Trends in Cancer

CellPress

Focus issue: Tumor metabolism

Review

Bioengineered systems to exploit tumor microenvironment metabolism

Christine Sanganoo [1,#], Ilaria Caturegli [2,#], Zachary Mattes [3,#], Jordan Ryan [4], Wilson W. Wong [5,*], and Mark W. Grinstaff [1,3,5,*]

Our understanding of cancer metabolism has afforded the opportunity to develop therapies specific to tumor metabolic dysregulation. While molecular therapeutics targeting cancer metabolism have found success in the clinic, bioengineering approaches are nascent. Here, we describe key metabolic pathways and their genetic dysregulations in the tumor microenvironment (TME) that are ripe for intervention. We examine bioengineered biomaterial and cellular systems that harness the metabolic and immune landscape of the TME to target metabolic dependencies of tumor growth. These therapeutic strategies include, for example, preventing the uptake of essential metabolites, delivering metabolic inhibitors, and restoring an immunostimulating environment. With a focus toward clinical applications and tolerability, we identify key limitations and conclude with future directions.

Highlights

The tumor microenvironment undergoes metabolic reprogramming via somatic oncogenic mutations, and these metabolic changes represent exciting new therapeutic targets.

Metabolic changes in the tumor microenvironment occur across multiple cell types, including stromal and immune cells.

Engineered systems, including biomaterials, cellular technologies, and synthetic biology, are emerging as powerful tools to target specific metabolic phenomena.

As therapeutic efficacy depends on the tumor microenvironment and resulting metabolism, new primary, auxiliary, or synergistic agents that correct metabolic dysregulation are highly sought after.

The unique metabolic landscape of the tumor microenvironment (TME)

Aberrant genomic alterations transform healthy cells and impair metabolic homeostasis [1]. The resulting driver mutations uniformly yield uncontrolled replication; however, their metabolic manifestations are often divergent and lead to a variety of targetable metabolic constraints [2]. While intrinsic factors, including genomic mutations, initiate dysregulated metabolic programs, the metabolic state during tumor growth depends on a plethora of extrinsic factors, that is, determinants of the metabolic state of the tumor microenvironment (TME) (e.g., anatomic or physical constraints [3], metabolite availability in the tissue of origin [4], and dynamic interaction with the metabolism of vascular, stromal, and/or immune cells [5]).

Metabolic flux is a universal prerequisite for benign and malignant proliferation [6]. The enigmatic metabolic complexity of the TME presents an unrivaled opportunity to develop novel therapeutic strategies. Biomaterial and cellular therapies are particularly well-suited to address metabolic dysregulation, given their ability to deliver diverse cargos to diseased tissue, including ions, regulatory metabolites, oxygen, biocatalysts, and entire metabolic systems [7,8]. Furthermore, the modular chemical properties of biomaterials allow for tunable mechanical properties, which are sensed by cells that influence metabolism [9]. In addition, bioengineered cellular therapies enable immune cells to overcome the metabolic bottlenecks imposed by the TME and regain the anticancer immune response. Establishing a clear understanding of the metabolic requirements for the function of different cell types in the TME is vital for developing biomaterial and bioengineering strategies to prevent tumor progression. In this review, we (i) address the genetic origins of metabolic dysfunction in cancer cells; (ii) unveil the metabolic interworking of cells in the TME; and (iii) discuss biomaterial strategies and bioengineered systems that exploit the metabolic constraints of tumors at the clinical and preclinical stages of development. Finally, we identify areas that merit further investigation and highlight outstanding questions.

[1]Department of Pharmacology, Physiology & Biophysics, Chobanian and Avedisian School of Medicine, 700 Albany St W302, Boston, MA 02215, USA
[2]Division of Surgical Oncology, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, 1620 Tremont Street, Boston, MA 02120, USA
[3]Department of Chemistry, Boston University, 590 Commonwealth Avenue, Boston, MA 02215, USA
[4]Division of Thoracic Surgery, Department of Surgery, Massachusetts General Hospital, Boston, MA 02114, United States
[5]Department of Biomedical Engineering, Boston University, 590 Commonwealth Avenue, Boston, MA 02215, USA
[#]Contributed equally.

*Correspondence:
wilwong@bu.edu (W.W. Wong) and
mgrin@bu.edu (M.W. Grinstaff).

Genetic origins of metabolic dysfunction in cancer cells

Metabolic changes supporting tumorigenesis

Tumor cells modulate a variety of metabolic pathways (See Box 1) within the TME. Augmented aerobic glycolysis, known as the Warburg effect, was identified in cancer cells almost a century ago [10]. Despite elevated levels of glucose consumption under oxygen-replete conditions, many cancer cells depend on cellular respiration and metabolic flux through the tricarboxylic acid (TCA) cycle to grow [11]. Even in cases where cancer cells do not depend on respiration, nonrespiratory mitochondrial metabolism is a frequent requirement for tumor growth [12]. Though diverse cancer types largely share these characteristics, there remains significant tumor heterogeneity in gene expression programs, thus leading to limited success or resistance to therapeutic strategies. These changes emerge not only through direct mutations of genes but also through epigenomic modifications, including DNA and histone modifications [13]. Within the epigenomic space, the emerging concept of metabolite-mediated covalent and noncovalent modifications further emphasizes the impact of TME metabolic crosstalk and the importance of investigating these changes as druggable targets.

Metabolic reprogramming via somatic oncogenic mutations

Recent work establishes relationships between the oncogenic mutations that transform healthy cells and the metabolic changes that support tumorigenesis and identifies the unique and

Box 1. Overview of glucose, lipid, and amino acid metabolism

Glucose, lipid, and amino acid metabolism are essential pathways in which cells consume and produce energy to maintain homeostasis.

Glucose metabolism

After import by GLUT, glucose in the cytosol can enter the glycolysis pathway, where glucose is converted to pyruvate, and ATP, NADH, H_2O, and H^+ are produced. The pyruvate is either converted to lactate (under anaerobic conditions) or shuttled into the mitochondria, where pyruvate dehydrogenase uses it to produce acetyl-CoA. Acetyl-CoA is oxidized in the TCA cycle by citrate synthase, aconitase, isocitrate dehydrogenase, α-ketoglutarate dehydrogenase, succinate dehydrogenase, fumarase, and malate dehydrogenase. This process produces ATP, NADPH, $FADH_2$, and CO_2. Under aerobic conditions, electrons from NADPH and $FADH_2$ are used to pump protons into the inner mitochondrial membrane via complexes I–IV. This gradient drives the OXPHOS of ADP by ATP synthase to produce ATP. In the oxidative phase of the PPP, glucose-6-phosphate is converted to ribulose-5-phosphate, and NADPH is produced. The nonoxidative phase of the PPP converts ribulose-5-phosphate to ribose-5-phosphate for use in nucleotide synthesis and reductive processes, including fatty acid synthesis and protection against oxidative stress [188].

Lipid metabolism

Fatty acids are activated to acyl-CoA in the cytosol by acyl-CoA synthase. Long-chain acyl-CoA enters the mitochondria through the carnitine shuttle (CPT1/2) for β-oxidation. While releasing NADH and $FADH_2$, β-oxidation removes 2-carbon units at a time using acyl-CoA dehydrogenase, enoyl-CoA hydratase, hydroxyacyl-CoA dehydrogenase, and thiolase until one acetyl-CoA is produced. The acetyl-CoA can enter the TCA cycle or be used for ketogenesis in the liver. In the cytosol, acetyl-CoA carboxylase converts acetyl-CoA to malonyl-CoA. Fatty acid synthase catalyzes the addition of 2-carbon units onto malonyl-CoA, thus forming elongated fatty acid chains. This process is energy intensive and uses NADPH. The synthesis of cholesterol from acetyl-CoA is also energy-demanding and involves the key enzyme HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase [189].

Amino acid metabolism

Transamination reactions catalyzed by aminotransferases transfer amino groups to α-ketoglutarate to form glutamate. Glutamate deaminase releases NH_4^+ for urea cycle detoxification via carbamoyl phosphate synthetase I, ornithine transcarbamylase, and arginase. Carbon skeletons such as alanine, glutamate, and aspartate are converted to TCA intermediates pyruvate, α-ketoglutarate, and oxaloacetate, respectively, for energy or gluconeogenesis. Branched-chain amino acids such as valine, leucine, and isoleucine undergo transamination and oxidative decarboxylation via branched-chain α-ketoacid dehydrogenase. Key regulators AMP-activated protein kinase, insulin, and glucagon coordinate fluxes between glycolysis, gluconeogenesis, lipogenesis, and β-oxidation, depending on energy and nutrient availability [190].

actionable metabolic dependencies of cancer cells, as well as the adaptations necessary to rectify them, thereby charting the course for therapeutic strategies to target them [14].

Somatic mutations infrequently occur in healthy cells [15]. Once transformed by an oncogenic mutation, the cellular mutation frequency vastly increases, allowing for somatic evolution or adaptation [16]. Despite the fluctuating nature of cancer genomes, initial oncogenic mutations are associated with distinct metabolic adaptations. We cover the most prominent somatic oncogenic mutations and their associated metabolic phenotypes, while also examining selected examples of less common mutations that result in metabolic changes (Figure 1). Additionally, we discuss the oncogenic mutation(s)-associated metabolic changes in descending order of frequency observed in the clinical setting: *TP53* (35%), *PIK3CA* (13%), *KRAS* (11%), and *MYC,* as well as the less frequently mutated *IDH1/2* [17].

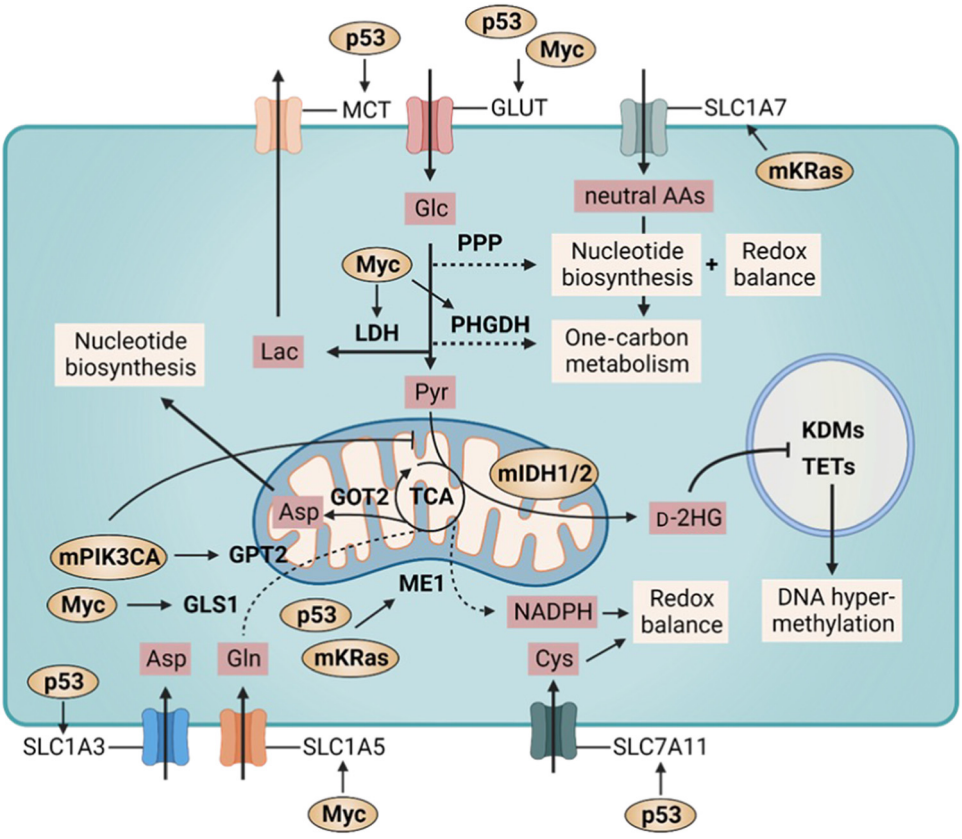

Figure 1. Oncogenic mutations are key determinants of metabolism in cancer cells. Commonly occurring oncogenic mutations in *TP53*, *PIK3CA*, *KRAS*, *MYC*, and *IDH1/2* lead to metabolic reprogramming in cancer cells by altering the expression levels of metabolite transporters and enzymes that control glycolysis and glutaminolysis, and, in the case of *IDH1/2*, by altering enzyme function. These alterations improve cancer cell fitness by increasing biomass synthesis, balancing oxidative stress, and allowing for survival in metabolite-depleted tumor microenvironments. D-2HG: D-2-hydroxyglutarate; GLS1: glutaminase; GLUT: glucose transporter; GOT2: glutamine oxaloacetate transaminase; GPT2: glutamine pyruvate transaminase; KDM: lysine demethylase; LDH: lactate dehydrogenase; MCT: monocarboxylate transporter; PGDH: phosphoglycerate dehydrogenase; PPP: pentose phosphate pathway; SLC1A3: glutamate-aspartate transporter; SLC1A5: glutamine transporter; SLC7A11: cysteine transporter; TCA: tricarboxylic acid; TET: ten-eleven translocation methylcytosine dioxygenase; AA: amino acid; mPIK3CA: mutant phosphatidylinositol-4,5-bisphosphate 3 kinase catalytic subunit alpha; mIDH1/2: mutant isocitrate dehydrogenase 1/2. Created with BioRender.com.

