgroup of $CD4^+$ T cells), MDSCs, and anti-inflammatory TAM2 cells [for review, see Caruana et al. (188)]. Of note, tumor-infiltrating lymphocytes (TILs) are often organized to form tertiary lymphoid structures together with DCs (189). The high consumption of nutrients by cancer cells contributes to exhaustion (nonresponsiveness) of cytotoxic immune cells, while waste products secreted by cancer cells (lactate, NO, polyamines, adenosine, and $NH4^+$) further stimulate local immunosuppression and/or the proliferation of cancer cells (190). For example, adenosine generated from ATP degradation exerts local immunosuppression (191). The manipulation of the chemical milieu can promote a hostile TME for cancer development and may be an "ecological" strategy, which could improve cancer therapy.

How to improve the cytotoxic immune response?.

The development of cancer cells is influenced by the number, nature, and activity of immune cells within tumors. Immunotherapy aims to restore the activity of cytotoxic T lymphocytes, and this strategy has dramatically improved the prognosis in certain types of cancers. The immune checkpoints programmed death (PD)-1 (PD-1) and its ligand (PD-L1), as well as T-lymphocyte–associated protein 4 (CTLA-4) are located on the membrane of T cells; they favor the inhibition of the cytotoxic function of TILs and stimulate immunosuppressive Tregs (188).

The dense infiltration of tumors with active TILs and proinflammatory TAM1 correlates with a better outcome (192, 193). Shifting T cells from a quiescent state to a highly active effector phenotype (activation, proliferation, migration, and differentiation with cytokine secretion) is a process that requires the large availability of nutrients (glucose, glutamine, and FA) and the rapid production of energy provided by glycolysis and OXPHOS (194, 195). The inhibition of PD-1 and PD-L1 results in an intense activation of glycolysis-dependent $CD8^+$ T cells, leading to the secretion of IFN-γ (196, 197). TAM1 activation also results from the activation of glycolysis, PPP, and FAS (198). However, cancer cells outsmart the proliferation and activation of cytotoxic TILs and TAM1 by diverting nutrients for their own profit—in particular, glucose and amino acids (196–198). As a result, the loss of nutrients in the TME alters the cytotoxic function of effector T cells while it favors the anti-inflammatory effect of immunosuppressive cells. Of note, immunosuppressive cells are less demanding in glucose than cytotoxic T cells, and are mainly supported by FAO (26). Deprived in nutrients, T-cytotoxic cells progressively enter a dysfunctional and exhausted state, associated with the downregulation of glycolysis and OXPHOS, and loss of mitochondria induced by endoplasmic reticulum stress (199, 200). In this context, immune tolerance is promoted, while glucose and other nutrients are left for use in cancer cell proliferation.

Two main strategies can counteract the imbalance that is beneficial for cancer cells, and these strategies can be combined if they are well tolerated: *1*) counteracting the absorption of nutrients by cancer cells and immunosuppressive cells, thus redirecting these nutrients to cytotoxic cells, and *2*) suppressing secretion and recycling of waste products in the TME where they promote immunosuppressive cell activation.

The first strategy—that is, inhibition of nutrient uptake (glucose, glutamine, arginine, methionine, and FAs) and/or

their conversion in cancer cells—has been partly described above. In this setting, the inhibition of arginase 1 (ARG1) promotes the activation of cytotoxic and proinflammatory cells, while anti-inflammatory and immunosuppressive cells are inhibited (199). Another example is targeting tryptophan metabolism, which can both counteract cancer cell growth and promote the activation of cytotoxic cells. Indeed, tryptophan is transformed by indoleamine 2–3 dioxygenase (IDO) into kynurenine, an immunosuppressive molecule. IDO can be inhibited by molecules such as indoximod (201, 202), but also by inhibitors of cyclooxygenase (COX)-2 (COX-2) as it produces prostaglandin E2 (PGE2), which upregulates IDO. COX-2 inhibition can be of particular importance because it concomitantly blocks ARG1 in MDSCs (203). PGE2 also binds to E type prostanoid 4 (EP4) promoting activation of immunosuppressive cells such as MDSCs; thus, several EP4 antagonists are currently being tested in clinical trials (203). In addition to amino acid metabolism, it could be important to target lipid metabolism, since lipid accumulation in the TME promotes cancer development, suppressing the immune response, particularly in prostate cancer (204). FAO inhibition could act against immunosuppressive cells (such as Tregs), relying preferentially on FA catabolism for their activation and/or maturation (205).

