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Metabolism-Regulating Nanomedicines for Cancer Therapy

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Cancer cells undergo significant metabolic reprogramming to meet their increased bioenergetic and biosynthetic needs, supporting rapid proliferation and survival. Key metabolic pathways, including those involved in glucose, lactate, amino acid, lipid, and nucleotide metabolism, are altered to facilitate cancer development, maintenance, and metastasis. Therefore, targeting cancer metabolism emerges as a promising therapeutic strategy. However, because of their short half-life, limited bioavailability, and inadequate specificity in metabolic regulation, these agents often result in unsatisfactory therapeutic outcomes. Recently, innovative nanomedicines that target metabolic processes have gained attention as a promising cancer therapy strategy, potentially helping to overcome the limitations of individual therapies and enhance treatment efficacy. This review provides an overview of tumor metabolic characteristics and explores recent progress in developing functional nanomedicines targeting tumor metabolism for cancer treatment. Finally, this review discusses the challenges and prospects for advancing nanotechnology-driven metabolic therapies.

1. Introduction

Cancer metabolism was initially identified by Otto Warburg in 1924, who observed that many tumors, even in the presence of oxygen, tend to convert glucose into lactate—a process called "aerobic glycolysis" or the "Warburg effect".[1] Currently, studies have demonstrated that tumor cells undergo significant metabolic reprogramming, involving shifts in glucose, lactate, amino acids, lipids, and nucleotide metabolism to support their heightened bioenergetic and biosynthetic needs.[2–7] Evidence also highlights the significant connection between altered tumor metabolism and processes such as drug resistance, immune evasion, and epigenetic modifications.[8–12] Consequently, metabolic reprogramming has been identified as a hallmark of malignant tumors,[13,14] offering new avenues for targeting metabolic dependencies in cancer treatment.

Several anti-metabolite medications, particularly those that inhibit nucleotide synthesis, have received approval for clinical use.[15] For example, Sidney Farber reported the antifolate agent aminopterin, which could induce remission in pediatric acute lymphocytic leukemia (ALL), laying the groundwork for chemotherapy in oncology.[16,17] Beyond that, numerous other antimetabolic drugs have received clinical approval, including methotrexate (MTX), a folate metabolism inhibitor, and various agents that hinder nucleotide synthesis (**Table 1**).[15,18] However, progress in targeting non-nucleotide metabolic pathways of cancer has been limited over the past decades (Table 1).[2,19] For instance, 2-deoxyglucose (2-DG), a glycolysis inhibitor, was shown to have limited efficacy in humans,[20–22] and CB-839, a glutaminase inhibitor, has shown encouraging outcomes in preclinical studies and early-phase trials, yet its long-term effectiveness remains limited.[23,24] The limited clinical success of metabolism-targeted cancer therapies mainly arises from three interconnected challenges inherent to tumor metabolic biology. First, the metabolic flexibility of cancer cells results in highly linked pathways, where blocking one pathway can lead to compensation through alternative metabolic processes.[25–27] Second, drugs can cause off-target effects by accumulating in healthy tissues, as both normal and cancer cells share many metabolic pathways.[15,28,29] These biological complexities are exacerbated by the pharmacological limitations of current metabolic modulators, including suboptimal pharmacokinetic properties, poor aqueous solubility, rapid clearance, and limited tumor specificity.[30–34] Thus, it is essential to develop more accurate and efficient treatment strategies to navigate the intricate nature of tumor metabolism.

Building on the increasing demand for precise and effective tumor metabolism targeting, advances in biomaterial science and nanotechnology offer innovative solutions that overcome the limitations of traditional metabolism regulation drugs. As shown in **Figure 1**, contemporary nanomedicine platforms show transformative potential with three main technological advantages: 1) improved pharmacokinetics and tumor-specific accumulation through enhanced permeability and retention (EPR)

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Table 1. Small molecules that regulate cancer metabolism.

Target	Name	Function	Indications
Approved cancer metabolic drugs			
DNA incorporation	Fludarabine	Nucleotide analogs	CLL
	Gemcitabine	Nucleotide analogs	PC, BC, OC, NSCLC
TYMS	5-Fluorouracil	dUMP to dTMP conversion	CRC, BC, gastric cancer
	Pemetrexed	Folate to THF conversion; dUMP to dTMP conversion	NSCLC
RNR	Hydroxyurea	Ribonucleotide to deoxyribonucleotide conversion	CML, HNSCC
PPAT	6-Mercaptopurine	Purine synthesis	ALL
DHFR	Methotrexate	Folate to THF conversion	BC, HNSCC, LC, non-Hodgkin lymphomas
IDH2 inhibitor	Enasidenib	2-Hydroxyglutarate synthesis	AML
IDH1 inhibitor	Ivosidenib	2-Hydroxyglutarate synthesis	AML
BCL-2	Venetoclax	Inhibition of BCL-2 protein; restoration of apoptosis	CLL, AML
Metabolic inhibitors in cancer clinical trials			
Mitochondria	IACS-010 759	Complex I	AML, advanced solid tumors
	CPI-613	Oxidative metabolism	PC, AML, solid tumors, lymphoma
	IM156	Complex I	Solid tumors, lymphoma
Glutaminase	CB-839	Glutamine to glutamate conversion	Leukemia, CRC, breast cancer, RCC
	IPN60090	Glutamine to glutamate conversion	Advanced solid tumors
Glutamine-utilizing enzymes	DRP-104	Glutamine-dependent enzymes	NSCLC, NHSCC, advanced solid tumors
FASN	TVB-2640	Fatty acid synthesis	NSCLC, CRC, BC, astrocytoma
MCT1	AZD-3965	Lactate symporter	Advanced cancers
Tyrosine metabolism	SM-88	Oxidative stress	Sarcoma, prostate, BC, pancreatic cancer
MAT2A	AG-270	Production of S-adenosylmethionine	Advanced solid tumors or lymphoma
IDO1	Indoximod	Kynurenine synthesis	Melanoma, BC, and pancreatic cancer
	Epacadostat	Kynurenine synthesis	BC, HNSCC, NSCLC, melanoma, RCC
DHODH	Brequinar	DHODH inhibitor	AML
	AG-636	DHODH inhibitor	Lymphoma, AML
Metabolic inhibitors in cancer pre-clinical trials			
GLUT	STF-31	Selective GLUT	BC, Colorectal Cancer
	BAY-876	A selective inhibitor of GLUT, induces disulfidptosis	OC, Triple Negative Breast Cancer
	Glutor	Selective inhibitor of GLUT	Solid Tumors, BC
PHGDH	NCT-503	Serine synthesis	Triple Negative Breast Cancer
	PH-755	Serine synthesis	BC, Colon Cancer
SHMT	AGF347	Serine to glycine conversion	PC, OC
	SHIN2	Serine to glycine conversion	PC, OC
LDHA/B	GNE-140	Pyruvate to lactate conversion	Cancer
	NCI-006	Pyruvate to lactate conversion	PC
	GSK2837808A	Pyruvate to lactate conversion	BC
GLS1	DON	Glutamine to glutamate conversion	NSCLC
	CB-839	Glutamine to glutamate conversion	PC
	IPN60090	Glutamine to glutamate conversion	OC
LAT1	JPH203	Essential amino acids transport	Thymic lymphoma
ASCT2	V-9302	Glutamine and other neutral amino acids transport	Melanoma
FASN	C75	FASN inhibitors	Cancer
	TVB-2640	FASN inhibitors	LC, BC
ACC	TOFA	Acetyl-CoA to malonyl-CoA conversion	BC, LC
	ND-646	Acetyl-CoA to malonyl-CoA conversion	BC, LC
ACSS2	VY-3-135	ACSS2 inhibitors	BC

Table 1. Continued.

Target	Name	Function	Indications
ACLY	NDI-091143	ACLY inhibitor	Cancer
HK2	Benitrobenrazide	Selective inhibitor of HK2	PC, Colorectal Cancer
PPAT	6-Mercaptopurinol	Purine analog	ALL, Acute Promyelocytic Leukemia
CAMKK2, PFK1	Citric acid/Citrate	CAMKK2; TCA cycle; Lipid synthesis	OC, BC, Colon Cancer

LC, lung cancer; OC, ovarian cancer; BC, breast cancer; PC, pancreatic cancer; IMPDH, inosine monophosphate dehydrogenase; GLUT, glucose transporter; HK2, Hexokinase 2; SHMT, serine hydroxymethyltransferase; LDHA/B, lactate dehydrogenaseA/B; LAT1, L-type amino acid transporter 1; SCD1, stearoyl-coenzyme A Desaturase 1; ACSS2, acetyl-CoA synthetase 2; DHODH, dihydroorotate dehydrogenase; ACLY, ATP citrate synthase; AML, acute myeloid leukemia; NSCLC, nonsmall-cell lung cancer; CLL, chronic lymphocytic leukemia; CRC, colorectal cancer; PPAT, phosphoribosyl pyrophosphate amidotransferase; DHFR, dihydrofolate reductase; FASN, fatty acid synthase; ALL, acute lymphatic leukemia; MCT1, monocarboxylate transporter 1; IDO1, indoleamine 2,3-dioxygenase 1; RNR, ribonucleotide reductase; RCC, renal cell carcinoma; TYMS, thymidylate synthase; IDH, isocitrate dehydrogenase; HNSCC, head and neck squamous cell carcinoma; THF, tetrahydrofolate; MAT2, S-adenosylmethionine synthase isoform type 2; CML, chronic myeloid leukemia; CaMKK2, calcium/calmodulin-dependent protein kinase kinase 2.