TP53. Loss-of-function (LOF) mutations in the tumor suppressor gene *TP53* lead to dysregulation of genes involved in the following processes: (i) glycolysis, including glucose transporters (*GLUT1/4*) [18], monocarboxylate transporter (*MCT1*) [19], and phospho-fructo-kinases (*PFKFB3/4*) [20]; (ii) mitochondrial metabolism and respiration, including cationic amino acid transporter (*SLC7A3*) [21], glutamate aspartate transporter (*SLC1A3*) [22], glutaminase (*GLS2*) [23], malic enzymes (*ME1/2*) [24], ornithine transcarbamylase (*OTC*) [25], carbamoyl phosphate synthetase (*CPS1*) [25], arginase (*ARG1*) [25], pyruvate carboxylase (*PC*) [26], and peroxisome proliferator-activated receptor (PGC1α) [27]; and (iii) redox homeostasis, including cystine transporter (*SLC7A11*) [28]. Inactivation of TP53 prevents its function as a transcription factor that directly binds to DNA to suppress cell growth, metabolism, and proliferation pathways and enhance cell death cascades in response to cellular stress [29]. This enhances glycolysis in cancer cells while simultaneously increasing mitochondrial metabolic flux through the urea and TCA cycles [30]. Stress-induced *TP53* expression enables cancer cells to survive in glutamine-depleted states through the uptake of exogenous arginine and aspartate, regardless of mutational status [21]. The most commonly affected cancer types are small cell lung, colorectal, ovarian, pancreatic, non-small cell lung, small bowel, endometrial, head and neck, breast, glioma, and bladder cancers [31].

PIK3CA. Gain-of-function (GOF) mutations in the *PIK3CA* gene, which encodes the catalytic subunit of phosphatidylinositol-4,5-bisphosphate 3-kinase (p110α), result in enhanced enzymatic activity that leads to various downstream metabolic manifestations [32], including (i) activation of the transcription factor ATF4, which results in the upregulation of glutamate pyruvate transaminase (*GPT2*) to increase glutaminolysis [33]; (ii) dependence on 2-oxoglutarate dehydrogenase (*OGDH*) for downstream aspartate production [34]; (iii) promotion of anaerobic glycolysis via AKT (protein kinase B)-directed phosphorylation; (iv) activation of pyruvate dehydrogenase kinase (PDK1) [35]; and (v) upregulation of arachidonic acid metabolism through activation of phospholipase (*cPLA2*) [36]. GOF mutations in *PIK3CA* decrease metabolic flux from glycolysis into the TCA by inactivating pyruvate dehydrogenase. This decrease in metabolic flux results in the reliance of mutant *PIK3CA* on glutaminolysis to feed oxidative production of TCA outputs, revealing a key dependency that presents multiple prospective targeted therapeutic approaches. Furthermore, mutant *PIK3CA* leads to elevated prostaglandin (PG) production and proinflammatory immune response, which can be mitigated by genetic cPLA2 inhibition and dietary fat restriction [36]. Mutations in *PIK3CA* are highly prevalent in colorectal cancer, followed by gastric, bladder, cholangiocarcinoma, sarcoma, and bladder cancers, as determined by next-generation sequencing [37].

KRAS. GOF mutations in *KRAS*, encoding for a GTPase in the RAS/MAPK (mitogen-activated protein kinase) signaling pathway, reshape cellular metabolism [38]. K-Ras activation upregulates glutamate oxaloacetate transaminase (*GOT1*) [39] and, in concurrence with mutant *LKB1*, upregulates carbamoyl phosphate synthetase (*CPS1*) [40]. Mutations in *KRAS4A* interact with and activate hexokinase (*HK1*) [41] to increase glycolytic flux while simultaneously increasing the expression of glucose transporters. GOF *KRAS* mutations with simultaneous LOF mutations in *APC* lead to glutamine dependence, not for consumption but instead for use as a counterion to support the function of the neutral amino acid transporter (*SLC1A7*) [42]. Additionally, upregulation of *GOT1* by m*KRAS* allows cells to maintain flux in the aspartate-malate shuttle to ensure reduced pools of NADPH, a key metabolic liability in pancreatic cancer cells [39,43]. Furthermore, upregulation of ferrireductase STEAP3 and downregulation of the iron exporter ferroportin, induced by *KRAS* overactivation, promote intracellular labile iron accumulation and thereby disrupt iron and redox homeostasis [44]. *KRAS* mutations are frequent in pancreatic adenocarcinoma, colorectal, and non-small cell lung cancers [45].

MYC and IDH1/2. Translocation or gene amplification of *MYC*, a proto-oncogene, increases glutaminolysis by inducing the transcription of glutaminase (*GLS1*) [46] and the glutamine transporter (*SLC1A5*) [47] while also increasing glycolysis by upregulating the glucose transporter (*GLUT1*) [48] and lactate dehydrogenase A (*LDHA*) [49], maintaining redox homeostasis through serine metabolism via regulation of serine hydroxy methyltransferase (*SHMT2*) [50]. Mutations in *MYC* are common in ovarian, esophageal, squamous lung, and breast cancers [51].

Mutations in isocitrate dehydrogenases (*IDH1/2*) are the most common enzyme mutations found in cancer [52]. Wild-type *IDH1/2* genes produce dehydrogenases that catalyze the oxidative decarboxylation of D-isocitrate to 2-oxoglutarate (2OG). m*IDH1/2* genes produce dehydrogenases with altered function, catalyzing the conversion of 2OG to D-2-hydroxyglutarate (D-2HG) [53]. D-2HG inhibits the activity of histone lysine demethylases (KDMs) and ten-eleven translocation dioxygenases (TETs), leading to DNA hypermethylation [54].

The inhibition of the mIDH1/2 proteins after cancer cells reach a hypermethylated epigenetic state is ineffective in decreasing proliferation [55]. The mutations in *IDH1/2* illustrate that mutational correction or direct inhibition of the oncogene in question is often insufficient to prevent tumor progression once driver mutations have accumulated and cancer cells have acquired a significantly altered metabolic state. Tumor progression beyond the initial stages of malignant transformation depends on extrinsic factors, including the availability of systemic metabolites, stromal cells to metabolically support tumor development, and the presence of an inflammatory and tolerogenic immune response to support immune evasion [56–58]. Cancers with IDH1/2 mutations are typically gliomas and acute myeloid leukemias [59].

Epigenomic metabolic regulation in tumors

Beyond genetically encoded changes, epigenomic modifications also play an important role in the regulation of tumor metabolism in hematological and solid tumors, as well as contribute to heterogeneity [13]. Epigenomic alterations are reversible modifications to DNA or histones that alter gene expression without mutating the DNA sequence. Modifications can be covalent (adding or removing chemical groups to DNA or histone tails) or noncovalent (not altering the DNA or histones directly). Key alterations include DNA methylation, which inactivates gene expression, and histone modifications that activate or inactivate gene expression by promoting the winding and unwinding of DNA, depending on the location. These changes in the various cell types of the TME drive processes such as tumor progression, invasion, metastasis, and metabolic reprogramming or occur as a result of the signals disseminated by these processes [13]. For example, the tumor metabolite 2-hydroxyglutaric acid (2-HG) inhibits the activity of α-ketoglutaric acid-dependent dioxygenases and thus suppresses the function of DNA and histone demethylases [60]. This results in hypomethylation of DNA, which is linked to oncogene activation in breast cancer, prostate cancer, and acute myeloid leukemia, to name a few [61–63]. On the contrary, CpG hypermethylation in the promoters of tumor suppressor genes aids tumor progression [64]. Histone acetyltransferases use acetyl-coenzyme A (CoA) to acetylate histone lysine residues, which loosens chromatin and promotes upregulated gene expression of several interconnected pathways in the TME, including glycolysis, angiogenesis, and proliferation [65]. Furthermore, increased metabolic flux provides excess lactate for the enzymatic and nonenzymatic lactylation of histones and DNA, promoting metabolic adaptation and immunosuppressive signaling [66]. In the clinic, screening for histone and DNA modifications enables early detection of cancer and may provide information about the key dysregulated pathways driving progression [67].

The metabolic landscape of the tumor microenvironment

The rapid growth of cancer cells, coupled with aberrant yet optimized angiogenesis, results in the formation of metabolic gradients within solid tumors that intensify with tumor progression [68]. The metabolic landscape of the TME is one of competition between cancer cells, stromal cells including endothelial cells, and immune cells (Figure 2) [69]. Glycolysis in cancer cells supports nucleotide and NADP production through the pentose phosphate pathway (PPP), as well as serine and α-ketoglutarate synthesis through phosphoglycerate dehydrogenase [70]. Lactic acid produced in this process accumulates in the TME and is recycled by cancer cells [71].

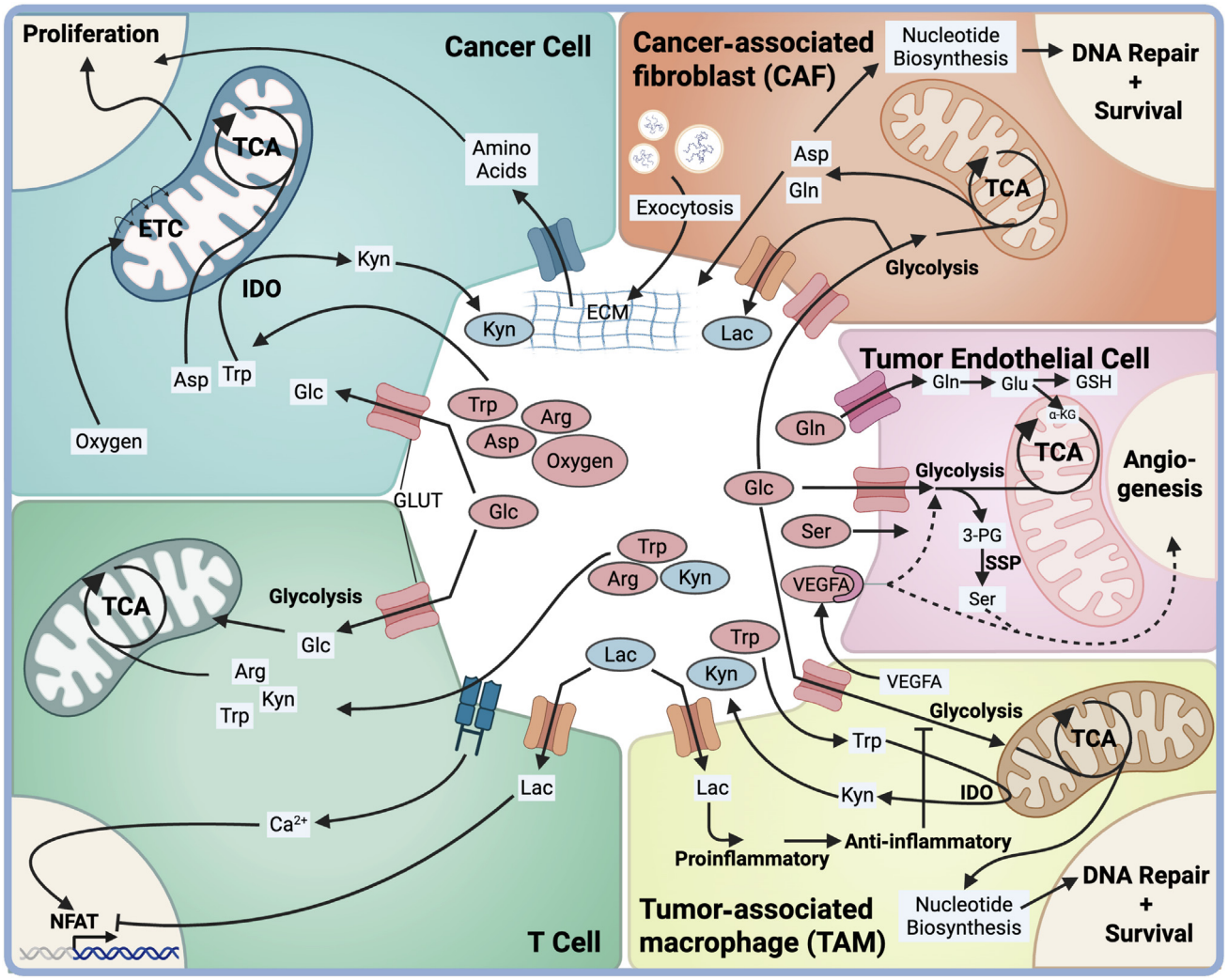

Figure 2. The composition and behavior of resident cells dictate the metabolic characteristics of the TME. Cancer cells rapidly consume glucose, amino acids, and oxygen from the TME while excreting immunosuppressive kynurenine and lactate. Cancer-associated fibroblasts support cancer cells by excreting ECM proteins that can be broken down by excreted proteases, as well as by excreting glutamine or aspartate in a context-dependent manner. T cells in the TME depend upon arginine and tryptophan uptake for function, and kynurenine inhibits tryptophan uptake. T cells compete with cancer cells for glucose and require glycolysis to maintain effector status. Lactate inhibits continued NFAT activation after antigen detection. Tumor-associated macrophages consume glucose and tryptophan from the TME, excreting lactate and kynurenine. Lactate can polarize TAMs toward an anti-inflammatory state. Vascular endothelial cells primarily use glycolysis to produce ATP. Glutamine and its derivatives are essential for angiogenesis. ECM: extracellular matrix; ETC: electron transport chain; Glc: glucose; GLUT: glucose transporter; IDO: indoleamine 2,3-dioxygenase; Kyn: kynurenine; Lac: lactate; MCT: monocarboxylate transporter; NFAT: nuclear factor of activated T cells; TAMs: tumor-associated macrophages; TCA: tricarboxylic acid; TCR: T cell receptor; TME: tumor microenvironment. SSP: serine synthesis pathway; VEGFA: vascular endothelial growth factor A. Created with BioRender.com.