The second main strategy targets waste products secreted and recycled in the TME where they favor immunosuppression by various mechanisms described in detail elsewhere (206, 207). As an example, the adenosine pathway can be blocked by inhibitors of adenosine-generating enzymes (such as CD73) and/or adenosine receptors [for a list of ongoing trials, see Allard et al. (208)]. The inhibition of lactic acid metabolism can be attempted by using diclofenac (209), LDH inhibitors such as oxamate (210), MCT1/4 inhibitors (159), or by promoting PDH functioning by molecules such as lipoic acid (46) or dichloroacetate (211). Lactate transporter inhibition, in particular, targeting MCT1, was found to be a promising strategy for stopping cancer cell growth (159, 211), reducing the risk of metastasis in melanoma mouse models (212). Targeting an extracellular acid pH could be attempted as this pH decreases drug penetration in cancer cells and stimulates immunosuppression (213). Reversing the pH on both sides of the cellular membrane by the inhibition of Na^+/H^+ exchanger (NHE) 1 (NHE1) can slow down the proliferation process (214, 215). However, the redundancy of membrane pH-regulating proteins including carbonic anhydrases (CAs), NHEs, $Na^+/HCO3^-$ co-transporters (NBCs), and MCTs prevents effective pH reversing if a sole individual protein is targeted (215). Interestingly, the oral administration of bicarbonate prevents the occurrence of metastases in breast cancer mouse models (216). In preclinical studies, the administration of sodium bicarbonate favors the penetration of cytotoxic drugs (doxorubicin, in particular) (217, 218), increases the response to mTOR inhibitors (218), and stimulates TILs in tumors (219). Sodium citrate is also a basic salt, increasing cytotoxic response to drugs such as cisplatin and T-cell infiltration in tumors (179–182). Co-administration or pretreatment of clinical doses of proton pump inhibitors in patients receiving cisplatin and fluorouracil results in lower extracellular acidification, enhancing the sensitivity of the tumor cells to anti-cancer agents (220).

Targeting nonimmune cancer-associated cells, such as CAFs.

CAFs produce fibronectin and rich proline molecules (such as type I and III collagen), which, along with type IV collagen (entering the basement membrane produced by cancer cells) (221, 222), form a fibrotic tumor stroma stimulated by hypoxia and HIF-1 (223, 224). A thick tumor stoma leads to a "desmoplastic reaction" of poor prognosis, which increases interstitial fluid pressure and constitutes a physical barrier against drug delivery and antitumor immune response (221). Thus, targeting these cells can be important in establishing a TME hostile to cancer cell development. As CAFs use glycolysis to produce lactate for cancer cells, a process known as the "reverse Warburg effect" (224), targeting lactate secretion and exchanges by the aforementioned strategies can participate in the inhibition of CAF activity, thus counteracting cancer cell development.

Targeting the perverted metabolism of the host supporting the growth of the "cancer parasite"