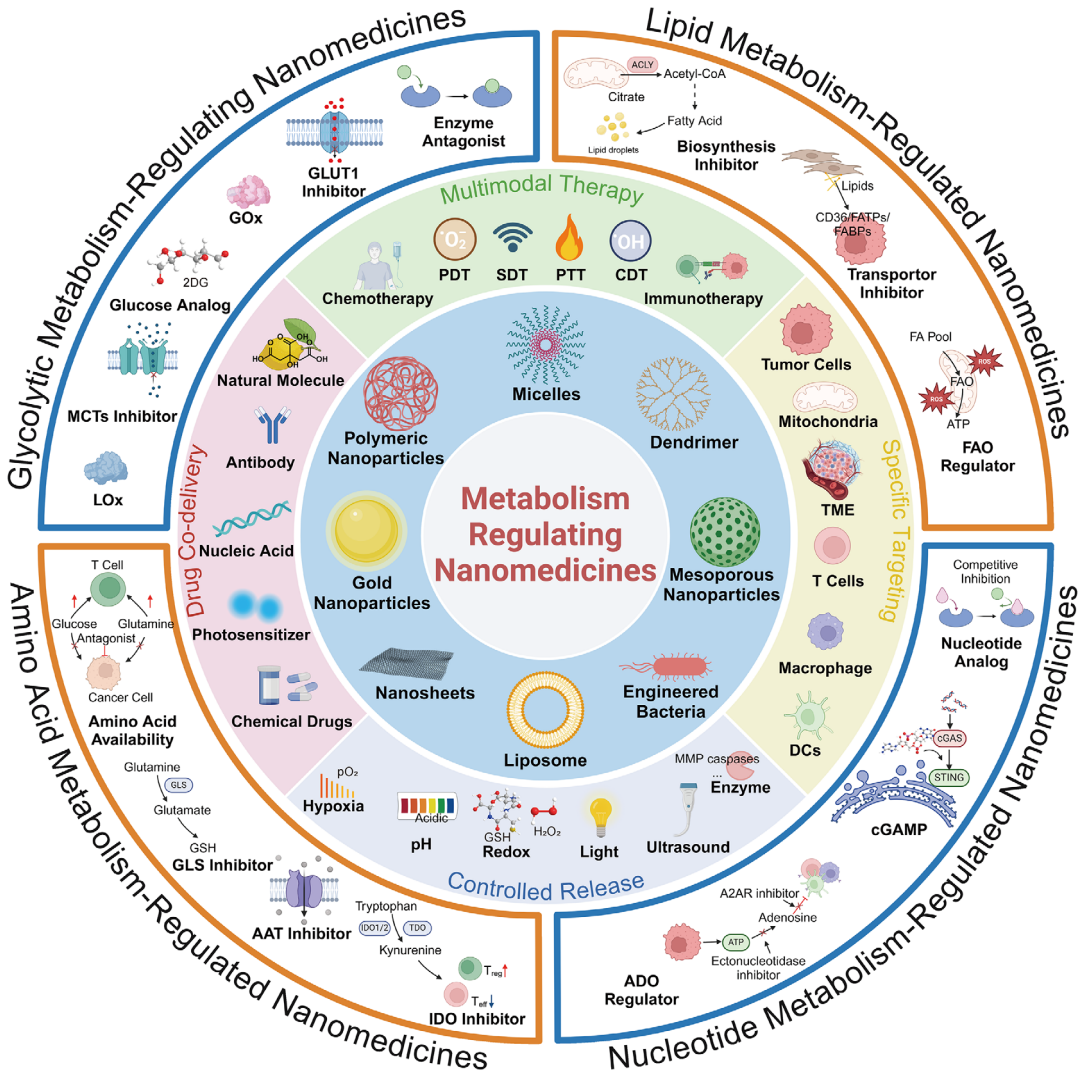

Figure 1. Metabolism-regulating nanomedicines for cancer therapy.

effects or active targeting moieties;[32,33,35–37] 2) spatiotemporally controlled drug release that responds to specific physical or biochemical conditions in the tumor microenvironment (TME), such as changes in pH, enzyme activity, reactive oxygen species (ROS), or glutathione (GSH) levels;[38–41] and 3) multimodal integration of complementary therapies through rational codelivery

systems. Specifically, advanced nanocarriers—such as polymeric micelles, lipid nanoparticles (LNPs), and hybrid nanostructures—allow for precise metabolic modulation. Optimized biodistribution profiles reduce off-target effects while maintaining therapeutic drug levels at the tumor site.[35] In addition, nanomedicine platforms can simultaneously deliver metabolism-regulating agents along with other therapies, such as chemotherapy,[42–47] radiotherapy,[48–51] chemodynamic therapy (CDT),[52–57] photodynamic therapy (PDT),[58–63] photothermal therapy (PTT),[64–69] and sonodynamic therapy (SDT).[57,70–72] This combined strategy not only interrupts compensatory metabolic adaptations by inhibiting parallel pathways but also initiates therapeutic cascades.

This review briefly outlines the key aspects of tumor metabolism, with particular focus on emerging nanomedicines that therapeutically modulate metabolic pathways. We highlight nanoengineering approaches focused on targeting key metabolic pathways in tumor cells—including those involving glucose, lactate, amino acids, lipids, and nucleotides (Figure 1). Additionally, we discuss current challenges and future directions for advancing nanotechnology-mediated metabolic interventions in cancer therapy.

2. Tumor Reprogrammed Metabolism

Malignant cells, in contrast to normal cells, adapt their metabolism to fulfill their heightened bioenergetic and biosynthetic requirements. These metabolic reprogramming efforts involve changes in glucose, lactate, amino acids, lipids, and nucleotides. The high metabolic activity of tumor cells enables them to adapt to different external pressures by altering substance transformation and exchange, increasing specific metabolic enzymes, and triggering both intracellular and intercellular signaling communication.[73–75] This enables cancer cells to consume nutrients such as glucose, amino acids, and lipids, which supply energy, support rapid biomass accumulation, and concurrently maintain intracellular redox balance and other signals that support tumor growth cascades.[74,76]

Specific genetic or epigenetic changes in well-known oncoproteins or oncosuppressors that directly drive cancer development also impact the metabolic profiles of tumor cells.[77–79] For example, activating mutations in KRAS and the genetic or epigenetic inactivation of tumor protein p53 (TP53) can directly influence catabolism or anabolism;[80–82] mTORC1 enhances the translation of MYC-regulated mRNAs to facilitate the uptake of amino acids, glucose, and fatty acids (FAs), thereby supporting the synthesis of nucleotides and proteins.[83–85] Tumor cells can undergo further metabolic changes as they evolve, adapting to the shifting microenvironment over space and time. For instance, malignant cells located away from blood vessels may respond to hypoxia by increasing hypoxia-inducible factors HIF1α and HIF2α, which then activate the glycolysis pathway.[86] Additionally, changes in metabolic processes can trigger oncogenic signaling, supporting tumor development and progression. For instance, cholesterol biosynthesis, mediated by MYC and p53, promotes tumor progression through the activation of oncogenic pathways;[87,88] Gain-of-function mutations in isocitrate dehydrogenase (IDH1 or IDH2), frequently observed in glioblastoma and leukemia, result in the accumulation of 2-hydroxyglutarate (2HG), a metabolite that encourages tumor proliferation.[89,90] In summary, metabolic pathways function as a complex interconnected network with feedback mechanisms, where alterations in one pathway can influence others, contributing to the development of a malignant phenotype.

Furthermore, specific cancer cells show cell-type-specific metabolism. In liver cancers, the enzymatic activities involved in glucose synthesis pathways are notably lower than in healthy liver tissue.[91] Similarly, melanin biosynthesis mediated by tyrosinase is significantly reduced in malignant melanoma.[92] Compared to healthy prostate epithelial cells, prostate cancer cells undergo a significant metabolic shift. It reduces citrate accumulation and reactivates mitochondrial adenosine triphosphate (ATP) generation via the tricarboxylic acid (TCA) cycle, creating a metabolic dependency that promotes neoplastic progression.[93] These cell-type-specific metabolic changes highlight the diversity of tumor metabolism and indicate potential therapeutic targets that leverage metabolic vulnerabilities in precision oncology approaches.