Alongside glycolysis, cancer cells rapidly consume essential and nonessential amino acids to support biomass synthesis [72]. Glutaminolysis in tumor cells supports both the reductive and oxidative directions of the TCA cycle [73].

Cancer-associated fibroblasts (CAFs) support tumor glycolysis and glutaminolysis by excreting lactate [74] and, under certain conditions, aspartate to feed glutathione production [75]. *In vivo* disruption of these metabolic circuits is efficacious in treating breast and ovarian tumors. CAFs further support tumor progression by secreting extracellular matrix proteins, including collagen, which functions as a source of amino acids for cancer cells [76].

Vascular cells in tumors are metabolically reprogrammed toward glycolysis and altered lipid and amino acid use, driving abnormal angiogenesis, contributing to a hypoxic environment, and promoting immune evasion. Endothelial cells, pericytes, and vasculogenic mimicry structures form a metabolically wired vascular niche that strongly shapes therapy response [77]. Normalizing this niche by targeting vascular metabolism is a promising route to improve chemotherapy and immunotherapy outcomes.

Many of the same metabolic pathways that cancer cells depend on for replication are required in other cell types found in the TME, obliging cells to compete for metabolic resources [78]. For example, T cell binding via the T cell receptor (TCR) leads to activation of glycolysis, and elevated glucose consumption becomes a requirement for effector function [79]. The inability to acquire glucose leads to T cell exhaustion [80]. T cells further depend on L-arginine to support oxidative phosphorylation (OXPHOS) and L-tryptophan [81], which is rapidly consumed in tumor cells with increased indoleamine 2,3-dioxygenase (IDO) expression [82]. Kynurenine, produced by IDO, then functions to inhibit L-tryptophan uptake in T cells. High extracellular lactate, which then leads to acidification of the TME, inhibits T cell glycolysis, reduces ATP production, suppresses cytokine (including IL-2) production, lessens interferon-gamma production, impairs cytotoxicity, reduces T cell proliferation, suppresses TCR signaling, and decreases T cell migration [83]. Additionally, fumarate inhibits histone demethylases, affording altered T cell differentiation and enhanced inflammatory gene expression [84], and fumarate derivatives activate nuclear factor erythroid 2-related factor 2 signaling, which results in modulation of inflammatory metabolism and regulation of oxidative stress responses [85].

Macrophage metabolism is similarly linked to the TME [86]. The polarization between the proinflammatory and anti-inflammatory phenotypes is influenced by metabolite availability [87]. This basic characterization of macrophages provides a general guideline, and the reader is referred to the review by Li *et al*. for a comprehensive description of macrophage classifications [88]. High lactate levels lead to anti-inflammatory polarization of tumor-associated macrophages (TAMs) and thus suppress inflammatory function [89]. TAMs depend on glutaminolysis to maintain an anti-inflammatory phenotype by promoting fatty acid oxidation, while inhibition of glutaminolysis reverts TAMs to proinflammatory [90]. Together, the cells of the TME exhibit a highly interconnected metabolic network, which could allow for the recovery of immune cell function if targeted appropriately.

Additionally, other immune cell types, such as B cells, natural killer (NK) cells, dendritic cells, and neutrophils, impact the metabolism within the TME. In general, immune cells compete for metabolic resources with the tumor cells. B cells release immunosuppressive cytokines, which suppress cytotoxic T cells and promote tumor-supportive metabolism, and metabolites such as lactate and adenosine pathway intermediates, as well as produce antibodies that activate complement and recruit macrophages and neutrophils [91]. Relative hypoglycemia and hypoxia produced by the tumor cells lead to decreased interferon-gamma production, granzyme and

perforin release, metabolic activity, and tumor-killing capacity in NK cells [92]. Tumor-derived lipids present in certain tumors lead to endoplasmic reticulum stress, reduced antigen presentation, and impaired T cell activation in dendritic cells [93]. Lastly, neutrophil extracellular traps, whose formation highly depends on glucose metabolism, capture circulating tumor cells, promote metastasis, and remodel extracellular matrix metabolism [94].

Metabolic remodeling of the TME results from a multitude of processes and varies with genetic background, environment, and disease stage. Recognizing when metabolism is upstream versus downstream of the intended target is important in decision-making regarding therapeutic prioritization [95]. Interventions that target causal metabolic dependencies or early metabolites, which shape immune phenotypes, are more likely to be disease-modifying. Targeting later and more adaptive metabolic alterations will sensitize tumors to other therapies or relieve symptoms rather than serve as curative therapies [96].

Bioengineering approaches for metabolic manipulation of tumors

While bioengineering research has traditionally focused on tissue regeneration and wound healing [97,98], recent work expands these design principles to drug delivery and cancer therapy, with an emphasis on metabolic manipulation [99,100]. In the past decade, research has interfaced cancer metabolism with novel biomaterial systems and platforms (Figure 3). We divide approaches to modulate tumor metabolism into the following four strategies: (i) prevent tumor uptake of essential metabolites; (ii) sustain the delivery of metabolic inhibitors; (iii) degrade essential or immunosuppressive metabolites within the TME; and (iv) produce toxic or immunostimulant metabolites.

Prevention of tumor uptake of essential metabolites

Clinically, transarterial embolization is used to treat well-vascularized, unresectable tumors, such as hepatocellular and renal carcinomas [101,102]. In this procedure, deployed polymer gels or microspheres of gelatin, poly(vinyl alcohol), or ethylene(vinyl alcohol) occlude the tumor vasculature and prevent metabolite uptake [103,104]. While capable of blocking vasculature and stunting tumor progression, incomplete embolization remains a concern with conventional therapies [105,106]. By improving intratumoral perfusion of oncolytic materials and exploiting the local metabolism of the TME, these innovative embolization technologies aim to enhance tumor extirpation and treatment efficacy. Such TME-responsive therapies leverage the hypoxia, acidity, immunosuppression, and neovascularization of the tumor to activate and enrich embolic agents. Responsive polymers that form *in situ* covalent hydrogels at body temperature or in response to the acidic pH of the TME, copper- and phosphate-activated nanochelators, and glutathione- and hydrogen peroxide-sensing nanoparticles are effective treatments for tumor embolization in rat kidney, mouse pancreatic, breast, and colon, as well as mouse and rabbit liver tumor models [107–111]. In China, a currently ongoing single-center, randomized controlled clinical trial is investigating the efficacy of surgery versus targeting intratumoral lactic acidosis transcatheter arterial chemoembolization (TILA-TACE) for resectable hepatocellular carcinoma. This technique produces smaller residual tumor volumes compared with TACE alone and improves overall survival in preliminary retrospective studies [112].

However, with these TME-engaging strategies, polymer diffusion is limited and incapable of achieving complete tumor perfusion before gelation. Several techniques are being developed to improve the perfusion of embolic agents and prevent premature embolic agent release while maintaining limited biotoxicity and multifunctional payloads. For example, tumor platelet depletion disrupts vascular barriers and increases the accumulation of nanoparticles. Tumor platelet-neutralizing antibodies, which are released in response to cleavage by tumor-associated matrix metalloproteases of the nanoparticle system [core consisting of copolymer poly(etherimide)-poly(lactic-co-glycolic acid), loaded with antiplatelet antibody and doxorubicin; shell layer

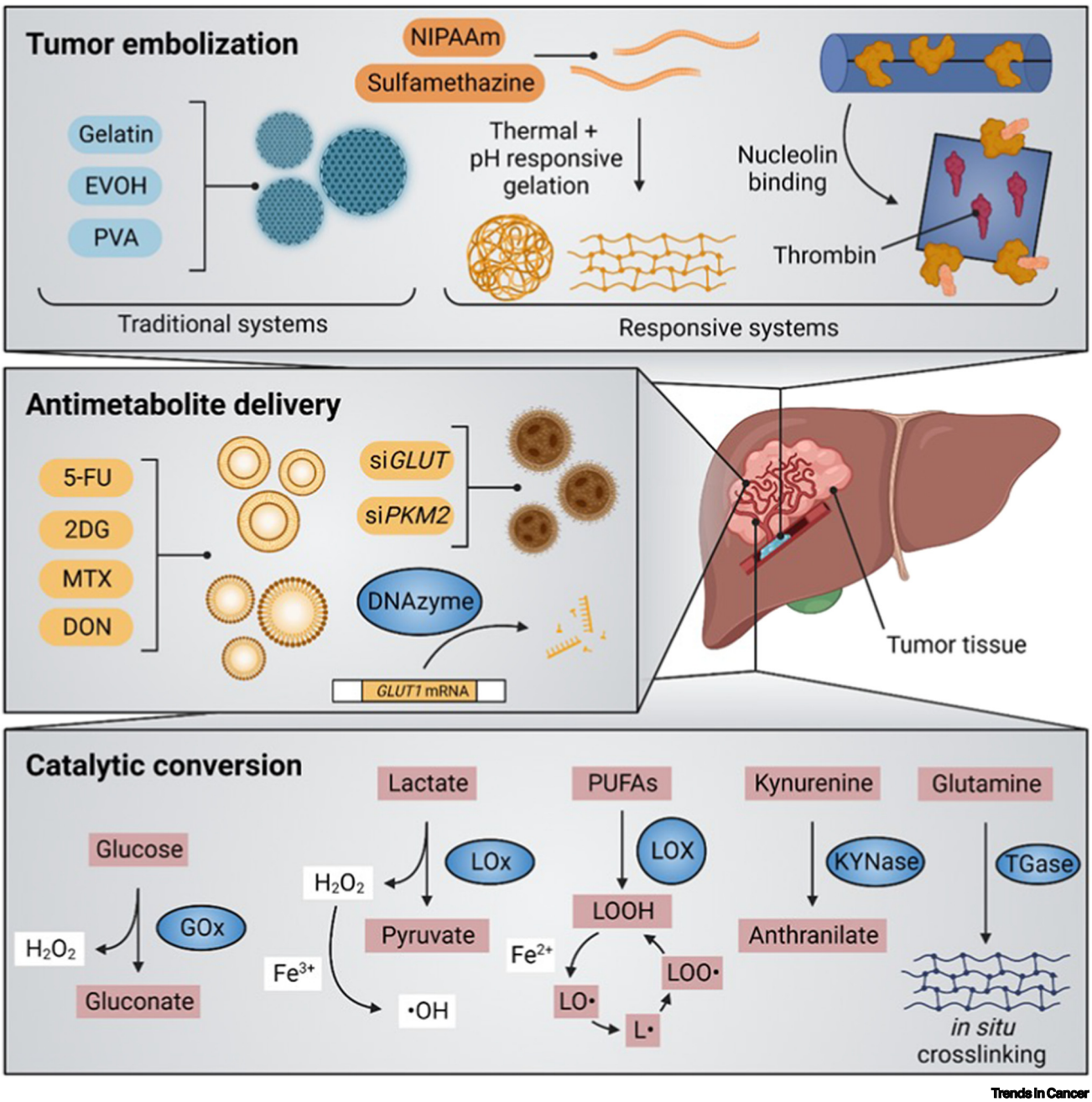

Figure 3. Biomaterials are effective modulators of metabolites in the TME. Embolizing biomaterials prevent tumor perfusion and block metabolite uptake. Numerous polymeric formulations have been used to block the blood vessels of hypervascularized tumors, but recently, materials have been developed that better penetrate into tumor vasculature and cause embolization in response to pH, temperature changes, MMP activation, and nucleolin binding. Small molecule antimetabolites have been delivered by various biomaterial systems, including liposomes, micelles, and polymeric nanoparticles. Small interfering RNAs have also been delivered in lipid nanoparticles to knock down metabolic targets, and Zn^{2+}-activated DNAzymes have also been used. Various biocatalytic biomaterials containing different enzymes—GOx, LOx, LOX, KYNase, and TGase—have been developed to consume tumor-dependent metabolites or to produce toxic metabolites, taking advantage of the metabolites present in the TME. 2DG: 2-deoxyglucose; 5-FU: 5-fluorouracil; DON: 6-diazo-5-oxo-L-norleucine; EVOH: ethylene vinyl alcohol; GLUT: glucose transporter; GOx: glucose oxidase; KYNase: kynureninase; L: lipid alkyl radical; LO: lipid hydroxyl radical; LOO: lipid peroxyl radical; LOOH: lipid peroxide; LOx: lactate oxidase; LOX: lipoxidase; MTX: methotrexate; NIPAAm: poly(*N*-isopropylacrylamide); PKM2: pyruvate kinase; PUFAs: polyunsaturated fatty acids; PVA: poly (vinyl alcohol); TGase: transglutaminase; TME: tumor microenvironment. Created with BioRender.com.

consisting of lecithins and phospholipids with covalently attached polyethylene glycol polymer chains], (PEGylated phospholipids) lead to tumor regression and metastasis inhibition in breast cancer tumor-bearing mice [113]. Nanocarriers co-encapsulated with chemotherapeutic and antifibrinolytic agents, as well as hypoxia-, ultrasound-, laser-, or thermal-activated agents, achieve activated, targeted tumor inhibition, limited widespread thrombosis, and reduced toxicity [113–119]. Perhaps most notably, Li *et al.* report a complex DNA robot for programmed embolization, whereby cylindrical robots localize to tumors by binding nucleolin, which triggers the opening and exposure of thrombin proteins, leading to tumor growth inhibition and necrosis in a breast and ovarian tumor-bearing mouse model [118].