Beyond the vicious exchanges occurring between cancer cells and their environmental niche, the tumor takes advantage of aberrant metabolic exchanges with its host, consuming muscles and fat reserves, and leading to cachexia (225). Cancer tumor can be viewed as a metabolic "parasite" sustained by daily food intake and liver gluconeogenesis, the latter pathway being supplied by glycerol (derived from lipolysis), alanine (derived from proteolysis), and lactate secreted by hypoxic tumor cells and muscles. Alanine consumption promotes proteolysis, loss of muscle, and finally the occurrence of sarcopenia (225), whereas lactate secreted by tumors can constitute a primary source of carbons for the TCA cycle of many cells in tissues and organs, except for the brain (226). This general recycling participates in glucose sparing for cancer cells—in particular, for highly glycolytic cells, which are often hypoxic and resistant to therapies (227). However, the metabolic requirements of the tumor-parasites should be less important than the distant metabolic effects exercised by the tumor on the "host," and the tumor burden is <1% in many cancers, even at an advanced stage (228). The relations between cancer and the host are complex and involve numerous interconnected factors, including the following *1*) chronic inflammation with deregulated mixes of cytokines (in particular IL-6) secreted by various cells (cancer cells, immune cells, CAFs, and organs cells, in particular, of the liver) (229); *2*) nutritional status and adipose tissue composition and conversion of white into brown fat, promoted in particular by PGC1α, a central modulator of cell metabolism (230); and *3*) endogenous hormone (in particular insulin and IGFs) synthesized by almost any tissue and supporting insulin resistance, diabetes, and obesity (231).

Targeting the deregulated lipid metabolism sustaining cancer development.
Excess consumption of caloric food promotes obesity, insulin resistance with increased circulating concentrations of insulin and IGFs, triglycerides, and nonesterified FAs (NEFAs). NEFAs trigger nonalcoholic fatty liver disease by endoplasmic reticulum stress, inflammation, necrosis, and fibrosis; all of these factors promote carcinogenesis and the development of liver cancer in particular (232, 233). Many factors contribute to this lipotoxic pathogenic sequence, such as free lipotoxic FA, several arachidonic and sphingolipid molecules, high expression of altered triglyceride lipase and acylcarnitines, as well as insulin resistance, cytokine production, micro-RNA (miRNA) dysregulation, NSCLC, and altered intestinal microbiota (234–236). The arachidonic pathway that promotes tumor growth could be targeted by natural products such as curcumin, resveratrol, and berberine (236). Upregulating the concentrations of proapoptotic sphingolipids (as ceramide and sphingosine) could also be beneficial (237).

Targeting the altered insulin–IGF-I pathway that promotes cancer development.
The insulin–IGF-I axis and its downstream effectors are involved in cancer metabolism as observed in several cancer models and cohorts of patients (238–240). Insulin resistance is frequent in cancer patients, a process characterized by increased hepatic gluconeogenesis. Unlike in type 2 diabetes, cancer patients have normal fasting glucose with high, normal, or low concentrations of insulin (241). The complex role of the IGF family (IGF-I and IGF-II) ligands, IGF-IR1–3, insulin receptor (IR), and IGF-binding proteins (IGFBP1–6) in the mechanisms of insulin resistance in cancer patients still requires exploration [for review, see Denduluri et al. (238) and Bowers et al. (239)]. The increased expression of IGF-I, IGF-II, and IGF-IR has been observed in a variety of malignancies (242, 243). Of note, IGF-IR gene mutations have been rarely documented in cancer and no evidence links IGF-IR mutation with cancer prognosis (242, 244). IGF-I signaling activates PI3K/AKT, thus promoting glucose metabolism with the inhibition of glucagon expression and secretion (239, 244). IGFBPs regulate IGF-I availability and have an essential role in subverting glucose metabolism and promoting cancer growth and insulin resistance (239, 240). In a mouse model of acute myeloid leukemia, leukemia cells induced a high secretion of IGFBP1 in adipose tissue, which promoted a diabetic state and leukemia progression; thus, in this situation, anti-IGFBP1 and antidiabetic drugs could be beneficial (244). Of note, IGF-IR–specific inhibitors were disappointing in trials—in particular, because IGF-IR is expressed ubiquitously and shares high homology with IR, while compensatory growth factor signaling demonstrates some redundancy with IGF-IR signaling (245). Interestingly, in vitro studies showed that several miRNAs and lipoic acid inhibits IGF-IR (246, 247), while small molecules can displace IGF-I from the IGF-I–IGFBP complex, thus suppressing IGF-I–induced proliferation (248).