2.1. Glycolytic Metabolism

Metabolic reprogramming, a hallmark of cancer, supports rapid cell growth and proliferation by modifying energy production pathways. Unlike normal differentiated cells that mainly generate ATP through mitochondrial oxidative phosphorylation (OXPHOS), most cancer cells rely on glycolysis for ATP generation, even in oxygen-rich conditions, resulting in increased lactate production. Although glycolysis yields only 2 ATP per glucose compared with 36 ATP from OXPHOS, its ATP production rate in tumors is ≈100 times faster, thereby compensating for its lower efficiency. Consequently, malignant cells commonly show high glucose uptake rates and increased expression of glucose transporter 1 (GLUT1) to ensure sufficient glucose intake.[5,94,95] Moreover, prominent glycolytic enzymes, namely hexokinase (HK), pyruvate dehydrogenase kinase 1 (PDK1), and pyruvate kinase M2 (PKM2), have been identified as essential oncological biomarkers (**Figure 2**).[27,96,97] Additionally, tumor cells depend on other metabolites like glutamine, serine, arginine, and FAs to generate energy for their proliferation.[4,26,74]

Lactate, an end product of glycolysis, is produced from pyruvate by lactate dehydrogenase A (LDHA) and exported outside the cell via monocarboxylate transporters (MCTs) (Figure 2). By rapidly removing excess lactate, cancer cells prevent intracellular acidosis while creating an acidic TME with lactate concentrations of 10–40 mM, far exceeding normal physiological levels (1.5–3 mM).[30] Notably, lactate efflux is not the end of its metabolic role. Secreted lactate from hypoxic cancer cells can serve as an energy substrate for oxidative cancer cells, entering the TCA cycle to produce energy.[98] This lactate-based metabolic symbiosis between hypoxic and oxidative cancer cells is essential for supporting tumor growth under hypoxic conditions.

Along with its role as a metabolic intermediate, lactate also functions as a signaling molecule that influences various biological processes within tumors. Excess lactate in the TME promotes cancer development and severity by supporting tumor growth, blood vessel formation, metastasis, and therapeutic resistance.[99] For example, lactate within tumors is recognized by the enzyme

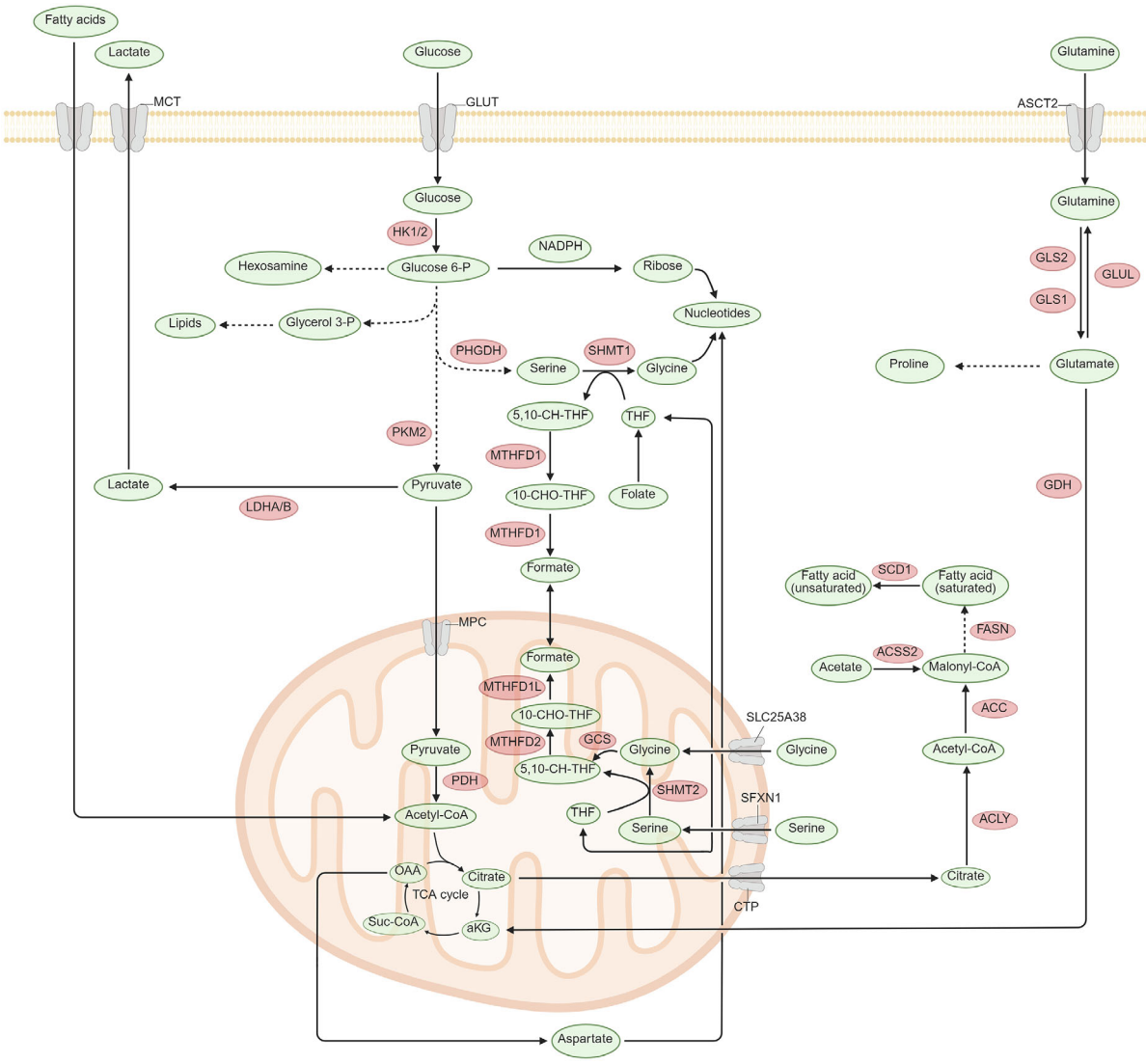

Figure 2. Metabolism in cancer cells. Glucose enters the cell through glucose transporters (GLUT) and is subsequently phosphorylated by HK1 or HK2, resulting in the production of Glucose 6-P. Glucose 6-P can be catabolized to yield pyruvate or alternatively diverted into biosynthetic pathways such as hexosamine production, glycerol 3-P production, or serine biosynthesis. Hexosamine is crucial for glycosylation, glycerol 3-P for lipid synthesis, and serine biosynthesis for amino acid and nucleotide metabolism via 1C metabolism. Among them, the generated pyruvate can enter the mitochondria or be converted to lactate under the action of LDHA/B. 1C metabolism, occurring in the cytoplasm and mitochondria, involves a critical reaction catalyzed by serine hydroxymethyltransferase (SHMT). This enzyme converts serine to glycine, generating 5,10-methylenetetrahydrofolate (5,10-CH_2-THF), which is further processed by MTHFD1/2 to form 10-CHO-THF or formate, supplying 1C units for nucleotide and protein synthesis. Pyruvate dehydrogenase (PDH) catalyzes the entry of pyruvate into the TCA cycle. Alternatively, pyruvate can be reduced to lactate through the action of lactate dehydrogenase (LDH), followed by its export from the cell. Glutamine serves as a major source of both carbon and nitrogen, entering cells primarily through transporters like ASCT2 and converted to glutamate by glutaminase (GLS1/2), then further processed by glutamate dehydrogenase (GDH) to form α-KG, fueling the TCA cycle and supporting biosynthetic processes. Acetyl-CoA, derived from fatty acid oxidation, glucose, or other sources, is exported from the mitochondria after the formation of citrate. ACLY catalyzes the conversion of citrate into acetyl-CoA, which is subsequently utilized by acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN) for the de novo synthesis of FAs. α-KG, α-ketoglutarate; OAA, oxaloacetate; Suc-CoA, succinyl-Coenzyme A; PHGDH, phosphoglycerate dehydrogenase; SHMT, serine hydroxymethyl transferase; PDH, pyruvate dehydrogenase; PKM2, pyruvate kinase muscle isozyme 2; CoA, Coenzyme A; CTP, citrate transporter protein. Created in BioRender. Lu, Y. (2025) https://BioRender.com/hclfpqo.