Sustained delivery of metabolic inhibitors

Biomaterial-based delivery systems accumulate in tumors when functionalized with a ligand that binds to a corresponding upregulated receptor on the tumor. Additionally, some tumors exhibit enhanced permeability and retention (EPR) of high molecular weight polymers and nanoparticles in the 20–500 nm size range [120,121]. The EPR effect is due to leaky tumor vasculature and poor lymphatic drainage, leading to the accumulation of biomaterials within tumors. This latter approach is widely investigated; however, the magnitude of the EPR effect in human tumors is smaller than in murine models, where tumors grow at relatively fast rates and possess greater vasculature [121]. Both factors are advantageous and increase drug delivery to tumors, limiting toxicity to healthy tissue. These strategies increase the efficacy of mitotic inhibitors [122,123], DNA intercalators [124,125], and antimetabolites [126]. For example, the safe delivery of antimetabolites that otherwise lead to intolerable systemic toxicity, including 2-deoxyglucose that blocks glycolytic flux [127]. The use of photodynamic nanoparticles provides a means to deliver 5-fluorouracil and methotrexate at otherwise unobtainable concentrations by intravenous administration via photoswitchable and caged drug release [128,129]. Another example is platinum–palladium nanoparticles that deliver 6-diazo-5-oxo-L-norleucine (DON), a reactive glutamine analog, to effectively block tumor glutaminolysis and cause redox imbalance [130,131]. Protein nanoparticles loaded with purpurin, an inhibitor of glutamine dehydrogenase (*GDH1*), afford similar antitumor effects with limited toxicity [132]. A multiresponsive poly(amino acid)-based polymer drug conjugate delivers an EGFR (epidermal growth factor) inhibitor in an acidic and ROS (reactive oxygen species)-responsive manner [133].

Biomaterial-based delivery systems also accommodate the delivery of larger cargo, including proteins and oligonucleotides, for cancer metabolism-focused therapy. These systems include DNAzymes capable of degrading *GLUT1* mRNA at superphysiological zinc concentrations [134] and nanoparticle delivery of small interfering RNAs (siRNAs) to disrupt the expression of *GLUT1* and *GLUT3* [135,136], and pyruvate kinase [72] (*PKM2*) [137,138], to inhibit glycolysis. Lipid nanoparticle-based systems enable the delivery of full-length mRNA transcripts, further expanding therapeutic potential for *in vivo* bioengineering of dysfunctional cancer metabolism. While multiple other metabolic targets are investigated *in vitro* or by constitutive expression of small hairpin RNA (shRNA) in tumor cells *in vivo*, translational strategies of genetic disruption are rarely explored concurrently. This contributes to the difficulty in assessing whether the metabolic targets that underpin deregulated cancer metabolism are also indispensable in healthy cells.

Depletion of essential or immunosuppressive metabolites

As discussed earlier, a key advantage of biomaterial systems is their ability to deliver proteins or nucleic acid cargos to cells and thereby restore, alter, or deplete critical metabolites. Glucose oxidase (GOx), one of the first enzymes investigated for biocatalytic metabolite regulation, rapidly consumes glucose and thus starves tumors of a significant carbon source at sufficient doses [139–141]. Furthermore, in the presence of L-arginine, the GOx byproduct H_2O_2 oxidizes L-arginine to produce nitric oxide, which suppresses tumor growth through multiple mechanisms,

including promoting oxidative [142]. Cancer cell debris can be metabolized to liberate key nutrients, making it a critical therapeutic target [143,144]. For example, nanoparticles consisting of lipoxidase (LOX) and an iron catalyst produce cytotoxic lipid radicals by utilizing the cellular debris of cancer cells as fuel for the reaction [145]. Glucose depletion nanotherapies induce transient systemic hypoglycemia, fatigue, reduced body weight, and, in more extreme cases, tau pathology and synaptic dysfunction in small animals [146,147].

Although immunosuppressive metabolites such as lactate, kynurenine, methionine, and PGs do not directly promote cancer cell proliferation, they facilitate tumor progression by suppressing immune cell activation. Therefore, reducing access to these metabolites slows tumor progression. For example, depletion of lactate in the TME by lactate oxidase (LOx) nanocapsules recovers activation of effector T cells and improves T cell infiltration, resulting in a more robust response to anti-PD-L1 therapy [148]. H_2O_2 produced by LOx elevates intratumoral concentrations of cytotoxic hydroxyl radicals when combined with ferric ions [149]. Similarly, kynureninase (KYNase) nanoparticles restore the proliferation and tumor infiltration of T effector cells to inhibit primary and metastatic disease by reducing TME kynurenine levels in indoleamine-2,3-dioxygenase (*IDO1*)-positive cancers [150]. While PGs have not yet been enzymatically depleted, nanoparticles delivering cyclooxygenase inhibitors limit PG secretion [151]. Gold nanoparticles decorated with lysine and glutamine target the abundance of anabolic enzyme transglutaminase (TGase) in the TME [152]. TGase catalyzes the crosslinking and polymerization of glutamine and lysine, which depletes these amino acids from the TME while promoting targeted intracellular aggregation of the cytotoxic gold nanoparticles. Reported toxicities of gold nanoparticles depend on particle size, surface coating, dose, biodistribution, and degradation rate and range from inflammatory responses to liver gene-expression changes to apoptosis [153].

Enzymes that deplete other critical metabolites, including aspartate, pyruvate, and 2OG, represent areas of significant opportunity for stunting tumor progression and have only been sparingly studied. Similarly, synthetic nanomaterials with enzymatic properties, also known as nanozymes, catalyze metabolic reactions including the consumption of glucose [154,155], generation of reactive oxygen species [156–160], consumption of reactive oxygen species and lactate [161–164], and depletion of amino acids such as glutamine and alanine through transamination [165]. The generation of reactive oxygen species also leads to oxidative damage of nontumor tissue and oxidative stress-driven inflammatory responses.

Biomaterials are also being developed to regulate metabolite availability by noncatalytic means, including functioning as metabolic sinks. Notably, Cui *et al.* describe mitochondrial-localizing nanoparticles composed of copper-chelating polymers to directly strip mitochondrial enzymes of copper, thereby blocking mitochondrial metabolism in cancer cells [166].

Restoration of toxic or immunostimulating metabolites with engineered cellular systems

While 'metabolic biomaterials' show substantial promise with examples of clinical success, few systems utilize two or more reactions. Given the complexity of restoring metabolic homeostasis, bioengineered cellular systems offer increased flexibility for metabolic design, as native cellular pathways and functions can be co-opted to produce treatments or diagnostics (Figure 4). Both bacterial and mammalian systems demonstrate significant therapeutic potential. Tumor-colonizing bacterial strains afford not only a therapeutic effect but also the ability to measure metabolite concentrations in the TME [167]. Metabolic engineering of tumor-colonizing *Escherichia coli* Nissle 1917 by Canale *et al.* restores sufficient intratumoral L-arginine levels to increase T-cell infiltration and proliferation in the TME [168,169]. The restoration of L-arginine, in combination with anti-PD-L1 (programmed death-ligand 1) therapy, markedly improves the

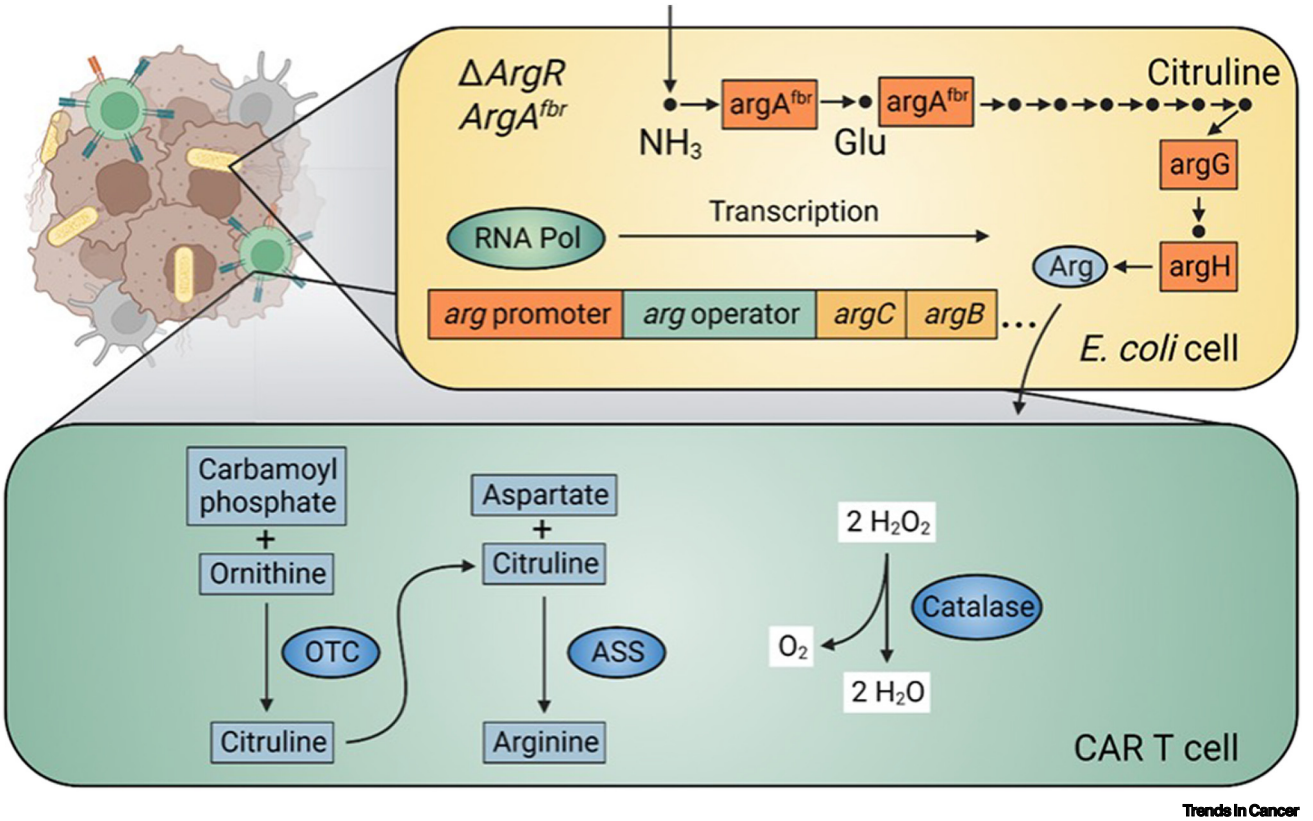

Figure 4. Bioengineering of cellular therapies overcomes the metabolic limitations imposed by the TME. Bioengineered *E. coli* cells have been engineered to supplement arginine concentrations in the TME to allow for proper immune cell function. Bacterial cells have also been used to compete with tumor cells for glucose within the TME (not shown). Chimeric antigen receptor (CAR) T cells have been metabolically bioengineered to express OTC and ASS proteins to supply activated T cells with arginine, which is highly limited in the TME. T cells have also been engineered to express catalase to allow for cell survival in highly oxidative TMEs. *ArgA*^{fbr}: bioengineered feedback-resistant ArgA; ArgR: arginine repressor; ASS: argininosuccinate synthase; OTC: ornithine transcarbamylase; RNA Pol: RNA polymerase; TME: tumor microenvironment. Created with BioRender.com.

antitumor immune response and impedes tumor progression. Nevertheless, in some cases, such as hepatocellular carcinoma, restoration of L-arginine promotes metabolic changes favoring tumorigenesis of cancer cells [170]. Therefore, further investigation is needed to determine the appropriate context for arginine modulation. In another example, bioengineered tumor-colonizing *E. coli* compete with tumors for glucose while simultaneously increasing reactive oxygen species or expressing cytolytic proteins [171,172]. To decrease their immunogenicity, tumor-colonizing *E. coli* are also functionalized with polymers such as poly(ethylene glycol) [173]. *Salmonella typhimurium* with surface-conjugated PEGylated Cu_2O nanoparticles selectively colonizes hypoxic solid tumors to acidify the TME, consequently improving immunogenicity and facilitating tumor-specific phototherapy [174]. Tumor-specific delivery of siRNA via bioengineered *S. typhimurium* knocks down oncogenic [175–177] or metabolic targets [178,179]. Additionally, the delivery of *S. typhimurium* overexpressing L-methionase to tumors results in depletion of methionine, causing methionine stress and inducing cell cycle arrest, thus inhibiting metastasis in murine models of breast, prostate, and liver cancer [180]. Metabolically engineered immune and bacterial cells present a route to overcome the metabolic constraints of wild-type immune cells in the TME.