Dietary interventions could protect healthy cells from the cytotoxic effects induced by chemotherapeutic drugs on cancer cells

The maintenance of a sufficient high BMI and/or a stable weight is a pledge of quality of life and response to anticancer therapies. In this context, proposing a diet may appear illogical and conterproductive. However, preclinical experiments have shown that fasting (FS) and caloric restriction (CR) increase the effectiveness of CT and RT by promoting cytotoxic stress, acute inflammation, and immune responses (249–251). In mice, 48–72 h of FS protects from the toxic side effects of CT (such as platinum-based drug combinations or doxorubicin and etoposide), reverses CT-induced DNA damage on healthy cells, improves regeneration of hematopoietic stem cells, and favors an effective immune response (251–254). Interestingly, FS and CR downregulate IGF-IR and PI3K/mTOR signaling pathways, thus arresting the proliferation of healthy cells (such as cells of the bone marrow, gastrointestinal tract, hair follicles, and heart), which switches their metabolism in an oxidative mode for repair and survival (252, 253, 255). In contrast, cancer cells continue to proliferate as they are strongly programmed by oncogenic factors to replicate. This distinct reaction supports the concept of "differential stress resistance" (DSR) (250, 251, 255–257).

The switch from glycolysis to oxidative metabolism—supporting DSR—is promoted by AMPK, which enhances FAO and consequently supplies cells with ATP and NAD^+ molecules (258). In healthy cells, proliferation is arrested and repair is regulated by various genes such as *TP53*, *CDKN1*, sirtuin 3 (*SIRT3*), and the protein kinase forkhead box protein O3 (*FOXO3*) (259, 260). Concomitantly, ROS neutralization is promoted by the mitochondrial NAD^+-dependent protein Sirt3, a deacetylase that stimulates superoxide dismutase 2 (MnSOD2) and inhibits the Warburg effect (260). In contrast, these censoring controls are frequently altered in cancer cells, which survive and continue to replicate, supported by altered mechanisms of autophagy, AMPK, and poly (ADP ribose) polymerases (PARPs) (261–263). However, repeated cycles of CR or FS associated with RT and CT could be lethal for cancer cells, in contrast to healthy cells that could better recover from metabolic stress (257, 264, 265). Interestingly, such metabolic strategies could improve the immune cytotoxic response in tumors, as suggested experimentally (265). DSR suggests therapeutic windows for metabolic interventions that could be associated or interspersed between CT, RT, or immunotherapy sessions to improve the cytotoxic effect on the tumor while protecting healthy cells.

In this setting, the significance of ketone body (KB) diets (KBDs) may appear more problematic, although proposed as a "metabolic therapy" in particular for brain tumors (266). The rationale of these diets—low in carbohydrates and rich in fat—is to starve tumor cells in glucose because

KBs (produced by the liver) cannot be metabolized by cancer cells, which lack relative mitochondrial enzymes (267). In contrast to tumor cells, many tissues and organs, in particular the brain, heart, and muscles, can use 3β-hydroxybutyrate (3β-OHB)—the main KB—as an efficient source of energy. Furthermore, 3β-OHB inhibits histone deacetylation in cancer cells, thus arresting their division (23). Accordingly, some studies have shown that KBDs reduce tumor growth [for review, see Branco et al. (267)], deplete TME in immunosuppressive cells, ad decrease the expression of inhibitory checkpoints (268). However, in other preclinical studies, KBDs had no effect and might even accelerate breast cancer growth (21, 23). These contradictory results could be related to the fact that many cancer cells display an oxidative metabolism and thus likely consume FA and KBs (269, 270). Furthermore, it is noteworthy that few studies (mainly carried out in cultured murine cells) demonstrate the assumption that cancer cells have lost enzymes metabolizing KBs (271). Moreover, some subclones can adapt to glucose starvation by promoting their glucose uptake, in particular through the overexpression of GLUT1 (272, 273) or by increasing their glutamine dependency (274). Therefore, the efficiency and relevance of KBDs warrant further demonstration by rigorous clinical trials, taking also into account that these diets are not easy to follow, often inducing significant weight loss. The results (not currently available) of randomized trials testing KBDs with CT and RT will clarify the benefits and relevance of KBDs [for recent lists of clinical trials associating KBDs and RT, see Icard et al. (275)].