lactylase AARS1, which attaches lactate to two key amino acid residues in the DNA-binding domain of the tumor suppressor protein p53. This lactylation event results in the inactivation of p53, thereby promoting cancer progression.[100] Lactate also plays an important role in immunosuppression, contributing to poor clinical outcomes. For example, acidification of the TME inhibits cytotoxic T cell function while promoting the growth of immunosuppressive regulatory T cells (Tregs).[101]

2.2. Lipid Metabolism

Lipids are fundamental components of cells, acting not only as a crucial energy reserve but also as key mediators of both intra- and extracellular signaling.[102] In response to hypoxia and nutrient deprivation, tumor cells not only increase glucose uptake and aerobic glycolysis but also reprogram their lipid metabolism to support malignant progression.[103] Particularly, FAs and cholesterol, as key components, along with other molecules such as phospholipids and signaling lipids (like prostaglandin E2 and lysophosphatidic acid), are essential for membrane synthesis, signaling, energy storage, and therapeutic resistance of tumors.[104]

Tumors fulfill their lipid demands primarily through two mechanisms: (1) enhanced uptake mediated by transporters such as scavenger receptor B2, CD36, and fatty acid transport proteins; and (2) de novo lipogenesis (DNL), which generates lipids from acetyl-CoA substrate.[105] Altered nutritional patterns intensify this process in tumors, with synthesized lipids mainly fueling metabolic pathways that promote modification of oncogenic activities.[106]

Notably, citrate—a pivotal metabolic intermediate—is exported to the cytoplasm by the mitochondrial citrate carrier (mCiC) and cleaved by ATP citrate lyase (ACLY) into acetyl-CoA, the central precursor for lipid biosynthesis (Figure 2).[107] This highlights citrate as a vital compound and key regulator, linking glycolysis to lipid metabolism and maintaining cellular energy balance. In addition, recent evidence reveals a paradoxical function of citrate in tumor biology. While serving as a crucial biosynthetic precursor for proliferating cells, Zhao et al.[108] demonstrated that supraphysiological citrate concentrations unexpectedly cause tumor suppression. Their mechanistic studies showed that citrate overload disrupts lipid homeostasis by inducing excessive lipogenesis, ultimately leading to cellular senescence and growth arrest in malignant cells. This discovery emphasizes the importance of balancing tumor lipid metabolism and suggests therapeutic potential through metabolic modulation. These findings have increased interest in lipid metabolism-targeted anticancer strategies, with current approaches focusing on reprogramming the choline metabolism,[109] modulating the intracellular phosphatidylinositol levels,[110] regulating lipid biosynthesis,[108] and lipid peroxidation.[111–113]

Anomalous lipid metabolism further modulates antitumor immunity by altering the abundance, activation, and function of immune cells within the TME, thereby promoting tumor adaptation.[103] Studies have demonstrated that fatty acid synthesis is crucial for the differentiation and function of inflammatory macrophages.[107] Accumulation of lipid metabolites drives the metabolic reprogramming and functional polarization of tumor-infiltrating myeloid cells—including tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and dendritic cells (DCs)—toward an immunosuppressive, anti-inflammatory phenotype.[105] Enhanced CD36 expression in CD8+ T cells leads to abnormal lipid accumulation, which hampers the release of crucial antitumor cytokines such as interferon gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), ultimately diminishing their antitumor capacity.[114] Therefore, blocking lipid uptake by inhibiting CD36 on cytotoxic CD8+ T cells or Tregs has been proposed as a way to enhance antitumor immune responses. Additionally, FAs in immune cells not only alter membrane composition or act as inflammatory mediators but also directly participate in intracellular signaling, further affecting immune functions.[115,116] This complex interaction places lipid metabolic reprogramming as a key regulator of immune function in cancer, providing actionable targets to counteract the immunosuppressive TME and enhance antitumor immune responses.

2.3. Amino Acids Metabolism

Amino acids are essential for tumor initiation and progression, acting as both structural components and signaling molecules that support cancer cell growth, survival, and immune evasion. Compared to normal cells, cancer cells require more amino acids to sustain rapid biosynthesis and energy demands, resulting in notable alterations in amino acid metabolism.[117]

Among the most crucial amino acids for cancer cells is glutamine, which promotes cell growth by serving as a carbon and nitrogen donor in biosynthesis, fueling the TCA cycle, aiding nucleotide and protein synthesis, and maintaining redox balance through GSH synthesis. (Figure 2).[118] Many tumors exhibit what is termed glutamine addiction, relying on extracellular glutamine to sustain these metabolic pathways.[119] Targeting glutamine metabolism, such as using glutaminase inhibitors like 6-diazo-5-oxo-L-norleucine (DON), has shown potential in inhibiting tumor growth.[120]

Serine and glycine, much like glutamine, are vital for tumor growth due to their participation in one-carbon (1C) metabolism, which is essential for the production of nucleotides and various cellular processes.[121] Cancer cells often increase the production of enzymes such as phosphoglycerate dehydrogenase (PHGDH), which converts glycolytic intermediates into serine. This process supports cell growth and strengthens antioxidant defenses by producing NADPH.[122] Furthermore, glutamate, cysteine, and glycine are essential for GSH synthesis, with glutamine enhancing cellular antioxidant capacity by providing glutamate and supporting NADPH production, which helps neutralize ROS, maintain redox balance, and protect cancer cells from oxidative stress (Figure 2).[123] Methionine plays a crucial role in cancer by influencing epigenetic modifications, as it serves as a precursor for S-adenosylmethionine (SAM), a methyl donor involved in regulating DNA and histone methylation.[117] Many types of cancer rely on methionine to maintain methylation patterns that support tumor development, and restricting methionine intake has been demonstrated to decrease tumor progression in preclinical studies by altering epigenetic regulation.[124–126]

Amino acid metabolism also plays a critical role in modulating the TME and promoting immune evasion. For example, the tryptophan catabolism mediated by indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO) generates kynurenine, an immunosuppressive metabolite that dampens cytotoxic T cell activity and promotes Treg expansion, thereby fostering a protumorigenic immunosuppressive environment.[127,128] Similarly, glutamine is essential for lymphocyte secretion, proliferation, and function maintenance.[129,130] During lymphocyte activation and proliferation in response to antigen

stimulation, glutamine serves as a precursor for nucleotide synthesis and provides energy. Along with glutamine, sulfur-containing amino acids (e.g., methionine, cysteine, and cystine) play crucial roles in immune regulation. For example, methionine can be converted into homocysteine, and elevated homocysteine levels can increase T cell adhesion, further impacting the immune response.[5]

2.4. Nucleotide Metabolism

Nucleotide metabolism encompasses the synthesis, conversion, and degradation of nucleotides, the fundamental building blocks of nucleic acids. Cancer cells, because of their rapid growth, require an abundant supply of nucleotides, making them particularly vulnerable to disruptions in nucleotide metabolism. Therefore, targeting nucleotide metabolism has become a promising approach for cancer therapy.

So far, there are three main approaches to disrupt nucleotide synthesis: inhibiting folate metabolism, using nucleotide analogs as competitive inhibitors, and blocking key synthetases.[131] Inspired by Sidney Farber's pioneering work, early treatments focused on inhibiting folate metabolism, which supplies 1C units essential for nucleotide biosynthesis. Drugs such as aminopterin and MTX, which inhibit DHFR, have been effective in treating ALL and other cancers. Moreover, purine and pyrimidine analogs, such as 6-mercaptopurine (6-MP), 5-fluorouracil (5-FU), capecitabine, gemcitabine, and fludarabine, are extensively used in clinical practice.[15] Serine and glycine are also crucial for nucleotide synthesis, as they contribute to 1C metabolism, which is essential for purine and thymidine synthesis (Figure 2). These amino acids provide the necessary carbon units for nucleotide synthesis, facilitating DNA replication and cell proliferation.[122]

Additionally, the increased demand for nucleotide synthesis in cancer cells boosts purine and pyrimidine synthesis, often at the expense of other cells in the TME.[132] Cancer cells further generate immunosuppressive metabolites via nucleotide catabolism. A notable example is adenosine (ADO), which suppresses immune cell proliferation and activation, thereby facilitating tumor immune evasion through impaired cytotoxic T and natural killer (NK) cell function.[133]

Overall, focusing on nucleotide synthesis continues to be a validated and promising approach in cancer treatment, supported by multiple FDA-approved agents and ongoing development of novel small-molecule inhibitors (Table 1).

3. Glycolytic Metabolism-Regulating Nanomedicines

A key metabolic feature of cancer cells, as highlighted herein, is their reprogramming toward glycolytic lactate production from glucose. Targeting tumor glycolysis could allow for more selective destruction of cancer cells. However, the high glucose uptake by tumor cells also hampers immune cell activation and differentiation. Additionally, lactate produced by tumor metabolism promotes immunosuppressive pathways. Therefore, suppressing glycolytic flux and eliminating lactate in the TME offers promising therapeutic approaches to potentiate antitumor immunity. This section reviews the recent progress in nanomedicine development aimed at modulating these metabolic processes.