Chimeric antigen receptor (CAR) T cells express engineered CARs targeting specific tumor-associated antigens. While CAR T cell modification imparts targeting of tumor cells, it does not

Table 1. Featured bioengineered technologies for tumor metabolic regulation

Therapeutic objective	Biomaterial type	Biomaterial system used	Delivery device	Application
Tumor uptake	Particulates	Microspheres	Core P (MAOETIB-GMA) microparticles [103]	Rat kidney tumor embolization model[b]
			GelMA microspheres [107]	Human hepatocellular carcinoma[a] Rabbit ears[c]
		Programmable	Thrombin-delivering DNA nanorobot [118]	Human breast cancer[b] Human ovarian cancer[b] Mouse melanoma[b]
			Thrombin-delivering erythrocytes [115]	Human triple-negative breast cancer in a mouse model[b]
		Hypoxia-activated NPs	TH-302 hypoxia-mediated release of DNA alkylator [58]	Human pancreatic cancer[d]
	Liquids/gels	Temperature responsive	Extravascular gelation shrinkage-derived internal stress strategy [108]	Human pancreatic cancer[b] Mouse mammary carcinoma[b]
		Inhibitor containing	Sodium oxamate TACE [106]	Rabbit VX2 liver tumor[b]
		pH-responsive	TILA-TACE [112]	Human hepatocellular carcinoma[d]
			TACE with bicarbonate infusion [105]	Rabbit VX2 liver tumor[b]
			Hyperbranched polyamino acids [109]	Mouse and human hepatocellular carcinoma[b] Rabbit squamous cell carcinoma[b]
	Mechanical occlusion	Aggregating/targeting nanoparticles	Manganese dioxide/verteporfin (BPD) nanocomposites [110]	Human hepatocellular carcinoma (orthotopic)[b]
			Ion-initiated Imi-OSi nanochelators [111]	Mouse mammary carcinoma[b] Mouse colon carcinoma[b]
			Photo-initiated gold nanorods [119]	Mouse breast cancer[b]
			Platelet-aggregating nanoparticles [117]	Human hepatocellular carcinoma[b]
			Antiplatelet-antibody-containing lipid–peptide nanoparticles [113]	Human breast cancer[b] Human lung cancer[a]
			Thrombin-delivering nanoparticles [114,116]	Mouse melanoma[b] Mouse mammary carcinoma[b]
Metabolic inhibitors	Nanoparticles	Protein-based mitotic inhibitor NPs	PTX-expansile NPs [122] Poly(1,2-glycerol carbonate)-graft-succinate-PTX NPs [123]	Human malignant pleural mesothelioma[b]
		Lipid-based DNA intercalators	DOX-loaded hydrophobic polymer [124] Doxorubicin-loaded gold NPs [125]	Human liposarcoma[b] Human chondrosarcoma[b] Human epidermoid carcinoma[a]
		Antimetabolite nanomaterials	Iron-oxide nanoparticle-based hyperthermia [126]	Human pancreatic cancer[d] Human liver cancer[d]
			2DG-PLGA NPs [127]	Mouse & human hepatocellular carcinoma[b] Human colorectal adenocarcinoma[b] Human renal cell carcinoma[b] Human pancreatic adenocarcinoma[b]
			Au-PCFU [128]	Human breast cancer[a]
			Phototrexate [129]	Human cervix adenocarcinoma[a]
			DON-loaded platinum–palladium nanoflower [131]	Mouse mammary carcinoma[b]
			Purpurin-loaded BSA-based NPs [132]	Human breast cancer[b]

(continued on next page)

Table 1. (continued)

Therapeutic objective	Biomaterial type	Biomaterial system used	Delivery device	Application
		Glycolytic inhibition materials	Multiresponsive polymer EGFR inhibitor conjugate [133]	Human lung adenocarcinoma[b]
			Anti-GLUT1 DNAzymes [134]	Mouse melanoma[b]
			Gold nanoparticle delivery of GLUT1 siRNA [136]	Human lung adenocarcinoma[b]
			Glycolysis-inhibiting siRNA NPs [135,137,138]	Human glioblastoma[b] Human colorectal carcinoma[a] Human hepatocellular carcinoma[b] Human ovarian cancer[b]
TME regulators	Metabolic biomaterials	Mitochondrial localizing NPs	Mitochondrial localizing copper-chelating NPs [166]	Human breast cancer[b]
		Enzyme-loaded NPs	Ultrasmall GOx–Fe_3O_4 NP-loaded silica NPs [139,141]	Mouse mammary carcinoma[b] Human hepatocellular carcinoma[b]
			GOx–polymer nanogels [140]	Human malignant melanoma[b]
			GOx- and L-Arg-functionalized black phosphorous nanosheets [142]	Mouse glioblastoma[b]
			Tumor-debris-fueled-nanoreactors [145]	Mouse mammary carcinoma[b] Human hepatocellular carcinoma[b] Mouse melanoma[a] Human breast adenocarcinoma[a] Rabbit squamous cell carcinoma[b]
			LOx nanocapsules [148]	Humanized mouse triple-negative breast cancer[b]
			PTFL NPs [149]	Mouse mammary carcinoma[b]
			KYNase NP systems [150]	Mouse melanoma[b]
			COX inhibitor NPs [151]	Mouse mammary carcinoma[b]
			Enzyme-triggered photothermal therapy [152]	Human melanoma[b]
		Nanozymes	Glucose-consuming nanozymes [154,155]	Human hepatocellular carcinoma[b] Mouse mammary carcinoma[b]
			Lactate modulating [164]	Mouse lung[b]
			ROS generators [156–160,163]	Mouse mammary carcinoma[b] Human glioblastoma[b] Mouse melanoma[b] Human breast adenocarcinoma[b] Human hepatocellular carcinoma[b]
			ROS consumers [161,162]	Mouse mammary carcinoma[b]
			NP-catalyzed transamination [165]	Human glioblastoma[a]
Toxins or immunostimulants	Prokaryotic cells	Tumor colonizing *E. coli*	Hypoxia, lactate, and pH biosensors [167]	Mouse B-cell lymphoma[a] Mouse colon carcinoma[b] Mouse non-small cell lung cancer[a] Mouse mammary carcinoma[a]
			L-Arginine-depleting, tumor-localizing *E. coli* [168,169]	Mouse colon adenocarcinoma[b] Mouse melanoma[b] Mouse breast, colon, and lung[b]
			DOX-loaded *E. coli* [171]	Mouse mammary carcinoma[b]
			HlyE-loaded *E. coli* [172]	Human colorectal adenocarcinoma[b]
			Polymer-coated bacteria codelivered with 5-fluorocytosine [173]	Mouse colon carcinoma[b]

Table 1. (continued)

Therapeutic objective	Biomaterial type	Biomaterial system used	Delivery device	Application
		Tumor colonizing *S. typhimurium*	Cu_2O@ΔSt microbiotic nanomedicine [174]	Mouse mammary carcinoma[b] Human pancreatic carcinoma[b]
			Salmonella-based DNA vaccination [175]	Mouse neuroblastoma[b]
			Autophagy-inhibited *Salmonella* [176]	Human liver cancer[a] Human gastric adenocarcinoma[a]
			Attenuated and dephosphorylated *Salmonella* [177]	Human monocyte leukemia[a] Mouse macrophage leukemia[a]
			shIDO-ST [178,179]	Mouse melanoma[b] Mouse pancreatic adenocarcinoma[b]
			Methionase-expressing *Salmonella* (SGN1) [180]	Human xenografts in mice: prostate and triple-negative breast cancer[b] Metastatic mouse models: human prostate, triple-negative breast cancer, and hepatocellular carcinoma[b]
	Eukaryotic cells	Metabolically engineered CAR-T cells	Arginine-low resistance CAR-T [183]	Human lung cancer[a] Human neuroblastoma[b] Human leukemia[b]
			CAR coexpressing catalase [184]	Human ovarian adenocarcinoma[a]
			HPSE-expressing CAR-T [185]	Human neuroblastoma[b] Human melanoma[b]

2DG: 2-deoxyglucose; COX: cyclooxygenase; DON: diazo-5-oxo-L-norleucine; PLGA: poly(lactic-co-glycolic) acid; Au-PCFU: fluorouracil conjugated gold nanoparticles; BPD: benzoporphyrin derivative; BSA: bovine serum albumin; DOX; doxorubicin; HPSE: heparanase; shIDO-ST: *Salmonella thyphimurium* transformed with shRNA against the immunosuppressive molecule indoleamine 2,3-dioxygenase 1; MAOETIB-GMA: 2-methacryloyloxyethyl (2,3,5-triiodobenzoate)-monomer glycidyl methacrylate; NP: nanoparticle; PTFL: tannic acid coordination complexes-coated perfluoroocyl bromide nanodroplets with lactate oxidases loading; PTX: paclitaxel.
[a]*In vitro*.
[b]*In vivo*.
[c]*Ex vivo*.
[d]Clinical trials.

guarantee tumor infiltration or their proliferation in the TME [181]. The metabolic requirements of CAR T cells are akin to those of wild-type T cells and, like most tumor cells, require large glycolytic inputs to function [182]. Metabolic reprogramming of CAR T cells via choice of signaling motifs to enhance persistence and genetic modifications is a strategy to improve tumor control. For example, the lack of L-arginine in the TME leads to reduced T cell proliferation, but the expression of argininosuccinate synthase or ornithine transcarbamylase in CAR T cells allows for unobstructed proliferation [183]. Alternatively, expression of catalase in CAR T cells prevents loss of effector function caused by high oxidative stress in the TME [184]. Finally, the expression of the catabolic enzyme heparinase allows CAR T cells to degrade the dense extracellular matrix of the TME and infiltrate into tumor tissue [185]. Together, these strategies (Table 1) demonstrate that altering the metabolic state of the TME or the metabolic requirements of cells within it disrupts the evasion of antitumor immunity and impedes tumor progression. That said, the known toxicities of CAR T therapies are cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome, chronic immune activation, prolonged cytokine signaling, metabolic exhaustion, and secondary malignancies (rarely), all of which are key limitations that need to be addressed. However, there are no specific metabolic toxicities.

Challenges in this field include the toxicity and stability of these technologies, given that metabolic targets are widely present in normal physiology. Short-term safety in animal models appears promising, although long-term metabolic effects remain unknown. In particular, the use of

nanoparticle-based technologies leads to off-target organ accumulation and, in some cases, persistence, which may afford chronic inflammation, long-term immune modulation, and repeated dosing toxicity [186]. Additionally, nanoparticles and biomaterials may trigger short-lived innate immune responses, such as complement activation (e.g., complement activation-related pseudoallergy), macrophage activation, cytokine release, and neutrophil recruitment [187]. Strategies to limit systemic toxicity include (i) leveraging targeted drug particles and employing stimulus-responsive catalysts activated only by tumor pH, reactive oxygen species, and enzymes; (ii) utilizing biodegradable materials that excrete metabolites; (iii) delivering drugs locally via intratumoral injection or implantable materials; and, (iv) employing genetic kill or 'off' switches in engineered immune cells if unintended toxicity occurs.

Concluding remarks and future perspectives

Natural, synthetic, and semi-synthetic bioengineered systems offer an alternative approach to limiting cancer cells' access to essential metabolites. Due to their modularity, these bioengineered systems, housed within nanoparticle and hydrogel delivery vehicles, can consume or produce metabolites of interest. The materials explored here are susceptible to degradation over time. Whether improving enzyme kinetics and physiological stability result in more robust systems is an open question. Similarly, whether these catalytic biomaterials can be extended to more complex metabolic cascades for *in situ* metabolite biosynthesis is an exciting future direction that remains to be scrutinized.