Concluding Remarks and Future Perspectives

There is a novel and increasing interest in metabolic interventions to improve the results of conventional therapies. However, as we have described, preclinical studies have shown that there is no universal cancer cell metabolism, and thus no universal metabolic strategy capable to arrest the growth of all cancer cells, every time. However, the addiction of numerous cancer cells to glucose could be their Achilles heel, a vulnerability that should be targeted, especially in cells relying on strong aerobic glycolysis. This is of primary interest because these cells are often the most hypoxic and treatment-refractory cells, and thus sustain recurrence and metastasis (276). Otherwise, several experimental studies have shown that drug-resistant cancer cells can be re-sensitized by targeting metabolic pathways supporting their development (277). As an example, 5-fluorouracil (5-FU)–resistant CRC cancer cells are destroyed if 5-FU is combined with an inhibitor of OXPHOS (278). Similar considerations apply to the glutamine addiction in platinum-resistant cancer cells such as ovarian cancer cells (74). However, the metabolism of cancer cells can adapt to various changes related to nutritional conditions or enzymatic inhibitions by developing alternative pathways. For example, glucose deprivation induces a decrease in ATP production, which can be counterbalanced by an increasing production sustained by OXPHOS and FAO (26), and this condition can

sometimes induce the selection of mutations that increase glucose uptake and glutaminolysis (272, 274). Acetyl-CoA—a key molecule in cell metabolism—can be obtained from several sources such as citrate and/or acetate (279), but also from glycolysis through transketolase-like 1 activity (37). Thus, reducing the concentration of acetyl-CoA in cancer cells may be difficult, almost impossible. The same is true for ribose 5-phosphate (R5P) because its synthesis can be supported by the oxidative part and/or the nonoxidative part of PPP, sustained by glycolysis or truncated gluconeogenesis. This latter pathway can be sustained by glutaminolysis and/or FAO. However, despite this adaptability, the metabolism of cancer cells can be inhibited by several strategies that can be simplified as follows: limiting the absorption of nutrients essential for cell growth; inactivating key regulatory and/or limiting enzymatic reactions; targeting metabolic enzymes linked with other processes that sustain cancer proliferation, such as cell cycle progression; stopping the production of ATP to cause an energy crisis; redirecting nutrients to cytotoxic immune cells; and suppressing waste secretion and recycling in TME.

However, without a comprehensive picture of whether metabolism supports the development of a particular tumor in vivo at a specific time, it is quite impossible to define the pathways or enzymes, which should be targeted in priority, considering also that the supplementation or starvation (in particular for KBs and several amino acids) may have dual effects. Furthermore, promoting oxidative metabolism instead of reductive metabolism (and vice versa) may paradoxically select resistant and/or metastatic cell clones (64, 65). Thus, while awaiting the development of new methods capable of specifying the metabolism of tumors in vivo, it may be advisable to concomitantly or sequentially target the glycolytic and oxidative behavior of cancer cells, and also to favor short cycles of "metabolic interventions" rather than prolonged interventions, which can select resistant clones and require stricter compliance. Further studies and clinical trials will define the modalities of metabolic interventions, their place among current treatments, their toxicity, and their repercussion on body physiology and immune response. It is time to develop new classifications including markers of cancer cell metabolism, immune response, and metabolic disorders to develop personalized treatments based on deeper knowledge of the specific metabolic vulnerabilities of both tumor and host, and actively test simple and inexpensive metabolic strategies that could improve the results of anti-cancer treatments.

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