3.1. Regulating Substrate Level

In nutrient-deprived tumor environments, glucose often remains the most abundant and essential metabolic substrate.[134] Consequently, malignant cells increase GLUT1 expression to facilitate glucose uptake, ensuring a sufficient supply for their metabolic needs. Given the critical role of glucose in sustaining glycolysis, inhibiting its metabolism has emerged as a promising anticancer strategy. This approach has spurred the development of numerous therapeutic agents in recent years. A notable example is 2-deoxy-D-glucose (2-DG), a glucose analog that is imported into cancer cells primarily via the GLUT1 transporter. Intracellularly, 2-DG is phosphorylated by hexokinase (HK) to yield 2-deoxyglucose-6-phosphate (2-DG-6P), a structural mimic of glucose-6-phosphate (G6P). However, unlike G6P, 2-DG-6P cannot proceed through the glycolytic pathway, effectively stopping glycolysis.[93] As a result, 2-DG has been widely studied as an antiglycolytic agent in early-phase clinical trials.[19,135,136] Yang et al.[46] developed a liposomal nanosystem codelivering doxorubicin (Dox) and 2-deoxy-D-glucose (2-DG) to achieve differential glucose stress sensitization between cancer and normal cells, thereby enabling tumor-specific chemotherapy. By inhibiting glycolysis, 2-DG synergizes with Dox to induce mitochondrial depolarization and promote apoptosis in cancer cells. Moreover, the glucose starvation effect caused by 2-DG mitigates Dox-induced toxicity in normal tissues, reducing overall side effects of chemotherapy (**Figure 3**a). This differential stress sensitization strategy could significantly advance the low- or nontoxic nanomedicines.

Another effective strategy for inhibiting tumor glycolysis is depleting intracellular glucose within cancer cells. Glucose oxidase (GOx) selectively targets tumor glucose by converting it into hydrogen peroxide (H_2O_2) and gluconic acid,[137] which deprives tumor cells of a vital energy source and produces ROS, reducing tumor viability. However, GOx is limited by immunogenicity, short in vivo half-life, systemic toxicity, and instability in biological environments,[138] which restricts its biomedical application. Meng et al.[139] coloaded GOx and 3-bromopyruvate (3-BrPA) within the core of a ZIF-8 framework, where GOx-driven glucose consumption can hinder cellular metabolism and induce energy deficits, while the excess H_2O_2 production can elevate toxicity by disrupting redox homeostasis. Additionally, 3-BrPA decreases oxygen and glucose utilization via glycolysis, enhancing the sensitivity of cancer cells to GOx-triggered apoptosis (Figure 3b). Consequently, the viability of the liver hepatocellular carcinoma cell line (HepG2) was markedly reduced, with in vivo results further validated in HepG2 tumor-bearing mice (Figures 3c–f). Phenylboronic acid (PBA), a well-known glucose sensor, has been explored for diabetes treatment and proposed as a potential therapeutic agent to reduce glucose availability by selectively binding to target molecules.[140,141] Lee et al.[142] developed a novel amphiphilic polymer that integrates glycol chitosan with PBA, enabling the formation of stable micelles under physiological conditions that are sensitive to variations in glucose levels. These micelles preferentially localize at tumor sites, where they deplete intracellular glucose, thus causing energy starvation by

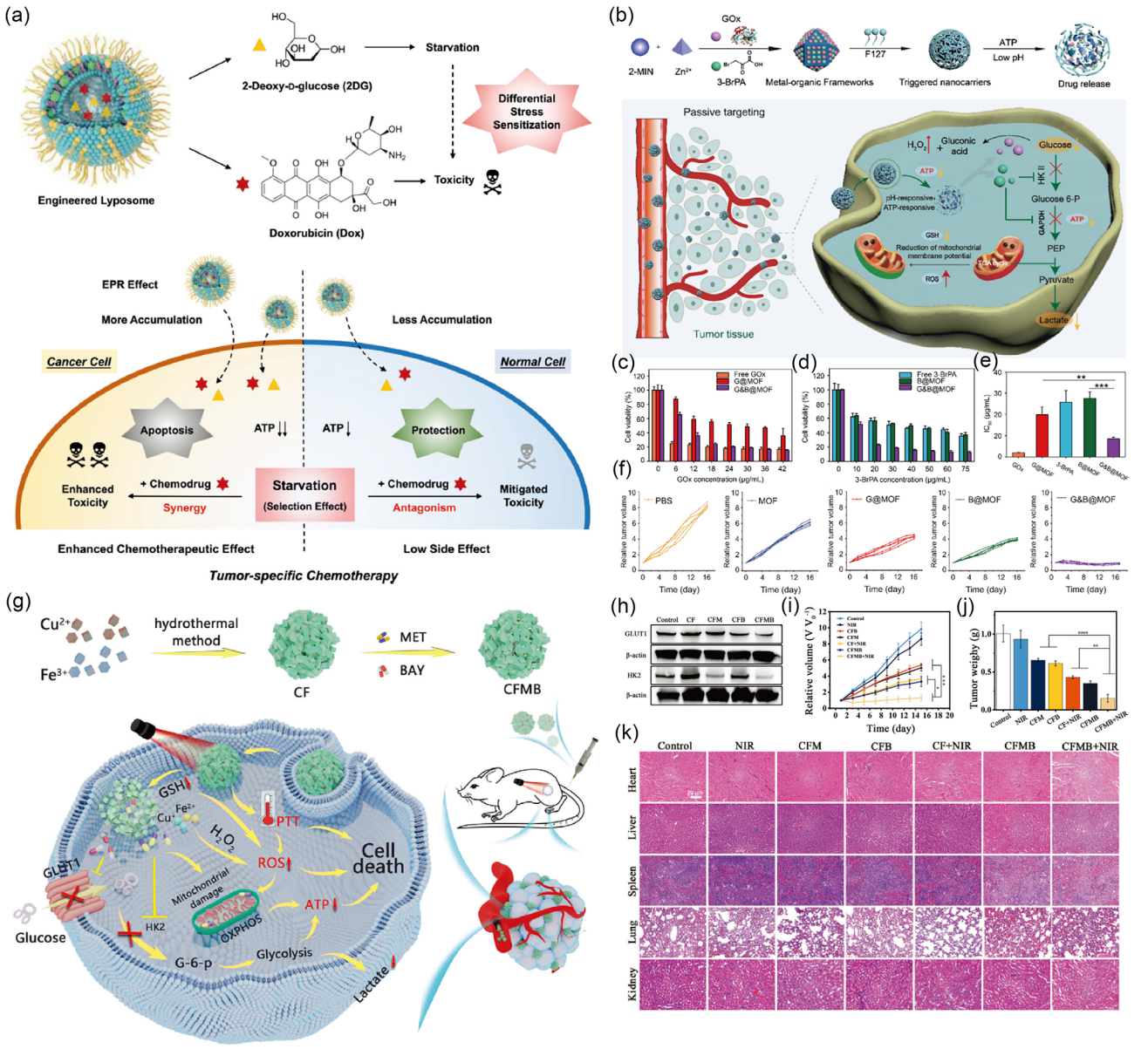

Figure 3. Nanomedicines for regulating substrate levels in cancer cells. a) Schematic of engineered liposomes coloaded with Dox and 2-DG for glucose metabolism-targeted chemosensitization. Reproduced with permission.[46] Copyright 2020, Wiley. b) Schematic of a nanoplatform codelivering GOx and 3-BrPA for synergistic inhibition of aerobic glycolysis, leading to energy depletion and enhanced ROS generation. c,d) Viability of HepG2 cells after treatment with metabolic suppression nanoparticles (G@MOF, B@MOF, G&B@MOF) at equal doses of (c) GOx and (d) 3-BrPA. e) IC_{50} values of HepG2 cells following treatment with each formulation. f) Tumor growth curves under treatment with PBS, MOF, G@MOF, B@MOF, and G&B@MOF (GOx and 3-BrPA each at 15 mg kg^{-1}). Reproduced with permission.[139] Copyright 2023, Elsevier. g) Synthesis and mechanism of CFMB nanoparticles for dual glycolysis/OXPHOS inhibition, enabling bioenergetic therapy synergized with CDT/PTT. h) Western blot analysis of GLUT1 and HK2 expression in 4T1 cells. i) Relative tumor volume in 4T1 models across treatment groups. j) Average tumor weight per group post-treatment. k) H&E-stained images of major organs after treatment. Reproduced with permission.[146] Copyright 2024, Wiley.

impeding aerobic glycolysis. This mechanism substantially suppresses tumor progression with minimal adverse effects. Utilizing nanomedicine approaches for targeted glucose depletion enhances treatment precision by improving the stability and tumor-specific delivery of metabolic agents, effectively exploiting the metabolic weaknesses of cancer cells to induce energy deprivation and oxidative stress.