Bioengineered cellular therapies allow the rerouting of metabolites through existing metabolic networks to enable multistep syntheses or multi-input systems. The many metabolic co-dependencies of distinct cell types within the TME complicate the approaches applied to the restoration or depletion of metabolites. Engineering immune cells with tumor-orthogonal metabolic requirements will lead to robust antitumor immunity. Alternatively, modifying metabolic proteins to be uninhibited by antimetabolites will allow for selective inhibition in cancer cells without hindering immune cell function. Ultimately, utilizing metabolic engineering in cellular therapies may allow for the re-establishment of homeostasis across metabolic diseases.

The TME and the metabolic requirements of the cells within it contribute to disease progression, although this varies by genotype, location, and cancer type. Key questions remain regarding how the co-occurrence of oncogenic mutations changes their metabolic manifestations in cancer cells, although some have already been elucidated, such as KRAS and TP53 (see Outstanding questions). Further investigations should also include identifying the cancer types and stages that are most sensitive or resistant to a given therapeutic strategy, especially as emerging evidence suggests that tumor metastases are metabolically adaptive. Restoring the TME to metabolic homeostasis in its entirety is likely unfeasible, but targeted strategies to restore singular functionality are astonishingly successful. However, key hurdles remain in identifying the extent of metabolic overlap between the TME and healthy cells in order to mitigate leakage when targeting specific processes. Furthermore, targeting tumor heterogeneity necessitates the use of aggressive combination therapies, thus increasing the likelihood of off-tumor, on-target toxicity. The TME also capitalizes on metabolic redundancy found within its gross network of cell types to acquire resources for tumor progression. In practical translation, further barriers, including regulatory and safety requirements, scalability, materials, and economic and commercialization strategies, will need to be addressed as these technologies reach later stages of development. To mitigate these obstacles, we recommend greater implementation of biomaterials and bioengineered technologies as a primary or adjuvant therapy. For example, a biomaterial implant at the tumor site that activates the therapy only at the tumor to reduce side effects, or an mRNA LNP (lipid nanoparticle) drug system that targets and only expresses in the tumor to produce an

Outstanding questions

How do the metabolic dependencies of metastatic lesions differ from primary tumors, and how should therapeutic strategies account for the interplay between tumor cell origin and the metabolic environment of the diseased organ?

What diagnostic tools need to be developed to define the best patient populations for each therapy?

How do comorbidities (e.g., diabetes) alter the tumor microenvironment and influence the responsiveness of the tumor microenvironment to these therapies?

How does diet influence the responsiveness of the tumor microenvironment to these therapies?

In which cancer stages are these therapeutics most efficacious?

How do we avoid collateral depletion of metabolites needed by tumor-infiltrating immune cells?

Many metabolic changes can be oncogenic or tumor suppressive depending on the context. How can their roles be more clearly defined?

enzyme that depletes a key metabolite. Development should also include more involved collaborations with clinicians to not only confirm the need for a new technology in a particular therapeutic niche but also ensure that the technology will be usable in the clinic from both technical and practical standpoints. As a nascent area with substantial promise to radically change clinical practice and patient outcomes, we advocate for further investigation and creative solutions.

Acknowledgments

Funding for this work was provided in part by the National Institutes of Health [NIH U01CA265713, R01EB029483, R01CA272637 (to W.W.W. and M.W.G.)], and the William Fairfield Warren Professorship (to M.W.G.). We also thank Drs. Tamar Babila Propp, Chandrajit P. Raut, and Yolonda L. Colson for their helpful comments and insights.

Declaration of interests

The authors have no conflicts of interest regarding this work.

Declaration of Generative AI and AI-assisted technologies in the writing process

No AI tools or writing instruments were used in the preparation of this manuscript—just red-pen markups and repeated drafts.

References

1. Martinez-Reyes, I. and Chandel, N.S. (2021) Cancer metabolism: looking forward. *Nat. Rev. Cancer* 21, 669–680
2. Punnasseril, J.M.J. *et al.* (2025) Metabolic reprogramming of cancer cells and therapeutics targeting cancer metabolism. *Cancer Med.* 14, e71244
3. DelNero, P. *et al.* (2018) Cancer metabolism gets physical. *Sci. Transl. Med.* 10, eaaq1011
4. Reznik, E. *et al.* (2018) A landscape of metabolic variation across tumor types. *Cell Syst.* 6, 301–313.e3
5. Mao, X. *et al.* (2021) Crosstalk between cancer-associated fibroblasts and immune cells in the tumor microenvironment: new findings and future perspectives. *Mol. Cancer* 20, 131
6. Okahashi, N. *et al.* (2025) Metabolic flux and flux balance analyses indicate the relevance of metabolic thermogenesis and aerobic glycolysis in cancer cells. *Metab. Eng.* 92, 185–193
7. Harimoto, T. *et al.* (2025) Delivering living medicines with biomaterials. *Nat. Rev. Mater.* 10, 191–210
8. Ma, C. *et al.* (2019) Biomaterial-based metabolic regulation in regenerative engineering. *Adv. Sci. (Weinh.)* 6, 1900819
9. Zbiral, B. *et al.* (2023) Characterization of breast cancer aggressiveness by cell mechanics. *Int. J. Mol. Sci.* 24, 12208
10. Warburg, O. (1925) The metabolism of carcinoma cells. *J. Cancer Res.* 9, 148–163
11. Cai, L. *et al.* (2025) High glucose contribution to the TCA cycle is a feature of aggressive non-small cell lung cancer in patients. *Cancer Discov.* 15, 702–716
12. Liu, Y. *et al.* (2022) Pyruvate carboxylase promotes malignant transformation of papillary thyroid carcinoma and reduces iodine uptake. *Cell Death Discov.* 8, 423
13. Xie, X. *et al.* (2025) Bridging epigenomics and tumor immunometabolism: molecular mechanisms and therapeutic implications. *Mol. Cancer* 24, 71
14. Pavinato, L. and Baggiolini, A. (2025) Oncogenic competence: balancing mutations, cellular state, and microenvironment. *Trends Cancer* 11, 276–285
15. Cagan, A. *et al.* (2022) Somatic mutation rates scale with lifespan across mammals. *Nature* 604, 517–524
16. Tibély, G. *et al.* (2022) Distinguishing excess mutations and increased cell death based on variant allele frequencies. *PLoS Comput. Biol.* 18, e1010048
17. Mendiratta, G. *et al.* (2021) Cancer gene mutation frequencies for the U.S. population. *Nat. Commun.* 12, 5961
18. Schwartzenberg-Bar-Yoseph, F. *et al.* (2004) The tumor suppressor p53 down-regulates glucose transporters *GLUT1* and *GLUT4* gene expression. *Cancer Res.* 64, 2627–2633
19. Liu, T. *et al.* (2023) Role of human monocarboxylate transporter 1 (hMCT1) and 4 (hMCT4) in tumor cells and the tumor microenvironment. *Cancer Manag. Res.* 15, 957–975
20. Ros, S. *et al.* (2017) 6-Phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 is essential for p53-null cancer cells. *Oncogene* 36, 3287–3299
21. Lowman, X.H. *et al.* (2019) p53 promotes cancer cell adaptation to glutamine deprivation by upregulating Slc7a3 to increase arginine uptake. *Cell Rep.* 26, 3051–3060.e4
22. Tajan, M. *et al.* (2018) A role for p53 in the adaptation to glutamine starvation through the expression of SLC1A3. *Cell Metab.* 28, 721–736.e6
23. Buczkowska, J. and Szeliga, M. (2023) Two faces of glutaminase GLS2 in carcinogenesis. *Cancers (Basel)* 15, 5566
24. Jiang, P. *et al.* (2013) Reciprocal regulation of p53 and malic enzymes modulates metabolism and senescence. *Nature* 493, 689–693
25. Li, L. *et al.* (2019) p53 regulation of ammonia metabolism through urea cycle controls polyamine biosynthesis. *Nature* 567, 253–256
26. Li, X. *et al.* (2016) The MDM2–p53–pyruvate carboxylase signalling axis couples mitochondrial metabolism to glucose-stimulated insulin secretion in pancreatic β-cells. *Nat. Commun.* 7, 11740
27. Sahin, E. *et al.* (2011) Telomere dysfunction induces metabolic and mitochondrial compromise. *Nature* 470, 359–365
28. Jiang, L. *et al.* (2015) Ferroptosis as a p53-mediated activity during tumour suppression. *Nature* 520, 57–62
29. Wang, H. *et al.* (2023) Targeting p53 pathways: mechanisms, structures and advances in therapy. *Signal Transduct. Target. Ther.* 8, 92
30. Wang, X. *et al.* (2025) Multiple roles of p53 in cancer development: regulation of tumor microenvironment, m6A modification and diverse cell death mechanisms. *J. Adv. Res.* 75, 539–560
31. Chen, X. *et al.* (2022) Mutant p53 in cancer: from molecular mechanism to therapeutic modulation. *Cell Death Dis.* 13, 974
32. Hoxhaj, G. and Manning, B.D. (2020) The PI3K–AKT network at the interface of oncogenic signalling and cancer metabolism. *Nat. Rev. Cancer* 20, 74–88
33. Takahashi, M. *et al.* (2023) Activating mutations in EGFR and PI3K promote ATF4 induction for NSCLC cell survival during amino acid deprivation. *Heliyon* 9, e14799
34. Ilic, N. *et al.* (2017) *PIK3CA* mutant tumors depend on oxoglutarate dehydrogenase. *Proc. Natl. Acad. Sci. U. S. A.* 114, E3434–E3443
35. Chen, W. *et al.* (2022) PIK3CA mutation affects the proliferation of colorectal cancer cells through the PI3K-MEK/PDK1-GPT2 pathway. *Oncol. Rep.* 47, 11
36. Koundouros, N. *et al.* (2020) Metabolic fingerprinting links oncogenic PIK3CA with enhanced arachidonic acid-derived eicosanoids. *Cell* 181, 1596–1611.e27

37. Kim, J. *et al.* (2025) Prevalence and clinical implications of PIK3CA aberrations across cancer types: a real-world next-generation sequencing approach. *Cancer Genet.* 296–297, 133–143
38. Kerk, S.A. *et al.* (2021) Metabolic networks in mutant KRAS-driven tumours: tissue specificities and the microenvironment. *Nat. Rev. Cancer* 21, 510–525
39. Kremer, D.M. *et al.* (2021) GOT1 inhibition promotes pancreatic cancer cell death by ferroptosis. *Nat. Commun.* 12, 4860
40. Kim, J. *et al.* (2017) CPS1 maintains pyrimidine pools and DNA synthesis in KRAS/LKB1-mutant lung cancer cells. *Nature* 546, 168–172
41. Amendola, C.R. *et al.* (2019) KRAS4A directly regulates hexokinase 1. *Nature* 576, 482–486
42. Najumudeen, A.K. *et al.* (2021) The amino acid transporter SLC7A5 is required for efficient growth of KRAS-mutant colorectal cancer. *Nat. Genet.* 53, 16–26
43. Son, J. *et al.* (2013) Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. *Nature* 496, 101–105
44. Jiang, H. *et al.* (2022) Ferrous iron–activatable drug conjugate achieves potent MAPK blockade in *KRAS*-driven tumors. *J. Exp. Med.* 219, e20210739
45. Yang, Y. *et al.* (2023) KRAS mutations in solid tumors: characteristics, current therapeutic strategy, and potential treatment exploration. *J. Clin. Med.* 12, 709
46. Tambay, V. *et al.* (2021) MYC rules: leading glutamine metabolism toward a distinct cancer cell phenotype. *Cancers (Basel)* 13, 4484
47. Zhao, X. *et al.* (2019) SLC1A5 glutamine transporter is a target of MYC and mediates reduced mTORC1 signaling and increased fatty acid oxidation in long-lived *Myc* hypomorphic mice. *Aging Cell* 18, e12947
48. Osthus, R.C. *et al.* (2000) Deregulation of glucose transporter 1 and glycolytic gene expression by c-Myc. *J. Biol. Chem.* 275, 21797–21800
49. Shim, H. *et al.* (1997) c-Myc transactivation of LDH-A: implications for tumor metabolism and growth. *Proc. Natl. Acad. Sci. U. S. A.* 94, 6658–6663
50. Zhang, Y. *et al.* (2022) SHMT2 promotes cell viability and inhibits ROS-dependent, mitochondrial-mediated apoptosis via the intrinsic signaling pathway in bladder cancer cells. *Cancer Gene Ther.* 29, 1514–1527
51. Duffy, M.J. *et al.* (2021) MYC as a target for cancer treatment. *Cancer Treat. Rev.* 94, 102154
52. Liu, S. *et al.* (2020) Isocitrate dehydrogenase variants in cancer—cellular consequences and therapeutic opportunities. *Curr. Opin. Chem. Biol.* 57, 122–134
53. Dang, L. *et al.* (2009) Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. *Nature* 462, 739–744
54. Gunn, K. *et al.* (2023) *(R)*-2-Hydroxyglutarate inhibits KDM5 histone lysine demethylases to drive transformation in *IDH*-mutant cancers. *Cancer Discov.* 13, 1478–1497
55. Wiehle, L. *et al.* (2017) mIDH-associated DNA hypermethylation in acute myeloid leukemia reflects differentiation blockage rather than inhibition of TET-mediated demethylation. *Cell Stress* 1, 55–67
56. Zhang, S. *et al.* (2024) Tumor initiation and early tumorigenesis: molecular mechanisms and interventional targets. *Signal Transduct. Target. Ther.* 9, 149
57. Zhao, Y. *et al.* (2023) Stromal cells in the tumor microenvironment: accomplices of tumor progression? *Cell Death Dis.* 14, 587
58. Wang, J. *et al.* (2022) Elucidating tumor-stromal metabolic crosstalk in colorectal cancer through integration of constraint-based models and LC-MS metabolomics. *Metab. Eng.* 69, 175–187
59. Dang, L. *et al.* (2016) IDH mutations in cancer and progress toward development of targeted therapeutics. *Ann. Oncol.* 27, 599–608
60. Xu, W. *et al.* (2011) Oncometabolite 2-hydroxyglutarate is a competitive inhibitor of α-ketoglutarate-dependent dioxygenases. *Cancer Cell* 19, 17–30
61. Batra, R.N. *et al.* (2021) DNA methylation landscapes of 1538 breast cancers reveal a replication-linked clock, epigenomic instability and *cis*-regulation. *Nat. Commun.* 12, 5406
62. Humphries, S. *et al.* (2023) Crosstalk between DNA methylation and hypoxia in acute myeloid leukaemia. *Clin. Epigenetics* 15, 150
63. Zhao, S.G. *et al.* (2020) The DNA methylation landscape of advanced prostate cancer. *Nat. Genet.* 52, 778–789
64. Sun, D. *et al.* (2022) DNA hypermethylation modification promotes the development of hepatocellular carcinoma by depressing the tumor suppressor gene *ZNF334*. *Cell Death Dis.* 13, 446
65. Wang, X. *et al.* (2024) Acetylation model predicts prognosis of patients and affects immune microenvironment infiltration in epithelial ovarian carcinoma. *J. Ovarian Res.* 17, 150
66. Peng, T. *et al.* (2024) Novel lactylation-related signature to predict prognosis for pancreatic adenocarcinoma. *World J. Gastroenterol.* 30, 2575–2602
67. Almalki, A.A. (2025) The role of epigenetics in cancer: from pathways to the clinic. *J. Family Med. Prim. Care* 14, 3104–3114
68. Carmona-Fontaine, C. *et al.* (2017) Metabolic origins of spatial organization in the tumor microenvironment. *Proc. Natl. Acad. Sci. U. S. A.* 114, 2934–2939
69. Jones, R.G. *et al.* (2025) Conversations at the interface of metabolism and immunity. *Cell* 85, 3730–3733
70. Zhou, D. *et al.* (2022) The significance of glycolysis in tumor progression and its relationship with the tumor microenvironment. *Front. Pharmacol.* 13, 1091779
71. Li, Z. *et al.* (2023) Lactate in the tumor microenvironment: a rising star for targeted tumor therapy. *Front. Nutr.* 10, 1113739
72. Jendrisek, G. *et al.* (2026) Beyond the membrane: rethinking EGFR signaling in physiology and cancer. *Cell. Mol. Life Sci.* 83, 109
73. Sharma, S. *et al.* (2022) Targeting fuel pocket of cancer cell metabolism: a focus on glutaminolysis. *Biochem. Pharmacol.* 198, 114943
74. Li, T. *et al.* (2025) Cancer-associated fibroblasts foster a high-lactate microenvironment to drive perineural invasion in pancreatic cancer. *Cancer Res.* 85, 2199–2217
75. Bertero, T. *et al.* (2019) Tumor-stroma mechanics coordinate amino acid availability to sustain tumor growth and malignancy. *Cell Metab.* 29, 124–140.e10
76. Kay, E.J. *et al.* (2022) Cancer-associated fibroblasts require proline synthesis by PYCR1 for the deposition of pro-tumorigenic extracellular matrix. *Nat. Metab.* 4, 693–710
77. Kane, K. *et al.* (2025) The influence of endothelial metabolic reprogramming on the tumor microenvironment. *Oncogene* 44, 51–63
78. Elia, I. and Haigis, M.C. (2021) Metabolites and the tumour microenvironment: from cellular mechanisms to systemic metabolism. *Nat. Metab.* 3, 21–32
79. Delgoffe, G.M. and Powell, J.D. (2015) Feeding an army: the metabolism of T cells in activation, anergy, and exhaustion. *Mol. Immunol.* 68, 492–496
80. Davern, M. *et al.* (2023) Nutrient deprivation and hypoxia alter T cell immune checkpoint expression: potential impact for immunotherapy. *J. Cancer Res. Clin. Oncol.* 149, 5377–5395
81. Geiger, R. *et al.* (2016) L-Arginine modulates T cell metabolism and enhances survival and anti-tumor activity. *Cell* 167, 829–842.e13
82. Pallotta, M.T. *et al.* (2022) Indoleamine 2,3-dioxygenase 1 (IDO1): an up-to-date overview of an eclectic immunoregulatory enzyme. *FEBS J.* 289, 6099–6118
83. Ho, P.-C. *et al.* (2015) Phosphoenolpyruvate is a metabolic checkpoint of anti-tumor T cell responses. *Cell* 162, 1217–1228
84. Pfefer, T. *et al.* (2026) Immunometabolites and cancer: the role of 2-hydroxyglutarate, succinate, fumarate and itaconate in tumour development and anti-tumour immunity. *Immunol. Lett.* 279, 107153
85. Saidu, N.E.B. *et al.* (2017) Dimethyl fumarate controls the NRF2/DJ-1 axis in cancer cells: therapeutic applications. *Mol. Cancer Ther.* 16, 529–539
86. Li, S. *et al.* (2022) Metabolism drives macrophage heterogeneity in the tumor microenvironment. *Cell Rep.* 39, 110609
87. Mehla, K. and Singh, P.K. (2019) Metabolic regulation of macrophage polarization in cancer. *Trends Cancer* 5, 822–834

88. Li, M. *et al.* (2023) Metabolism, metabolites, and macrophages in cancer. *J. Hematol. Oncol.* 16, 80
89. Noe, J.T. *et al.* (2021) Lactate supports a metabolic-epigenetic link in macrophage polarization. *Sci. Adv.* 7, eabi8602
90. Palmieri, E.M. *et al.* (2017) Pharmacologic or genetic targeting of glutamine synthetase skews macrophages toward an M1-like phenotype and inhibits tumor metastasis. *Cell Rep.* 20, 1654–1666
91. Pearce, E.L. and Pearce, E.J. (2013) Metabolic pathways in immune cell activation and quiescence. *Immunity* 38, 633–643
92. Steinert, E.M. *et al.* (2025) Mitochondrial respiration is necessary for $CD8^+$ T cell proliferation and cell fate. *Nat. Immunol.* 26, 1267–1274
93. Fu, Z. *et al.* (2025) Endoplasmic reticulum stress orchestrates tumor metabolism and immunity: new insights into immunometabolic therapeutics. *Front. Immunol.* 16, 1674163
94. Chen, L. *et al.* (2024) The lipid-metabolism enzyme ECI2 reduces neutrophil extracellular traps formation for colorectal cancer suppression. *Nat. Commun.* 15, 7184
95. Tufail, M. *et al.* (2024) Altered metabolism in cancer: insights into energy pathways and therapeutic targets. *Mol. Cancer* 23, 203
96. Liu, S. *et al.* (2024) Metabolic reprogramming and therapeutic resistance in primary and metastatic breast cancer. *Mol. Cancer* 23, 261
97. Sadtler, K. *et al.* (2016) Design, clinical translation and immunological response of biomaterials in regenerative medicine. *Nat. Rev. Mater.* 1, 16040
98. Cook, K.A. *et al.* (2021) *In situ* gelling and dissolvable hydrogels for use as on-demand wound dressings for burns. *Biomater. Sci.* 9, 6842–6850
99. Stine, Z.E. *et al.* (2022) Targeting cancer metabolism in the era of precision oncology. *Nat. Rev. Drug Discov.* 21, 141–162
100. Ekladious, I. *et al.* (2019) Polymer–drug conjugate therapeutics: advances, insights and prospects. *Nat. Rev. Drug Discov.* 18, 273–294
101. Fite, E.L. and Makary, M.S. (2024) Transarterial chemoembolization treatment paradigms for hepatocellular carcinoma. *Cancers (Basel)* 16, 2430
102. DePietro, D.M. *et al.* (2024) Chemoembolization beyond hepatocellular carcinoma: what tumors can we treat and when? *Semin. Intervent. Radiol.* 41, 27–47
103. Hagit, A. *et al.* (2010) Synthesis and characterization of dual modality (CT/MRI) core–shell microparticles for embolization purposes. *Biomacromolecules* 11, 1600–1607
104. Hu, J. *et al.* (2019) Advances in biomaterials and technologies for vascular embolization. *Adv. Mater.* 31, e1901071
105. Doemel, L.A. *et al.* (2022) Comparison of metabolic and immunologic responses to transarterial chemoembolization with different chemoembolic regimens in a rabbit VX2 liver tumor model. *Eur. Radiol.* 32, 2437–2447
106. Luo, Y. *et al.* (2024) Targeting metabolic reprogramming promotes the efficacy of transarterial chemoembolization in the rabbit VX2 liver tumor model. *Oncol. Lett.* 27, 111
107. Tian, S.J. *et al.* (2025) Photopolymerized pH-responsive GelMA microspheres with doxorubicin modification for embolization therapy. *J. Drug Deliv. Sci. Technol.* 114, 107446
108. Zhang, K. *et al.* (2019) Extravascular gelation shrinkage-derived internal stress enables tumor starvation therapy with suppressed metastasis and recurrence. *Nat. Commun.* 10, 5380
109. Lu, D. *et al.* (2020) Tumor noninvasive and target embolization therapy platform by intravenous injection based on acidic microenvironment-responsive hyperbranched poly(amino acid)s. *ACS Cent. Sci.* 6, 1977–1986
110. Wang, Y. *et al.* (2020) Tumor vessel targeted self-assemble nanoparticles for amplification and prediction of the embolization effect in hepatocellular carcinoma. *ACS Nano* 14, 14907–14918
111. Yang, Y. *et al.* (2019) Responsively aggregatable sub-6 nm nanochelators induce simultaneous antiangiogenesis and vascular obstruction for enhanced tumor vasculature targeted therapy. *Nano Lett.* 19, 7750–7759
112. Jin, K. *et al.* (2025) Bicarbonate-integrated transarterial chemoembolization (TACE) in real-world hepatocellular carcinoma. *Signal Transduct. Target. Ther.* 10, 281
113. Li, S. *et al.* (2017) Nanoparticle-mediated local depletion of tumour-associated platelets disrupts vascular barriers and augments drug accumulation in tumours. *Nat. Biomed. Eng.* 1, 667–679
114. Yin, J.J. *et al.* (2021) Thrombin based photothermal-responsive nanoplatform for tumor-specific embolization therapy. *Small* 17, e2105033
115. Zhu, Y.-X. *et al.* (2021) Repurposing erythrocytes as a "Photoactivatable Bomb": a general strategy for site-specific drug release in blood vessels. *Small* 17, 2100753
116. Shao, Y. *et al.* (2020) US-triggered ultra-sensitive "thrombus constructor" for precise tumor therapy. *J. Control. Release* 318, 136–144
117. Ma, Z.Y. *et al.* (2021) Selective thrombosis of tumor for enhanced hypoxia-activated prodrug therapy. *Adv. Mater.* 33, 2104504
118. Li, S. *et al.* (2018) A DNA nanorobot functions as a cancer therapeutic in response to a molecular trigger *in vivo*. *Nat. Biotechnol.* 36, 258–264
119. Hong, S. *et al.* (2022) Photo-initiated coagulation activation and fibrinolysis inhibition for synergetic tumor vascular infarction via a gold nanorods-based nanosystem. *CCS Chem.* 4, 1770–1787
120. Ulbrich, K. *et al.* (2016) Targeted drug delivery with polymers and magnetic nanoparticles: covalent and noncovalent approaches, release control, and clinical studies. *Chem. Rev.* 116, 5338–5431
121. Sun, R. *et al.* (2022) The tumor EPR effect for cancer drug delivery: current status, limitations, and alternatives. *Adv. Drug Deliv. Rev.* 191, 114614
122. Liu, R. *et al.* (2016) Nanoparticle tumor localization, disruption of autophagosomal trafficking, and prolonged drug delivery improve survival in peritoneal mesothelioma. *Biomaterials* 102, 175–186
123. Sabatelle, R.C. *et al.* (2022) Ultra-high drug loading improves nanoparticle efficacy against peritoneal mesothelioma. *Biomaterials* 285, 121534
124. Bressler, E.M. *et al.* (2022) Doxorubicin-loaded polymeric meshes prevent local recurrence after sarcoma resection while avoiding cardiotoxicity. *Cancer Res.* 82, 4474–4484
125. Foglietta, F. *et al.* (2025) Bespoke doxorubicin-loaded gold nanoparticles for ultrasound-guided cancer cell killing. *Biomed. Pharmacother.* 193, 118777
126. Kraus, S. *et al.* (2025) Case report: treatment with magnetic nanoparticle-based hyperthermia stabilizes metastatic disease in stage IV primary liver cancer patients. *Front. Oncol.* 15, 1742249
127. Sasaki, K. *et al.* (2021) Nanoparticle-mediated delivery of 2-deoxy-D-glucose induces antitumor immunity and cytotoxicity in liver tumors in mice. *Cell. Mol. Gastroenterol. Hepatol.* 11, 739–762
128. Agasti, S.S. *et al.* (2009) Photoregulated release of caged anticancer drugs from gold nanoparticles. *J. Am. Chem. Soc.* 131, 5728–5729
129. Matera, C. *et al.* (2018) Photoswitchable antimetabolite for targeted photoactivated chemotherapy. *J. Am. Chem. Soc.* 140, 15764–15773
130. Lemberg, K.M. *et al.* (2018) We're not "DON" yet: optimal dosing and prodrug delivery of 6-Diazo-5-oxo-L-norleucine. *Mol. Cancer Ther.* 17, 1824–1832
131. Chen, G. *et al.* (2022) Glutamine antagonist synergizes with electrodynamic therapy to induce tumor regression and systemic antitumor immunity. *ACS Nano* 16, 951–962
132. Xu, L. *et al.* (2021) Nanoparticle-mediated inhibition of mitochondrial glutaminolysis to amplify oxidative stress for combination cancer therapy. *Nano Lett.* 21, 7569–7578
133. Zhao, W. *et al.* (2025) A multi-responsive poly(amino acid) based polymer drug conjugate as a precision cancer therapy strategy for targeted EGFR inhibition. *Chem. Eng. J.* 524, 169540
134. Wu, S. *et al.* (2022) Nano-enabled tumor systematic energy exhaustion via zinc (II) interference mediated glycolysis inhibition and specific GLUT1 depletion. *Adv. Sci.* 9, 2103534