Targeting glucose import via transporters has emerged as a promising strategy to restrict nutrient availability and impair tumor cell metabolism. BAY-876,[143] a competitive GLUT1 antagonist, along with diclofenac[144] and quercetin,[145] suppresses GLUT1 expression and reduces glucose uptake, thereby limiting glucose availability in tumor cells. Wei et al.[146] developed a $CuFe_2O_4$ nanoplatform (CFMB) coloaded with metformin

(MET) and BAY-876 to enhance bioenergetic therapy via combined glycolysis and OXPHOS inhibition, synergizing with CDT/PTT. BAY-876 blocks glucose uptake by inhibiting GLUT1 (Figure 3h), while MET reduces HK2 activity and impairs mitochondria, depriving tumor cells of energy. In vivo, CFMB significantly suppressed tumor growth in mice without toxicity (Figure 3i–k). These results highlight the potential of nanoplatforms to target multiple tumor metabolic pathways.

Some intermediate compounds within the TCA cycle are also crucial to the metabolic processes of tumor cells, with their pathways affecting multiple cellular functions. For instance, increased levels of citrate, an essential TCA metabolite, have been shown to suppress the activity of phosphofructokinase-1 (PFK1), a central regulatory enzyme in glycolysis.[147] Several research findings also highlight the critical function of citrate in cancer development.[107] More interestingly, Li et al.[148] propose that citrate, as a precursor to α-KG, plays a significant role in the α-KG-mediated pyroptosis pathway, since α-KG can trigger pyroptosis through caspase-8-mediated cleavage of gasdermin C (GSDMC). Citrate is converted to isocitrate by aconitases and then to α-KG by IDHs. They also developed citrate sodium nanoparticles coated with PEGylated phospholipids (called PSCT NPs) to induce pyroptosis, which slowly release Na^+ and $C_6H_5O_7^-$ ions as they degrade. A rapid increase in these ions shifts osmolarity and redox balance, leading to ROS production and caspase-1 activation, which cleaves GSDMD. Elevated citrate disrupts cell metabolism and triggers caspase-8-mediated GSDMC cleavage (**Figure 4**a–d). The results show that PSCT NPs cause strong pyroptotic cell death, leading to notable antitumor immune responses and tumor growth suppression (Figure 4e). Wu et al.[149] also found that sodium citrate treatment reduced cytosolic Ca^{2+} levels by chelating calcium, which further inhibited the Ca^{2+}/calmodulin-dependent protein kinase kinase 2 (CaMKK2)/protein kinase B (Akt)/mTOR pathway, leading to suppression of the HIF1α-dependent glycolysis pathway and resulting in cell apoptosis. Interestingly, a recent report highlighted the key role of metabotissugenic citrate biomaterials in mediating the CaMKK2 signaling pathway for integrating metabolic regulation during bone regeneration.[150] Additionally, Lu et al.[151] developed tumor-derived succinate-loaded microparticles (SMPs) to reprogram the metabolic profile of TAMs. Specifically, SMPs drive macrophages towards an M1-like polarization state by boosting glycolytic flux and suppressing the TCA cycle. Other metabolite-based nanomedicines have been developed for tumor therapy,[152,153] revealing new possibilities for manipulating cancer cell metabolism.

3.2. Regulating Glycolytic Enzymes

The upregulation of crucial enzymes plays a central role in speeding up the metabolic processes of cancerous cells. These

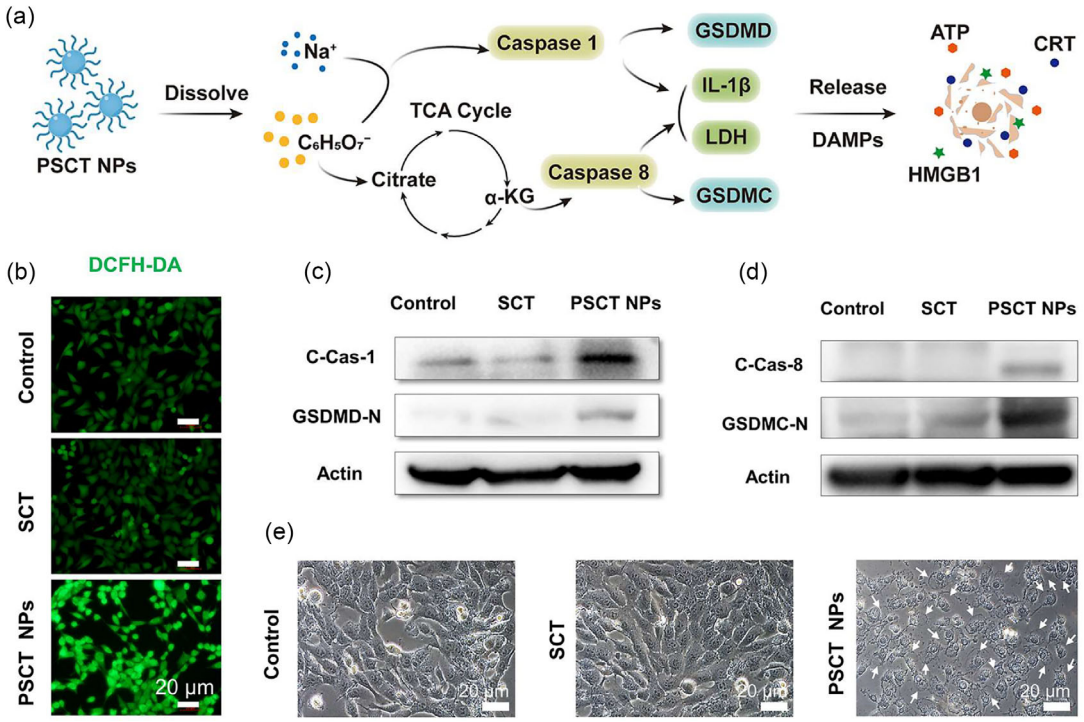

Figure 4. Nanomedicines for regulating TCA metabolites in cancer cells. a) Following endocytosis by tumor cells, PSCT NPs release Na^+ and citrate ions, triggering a rapid increase in intracellular ions, osmolarity, and ROS. This activates both caspase-1/GSDMD and caspase-8/GSDMC pyroptosis pathways, leading to the release of DAMPs and IL-1β and subsequent immune activation. b) Intracellular ROS levels detected using DCFH-DA fluorescence probing. c,d) Western blot analysis of (c) caspase-1 and GSDMD, and (d) caspase-8 and GSDMC expression. e) Representative cell morphology images under different treatments; white arrows indicate characteristic cell swelling and large bubbles indicative of pyroptosis in PSCT NP-treated groups. Reproduced with permission.[148] Copyright 2020, American Chemical Society.

enzymes typically exhibit markedly increased expression compared to their counterparts in normal tissues, along with distinct subtypes or mutations that confer advantages such as sustained proliferation and resistance to apoptosis.[154] Consequently, certain glycolytic enzymes, including PDK1, HK, and PKM2, have become promising targets for metabolic intervention in cancer therapy. Practical enzyme function relies on the availability of suitable substrates, accurate conformational dynamics, and proper activation.[155,156] To exploit these vulnerabilities, advanced delivery systems have been engineered for the targeted delivery of small-molecule inhibitors or functional materials to the tumor sites, providing innovative strategies to inhibit enzymatic activity and interfere with cancer cell metabolism.

The enzyme PDK1, which is highly expressed in mitochondria, acts as a key regulator to inactivate the pyruvate dehydrogenase complex (PDC), thereby preventing the conversion of pyruvate into acetyl-CoA.[157] This shift in metabolic flux redirects cellular metabolism from OXPHOS in mitochondria to glycolysis. By suppressing mitochondrial activity, PDK1 allows cancer cells to adapt to hypoxic conditions and maintain redox balance, thereby supporting their survival and proliferation. The efficacy of dichloroacetate (DCA), an inhibitor of PDK1, is hampered by poor cellular uptake and insufficient mitochondrial accumulation.[158,159] To overcome these limitations, Haddad et al.[160] designed a Zr-metal–organic framework (MOF) loaded with DCA and conjugated with triphenylphosphonium (TPP) to target mitochondria. The above drug delivery system significantly enhanced the efficacy of DCA, reducing the required dose to less than 1% of free DCA and ≈10% of the nontargeted MOF, highlighting the importance of precise targeting in improving the therapeutic effectiveness of metabolic inhibitors.