135. Xu, C.-F. *et al.* (2015) Targeting glucose uptake with siRNA-based nanomedicine for cancer therapy. *Biomaterials* 51, 1–11
136. Li, J. *et al.* (2024) Gold nanoparticle delivery of Glut1 siRNA facilitates glucose starvation therapy in lung cancer. *ChemBioChem* 25, e202400239
137. Goldberg, M.S. and Sharp, P.A. (2012) Pyruvate kinase M2-specific siRNA induces apoptosis and tumor regression. *J. Exp. Med.* 209, 217–224
138. Ma, C.B. *et al.* (2019) Knockdown of pyruvate kinase M inhibits cell growth and migration by reducing NF-κB activity in triple-negative breast cancer cells. *Mol. Cells* 42, 628–636
139. Huo, M. *et al.* (2017) Tumor-selective catalytic nanomedicine by nanocatalyst delivery. *Nat. Commun.* 8, 357
140. Zhao, W. *et al.* (2017) Glucose oxidase–polymer nanogels for synergistic cancer-starving and oxidation therapy. *ACS Appl. Mater. Interfaces* 9, 23528–23535
141. Zhang, X. *et al.* (2026) Large pore-sized organosilica nanoparticles with controlled release of glucose oxidase for tumor-specific cascaded catalytic therapy. *Biomater. Sci.* 14, 462–471
142. Huang, X. *et al.* (2022) Glucose oxidase and L-arginine functionalized black phosphorus nanosheets for multimodal targeted therapy of glioblastoma. *Chem. Eng. J.* 430, 132898
143. Jayashankar, V. and Edinger, A.L. (2020) Macropinocytosis confers resistance to therapies targeting cancer anabolism. *Nat. Commun.* 11, 1121
144. Garcia-Bermudez, J. *et al.* (2022) Adaptive stimulation of macropinocytosis overcomes aspartate limitation in cancer cells under hypoxia. *Nat. Metab.* 4, 724–738
145. Yang, Z. *et al.* (2021) Tumor-killing nanoreactors fueled by tumor debris can enhance radiofrequency ablation therapy and boost antitumor immune responses. *Nat. Commun.* 12, 4299
146. Fan, X. *et al.* (2023) Glutathione/glucose-depleting nanoparticles with NO generation for ferroptosis/starvation/NO-induced cancer therapy. *Chem. Mater.* 35, 3124–3137
147. Lauretti, E. *et al.* (2017) Glucose deficit triggers tau pathology and synaptic dysfunction in a tauopathy mouse model. *Transl. Psychiatry* 7, e1020
148. Cao, Z. *et al.* (2023) Lactate oxidase nanocapsules boost T cell immunity and efficacy of cancer immunotherapy. *Sci. Transl. Med.* 15, eadd2712
149. Tian, F. *et al.* (2021) Dual-depletion of intratumoral lactate and ATP with radicals generation for cascade metabolic-chemodynamic therapy. *Adv. Sci. (Weinh)* 8, e2102595
150. Zeng, Z. *et al.* (2021) Activatable polymer nanoenzymes for photodynamic immunometabolic cancer therapy. *Adv. Mater.* 33, 2007247
151. Feng, L.D. *et al.* (2022) Programmed albumin nanoparticles regulate immunosuppressive pivot to potentiate checkpoint blockade cancer immunotherapy. *Nano Res.* 15, 593–602
152. Liu, T. *et al.* (2019) Intracellular enzyme-triggered assembly of amino acid-modified gold nanoparticles for accurate cancer therapy with multimode. *ACS Appl. Mater. Interfaces* 11, 28621–28630
153. Hajrasouliha, A.R. *et al.* (2025) Toxicity analysis of gold nanoparticle formulations used for intraocular applications. *Sci. Rep.* 15, 19606
154. Ding, Y. *et al.* (2020) A nanomedicine fabricated from gold nanoparticles-decorated metal–organic framework for cascade chemo/chemodynamic cancer therapy. *Adv. Sci. (Weinh.)* 7, 2001060
155. Gao, S. *et al.* (2019) Nanocatalytic tumor therapy by biomimetic dual inorganic nanozyme-catalyzed cascade reaction. *Adv. Sci. (Weinh.)* 6, 1801733
156. Qi, C. *et al.* (2021) Tumor-specific activatable nanocarriers with gas-generation and signal amplification capabilities for tumor theranostics. *ACS Nano* 15, 1627–1639
157. Hu, X. *et al.* (2020) Biodegradation-mediated enzymatic activity-tunable molybdenum oxide nanourchins for tumor-specific cascade catalytic therapy. *J. Am. Chem. Soc.* 142, 1636–1644
158. Du, Q. *et al.* (2025) pH-responsive bimetallic MOF nanoparticles enable triple-synergistic radiosensitization for enhanced radiotherapy. *J. Mater. Chem. B* 13, 9418–9429
159. Liu, S. *et al.* (2026) A biodegradable self-cascading copper-based nanozyme for augmented cancer catalytic therapy and cuproptosis. *J. Colloid Interface Sci.* 701, 138692
160. Li, J. *et al.* (2025) Hemoglobin nanocatalyst with tunable autoxidation activity for tumor apoptosis-ferroptosis combination therapy. *Acta Pharm. Sin. B* 15, 6626–6637
161. Yang, Y. *et al.* (2019) NIR-II driven plasmon-enhanced catalysis for a timely supply of oxygen to overcome hypoxia-induced radiotherapy tolerance. *Angew. Chem. Int. Ed.* 58, 15069–15075
162. Lv, S. *et al.* (2020) Dual pH-triggered catalytic selective Mn clusters for cancer radiosensitization and radioprotection. *Nanoscale* 12, 548–557
163. Liu, C. *et al.* (2019) Biodegradable biomimic copper/manganese silicate nanospheres for chemodynamic/photodynamic synergistic therapy with simultaneous glutathione depletion and hypoxia relief. *ACS Nano* 13, 4267–4277
164. Zhao, S. *et al.* (2025) Lactate-modulating nanozyme-mediated mitochondrial respiration block for tumor immunosuppression remodeling. *Angew. Chem. Int. Ed.* 64, e202422203
165. Bonet-Aleta, J. *et al.* (2024) Nanoparticle-catalyzed transamination under tumor microenvironment conditions: a novel tool to disrupt the pool of amino acids and GSSG in cancer cells. *Nano Lett.* 24, 4091–4100
166. Cui, L. *et al.* (2021) Mitochondrial copper depletion suppresses triple-negative breast cancer in mice. *Nat. Biotechnol.* 39, 357–367
167. Chien, T. *et al.* (2022) Enhancing the tropism of bacteria via genetically programmed biosensors. *Nat. Biomed. Eng.* 6, 94–104
168. Canale, F.P. *et al.* (2021) Metabolic modulation of tumours with engineered bacteria for immunotherapy. *Nature* 598, 662–666
169. Cecil, A. *et al.* (2025) Endogenous gut microbiome and implanted intranasal *E. coli*-Nissle modulate cancer tissues metabolism in 4T1 syngeneic tumor bearing mice. *Biomed. Pharmacother.* 193, 118750
170. Mossmann, D. *et al.* (2023) Arginine reprograms metabolism in liver cancer via RBM39. *Cell* 186, 5068–5083.e23
171. Sun, M. *et al.* (2021) Both-in-one hybrid bacteria suppress the tumor metastasis and relapse via tandem-amplifying reactive oxygen species-immunity responses. *Adv. Healthc. Mater.* 10, 2100950
172. Chiang, C.-J. and Huang, P.-H. (2021) Metabolic engineering of probiotic *Escherichia coli* for cytolytic therapy of tumors. *Sci. Rep.* 11, 5853
173. Tang, W. *et al.* (2022) Chemically enhanced live probiotic for in vivo tumor targeting and inhibition. *ACS Appl. Polym. Mater.* 4, 1368–1376
174. Wu, W. *et al.* (2022) Bacterial metabolism-initiated nanocatalytic tumor immunotherapy. *Nanomicro Lett.* 14, 220
175. Berger, E. *et al.* (2013) Salmonella SL7207 application is the most effective DNA vaccine delivery method for successful tumor eradication in a murine model for neuroblastoma. *Cancer Lett.* 331, 167–173
176. Liu, B. *et al.* (2016) Blockage of autophagy pathway enhances *Salmonella* tumor-targeting. *Oncotarget* 7, 22873–22882
177. Kong, Q.K. *et al.* (2012) Phosphate groups of lipid A are essential for *Salmonella enterica* serovar Typhimurium virulence and affect innate and adaptive immunity. *Infect. Immun.* 80, 3215–3224
178. Blache, C.A. *et al.* (2012) Systemic delivery of *Salmonella typhimurium* transformed with IDO shRNA enhances intratumoral vector colonization and suppresses tumor growth. *Cancer Res.* 72, 6447–6456
179. Manuel, E.R. *et al.* (2015) *Salmonella*-based therapy targeting indoleamine 2,3-dioxygenase coupled with enzymatic depletion of tumor hyaluronan induces complete regression of aggressive pancreatic tumors. *Cancer Immunol. Res.* 3, 1096–1107
180. Zhou, S. *et al.* (2023) Targeted deprivation of methionine with engineered *Salmonella* leads to oncolysis and suppression of metastasis in broad types of animal tumor models. *Cell Rep. Med.* 4, 101070
181. Elia, I. (2021) Integrating metabolic engineering and immunotherapy. *Curr. Opin. Syst. Biol.* 28, 100361

182. Cascone, T. *et al.* (2018) Increased tumor glycolysis characterizes immune resistance to adoptive T cell therapy. *Cell Metab.* 27, 977–987.e4
183. Fultang, L. *et al.* (2020) Metabolic engineering against the arginine microenvironment enhances CAR-T cell proliferation and therapeutic activity. *Blood* 136, 1155–1160
184. Ligtenberg, M.A. *et al.* (2016) Coexpressed catalase protects chimeric antigen receptor–redirected T cells as well as bystander cells from oxidative stress–induced loss of antitumor activity. *J. Immunol.* 196, 759–766
185. Caruana, I. *et al.* (2015) Heparanase promotes tumor infiltration and antitumor activity of CAR-redirected T lymphocytes. *Nat. Med.* 21, 524–529
186. Cho, W.-S. *et al.* (2009) Acute toxicity and pharmacokinetics of 13 nm-sized PEG-coated gold nanoparticles. *Toxicol. Appl. Pharmacol.* 236, 16–24
187. Szebeni, J. (2014) Complement activation-related pseudoallergy: a stress reaction in blood triggered by nanomedicines and biologicals. *Mol. Immunol.* 61, 163–173
188. Zhang, S. *et al.* (2021) Glucose metabolic crosstalk and regulation in brain function and diseases. *Prog. Neurobiol.* 204, 102089
189. Chen, L. *et al.* (2019) Regulation of glucose and lipid metabolism in health and disease. *Sci. China Life Sci.* 62, 1420–1458
190. Ling, Z.-N. *et al.* (2023) Amino acid metabolism in health and disease. *Signal Transduct. Target. Ther.* 8, 345