HK is the initial rate-limiting enzyme in glycolysis, responsible for converting glucose into G6P.[161] Additionally, the interaction between HK and the mitochondrial outer membrane protein VDAC also contributes to apoptosis inhibition.[162] Several agents have been identified to directly or indirectly inhibit HK activity, including lonidamine (Lon),[163] 3-bromopyruvate,[164] benserazide,[165] and resveratrol.[166] Liu et al.[59] developed biomimetic nanomedicine by coating ZIF-8 nanoparticles with homologous tumor cell membranes (CM), coloading the photosensitizer chlorin e6 (Ce6) and the metabolic modulator Lonidamine (Lon). The nanomedicine disrupts tumor metabolic pathways and alleviates metabolite accumulation, thereby reversing immunosuppression in the TME through Lon release. Concurrently, Ce6-mediated PDT not only directly kills tumor cells but also induces immunogenic cell death (ICD), triggering a systemic immune response. Metabolic reprogramming synergistically enhances PDT-induced immunotherapy by reducing the abundance of Tregs, promoting CD8+ T cell infiltration, and stimulating proinflammatory cytokine secretion. Consequently, this combinational approach effectively suppresses both primary and metastatic tumors, highlighting the promise of metabolically targeted strategies for potentiating anticancer immunity.

In cancer, pyruvate kinase (PK)—the terminal glycolytic enzyme that generates ATP and pyruvate from phosphoenolpyruvate—is dysregulated through an isoform switch, resulting in preferential expression of PKM2. Tumor-related PKM2 dynamically switches between low-activity nuclear dimers that support biosynthesis and tetrameric forms that maintain glycolytic flow, with the predominance of dimers driving metabolic reprogramming that is essential for tumorigenesis.[167] While serine-mediated tetramer stabilization presents a natural regulatory mechanism, its transient effects limit therapeutic utility.[168,169] Addressing this constraint, Hou et al.[42] engineered O-GlcNAcase-responsive glycopeptide nanoassemblies that undergo tumor-specific structural transformation into serine-loaded nanofibers. The resultant spatial confinement promotes sustained PKM2 tetramerization, effectively blocking nuclear dimer translocation and sensitizing prostate cancer cells to Dox through metabolic synchronization. The results validate the therapeutic potential of glycopeptide-based PKM2-targeted nanoactivators, which reprogram tumor metabolic flux by stabilizing tetrameric enzyme structures, offering a groundbreaking approach over conventional enzyme inhibitors via bidirectional regulation of catabolic and anabolic processes reprogramming.

Interestingly, previous studies have reported that carbon monoxide (CO), an endogenous gas-signaling molecule, can act as a glycolytic inhibitor to reverse the "Warburg effect" by downregulating the expression of key enzymes in glycolysis pathway.[170,171] Cao et al.[172] developed an X-ray-activated CO-releasing nanoplatform for targeted metabolic suppression in pancreatic cancer. This system consists of cyclodextrin-modified gold nanoclusters (CD-AuNCs) as radiosensitizers, adamantane-conjugated iron–CO monoxide complexes (Ada-CO) as ROS-responsive CO donors, and a hyaluronic acid–adamantane (HA-Ada) coating for CD44-directed tumor targeting. Under X-ray irradiation, CD-AuNCs generate ROS, which not only directly damage cancer cells but also trigger CO release from Ada-CO, effectively suppressing glycolysis (**Figure 5**a). Both in vitro and in vivo evaluations demonstrated that the nanomedicine specifically targets CD44-overexpressing pancreatic tumors, where even low-dose X-ray irradiation induces potent antitumor effects via dual ROS/CO-mediated metabolic inhibition, demonstrating a favorable safety profile.

3.3. Regulating Lactate Levels

In hypoxic tumor cells, lactate is exported through MCT4 to prevent intracellular acidification and enable lactate shuttling. This process creates an acidic TME that promotes malignancy, including drug resistance, immune suppression, and metastasis.[101] Given its crucial role, targeting lactate metabolism has become an important therapeutic focus. Recent advances in lactate-targeting nanosystems have demonstrated promise, providing precise delivery of agents to disrupt lactate metabolism and improve cancer treatment. Notably, LDHA, which is overexpressed in glycolytic tumors, catalyzes the reduction of pyruvate to lactate, thereby promoting acidification and metabolic adaptation. Inhibiting it is associated with only mild exertional myopathy, making it a safe and attractive therapeutic target.[173] Yan et al.[71] developed HA-modified metal-phenolic nanomedicines (HPP-Ca@GSK) designed to deliver the LDHA inhibitor GSK2837808A, effectively inhibiting glycolysis within cancer cells. This results in a high-glucose, low-lactate TME that favors CD8+ tumor-infiltrating lymphocytes (TILs) while impairing Treg cells. Ultrasound-induced oxidative stress causes mitochondrial calcium overload, leading to mitochondrial dysfunction and

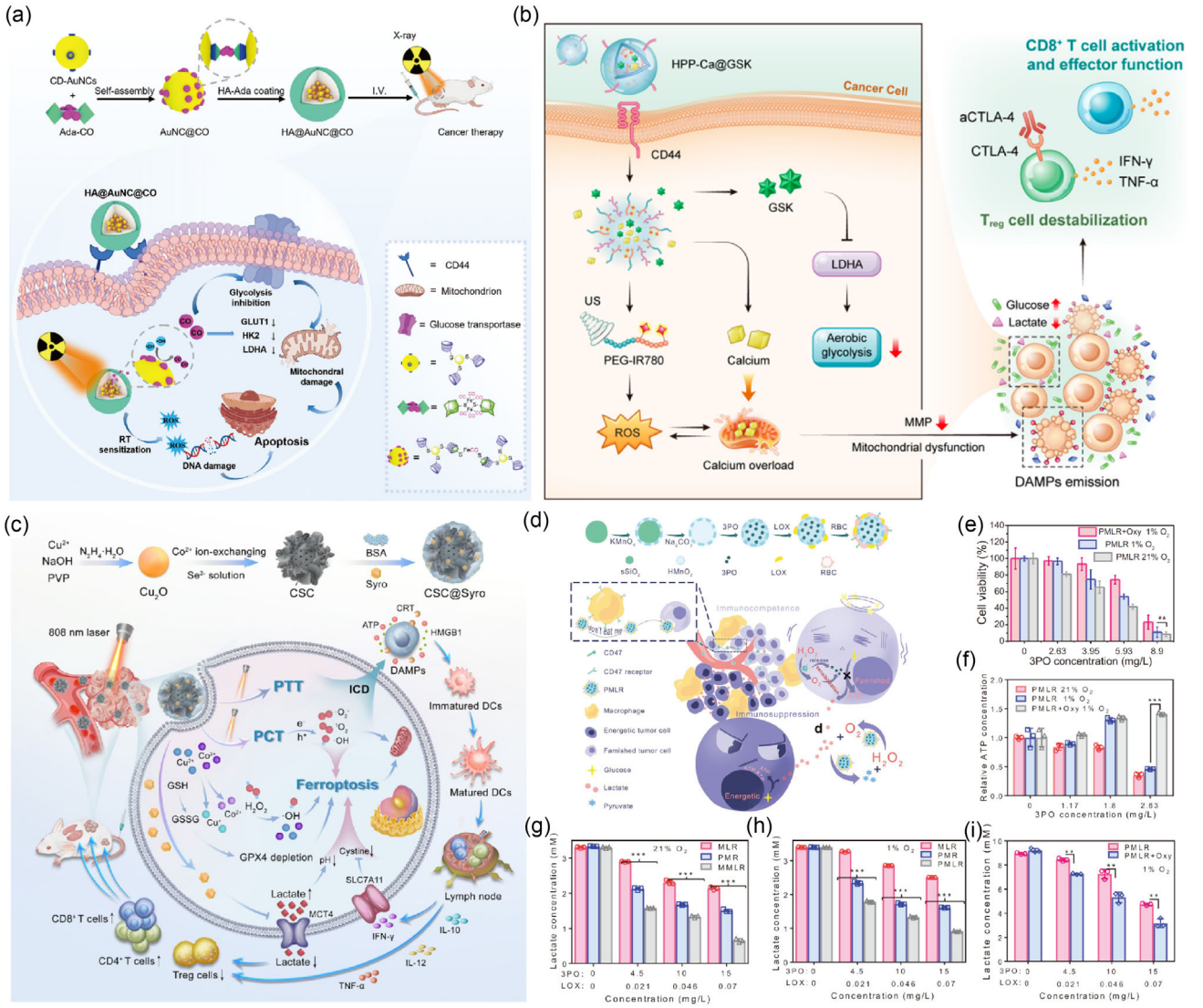

Figure 5. Nanomedicines for regulating glycolytic enzymes in cancer cells. a) Mechanism of X-ray-triggered CO release from HA@AuNC@CO for targeted radio-/gas synergistic therapy. Reproduced with permission.[172] Copyright 2024, Wiley. b) Schematic of HPP-Ca@GSK nanomedicine for enhancing antitumor immunity via sono-metabolic therapy. Reproduced with permission.[71] Copyright 2023, American Chemical Society. c) Activatable immunomodulatory nanoadjuvant promoting ferroptosis and photoimmunotherapy via blockade of intratumoral lactate efflux. Reproduced with permission.[175] Copyright 2023, American Chemical Society. d) Intra- and extracellular lactic acid depletion by the PMLR nanosystem. e) ATP inhibition by PMLR nanoparticles under normoxia, hypoxia, and hypoxia with Oxy (20 mg L^{-1}). f) Cytotoxicity of PMLR nanoparticles against B16F10 cells under the same conditions as in (e). g,h) Lactate consumption by MLR, PMR, and PMLR nanoparticles under normoxia (g) and hypoxia (h). i) Lactate depletion by PMLR nanoparticles under hypoxia with or without Oxy (20 mg L^{-1}). Reproduced with permission.[176] Copyright 2019, Wiley.

the release of DAMPs that activate CD8+ T cells (Figure 5b). Both in vitro and in vivo experiments demonstrate that the nanomedicine enhances anticancer responses, and combining it with anti-CTLA-4 antibodies further promotes Treg destabilization and improves therapeutic outcomes.

MCT4 is a key transporter that facilitates the removal of lactate anions and protons from within cells, helping cancer cells avoid harmful acid buildup caused by excess lactate. Inhibiting lactate transporters to limit lactate efflux is also an effective strategy for regulating lactate levels.[30] This approach disrupts the metabolic balance of tumor cells, leading to intracellular lactate accumulation and subsequent acidosis, which may synergize with other cancer treatments to enhance tumor elimination. For instance, ferroptosis, a promising cancer therapy, depends heavily on the iron-driven Fenton reaction, which transforms endogenous H_2O_2 into hydroxyl radicals (•OH) that oxidize lipids.[174] Since the Fenton reaction is more effective in acidic environments (pH = 3–6), cytoplasmic acidification could promote ferroptosis in tumor cells. Yang et al.[175] designed a hollow mesoporous CuSe/$CoSe_2$@syrosingopine (CSC@Syro) heterostructure coactivated by TME and NIR to reverse immunosuppressive TME and trigger antitumor immunity through

ferroptosis, PTT, and photocatalytic therapy (PCT). Especially, syrosingopine (Syro), an MCT4 inhibitor, blocks lactate efflux, induces cytoplasmic acidification to accelerate ferroptosis, and significantly alleviates immunosuppression. The CSC@Syro combinatorial platform demonstrates multimodal therapeutic efficacy by coordinating modulation of tumor bioenergetics, iron-dependent ferroptosis induction, and immune checkpoint activation, providing a promising strategy for enhanced immunotherapy through tumor metabolic regulation. Additionally, lactate oxidase (LOx) catalyzes lactate oxidation to pyruvate, depleting lactate levels while producing H_2O_2 as a byproduct, which can also enhance ferroptosis (Figure 5c). Wang et al.[56] developed LOx/HRP-aZIF, a therapeutic system that incorporates LOx and horseradish peroxidase (HRP) encapsulated in an amorphous zinc MOF, along with 3-indole-acetic acid (IAA). When it reaches the tumor, LOx oxidizes lactate into pyruvate and H_2O_2. Then, H_2O_2 collaborates with HRP to disrupt NADH-driven electron transport and GSH-dependent antioxidative defenses, thereby impairing mitochondrial function and making cancer cells more susceptible to oxidative damage. At the same time, HRP-mediated bio-orthogonal catalysis transforms IAA into free radicals, generating ROS that induce ferroptosis through lipid peroxidation. Overall, these findings highlight a new therapeutic approach by combining lactate metabolism modulation with ferroptosis induction, demonstrating an innovative strategy for synergistic, metabolism-focused anticancer treatments through iron-dependent cell death pathways.

In addition to depleting intracellular lactate, LOx can be engineered to degrade lactate in the TME, reducing the acidic conditions that promote immune suppression. Gao et al.[176] developed a cascade catalytic nanosystem (PMLR) composed of hollow MnO_2 ($HMnO_2$) nanoparticles coloaded with LOx and glycolysis inhibitor 3PO, within red blood cell membranes. In the TME, LOX catalyzes the oxidation of extracellular lactate to produce H_2O_2, which $HMnO_2$ further converts to generate O_2. After internalization by tumor cells, the nanosystem disassembles in acidic lysosomes, releasing 3PO to inhibit glycolysis, while the generated O_2 enhances the inhibitory effects of 3PO (Figure 5d). This effectively suppresses cell viability by consuming lactic acid and blocking ATP supply (Figure 5e–i). Importantly, this precise modulation of the microenvironment enables spatiotemporally controlled immune potentiation within tumor sites, synergistically boosting immune checkpoint blockade (ICB) therapy while avoiding the systemic inflammatory responses typically associated with global immune agonist administration.

4. Lipid Metabolism-Regulated Nanomedicines

Tumor cells exploit lipid metabolism to support biosynthesis and confer resistance to therapies. Additionally, lipids play a role in immunosuppressive signaling, aiding tumor immune evasion. This complex interaction positions lipid metabolic reprogramming as a promising therapeutic target for treatment. This section reviews recent nanomedicines targeting tumor lipid metabolism and their integration with immunotherapy.

4.1. Regulating Lipid Uptake

Exogenous lipids mainly derive from cancer-associated adipocytes (CAAs) and tumor-adjacent adipose tissues via lipolysis.[134] This phenomenon is particularly evident in breast cancer, which often arises within or near the mammary fat pad, a region rich in adipocytes, thereby connecting external lipids to tumor growth and adverse prognosis.[177,178] Additionally, other stromal cells, such as cancer-associated fibroblasts (CAFs), undergo lipidomic reprogramming, enriching for FAs and phospholipids, and transfer significant amounts of lipids to cancer cells via exosomes.[179] Since the uptake of exogenous lipids relies on transport molecules,[103] blocking these carriers could limit the lipid uptake of tumor cells. Rink et al.[180] developed high-density lipoprotein-like nanoparticles (HDL NPs) to treat diffuse large B-cell lymphoma (DLBCL). By utilizing the high-affinity interaction between HDL-mimetic nanoparticles (HDL NPs) and scavenger receptor class B type 1 (SCARB1), HDL NPs effectively lowered cellular cholesterol levels and triggered apoptosis by blocking cholesterol uptake. This approach provides a novel strategy for specifically targeting cholesterol metabolism as a cancer therapy.

The hypoxic TME activates HIF-1α signaling in cancer cells, thereby upregulating the expression of fatty acid transporters FABP3 and FABP7. These transporters facilitate fatty acid uptake and lipid-storage, thereby enhancing lipid droplet (LD) biogenesis.[181–183] LDs are lipid-storage organelles that facilitate efficient lipid transfer with membrane-enclosed organelles, maintaining phospholipid homeostasis and preventing lipotoxicity during cellular stress. Notably, LDs influence the ferroptotic response of tumor cells by sequestering polyunsaturated fatty acids (PUFAs) that are prone to oxidation.[184] To counteract this process, Zhang et al.[51] engineered a nanoscale multicomponent polymer, named TCPP-TK-PEGPAMAM-FA, capable of simultaneously delivering hafnium ions (Hf^{4+}) and siRNA targeting HIF-1α (siHIF-1α). The siHIF-1α disrupts the expression of FABP3/7 through the HIF-1α-FABP3/7 pathway, leading to decreased LD formation and heightened vulnerability of membrane lipids to oxidation. The Hf^{4+} ions boost the production of ROS upon radiation exposure, causing ferroptotic damage to key membrane structures. Furthermore, the membrane damage induced by TCPP@Hf-TK-PEGPAMAM-FA@siHIF-1α reveals tumor-associated antigens (TAAs), which enhance the effectiveness of subsequent low-dose radiation (LDR) immunotherapy and result in significant tumor regression in vivo (**Figure 6**a). This multifunctional nanoplatform leverages the tumor's lipid metabolic dependencies to improve LDR therapeutic outcomes by combining ROS-driven membrane disruption with immune activation, offering new insights into targeting tumor-specific lipid pathways for cancer treatment.

4.2. Regulating Lipid Biosynthesis

Cancer cells also initiate de novo lipogenesis to meet their elevated metabolic demands. Overexpression of cyclooxygenase (COX)-2 in tumor cells leads to the production of PGE_2, an immunosuppressive metabolite that promotes the accumulation of MDSCs and TAMs while inhibiting tumor infiltration and

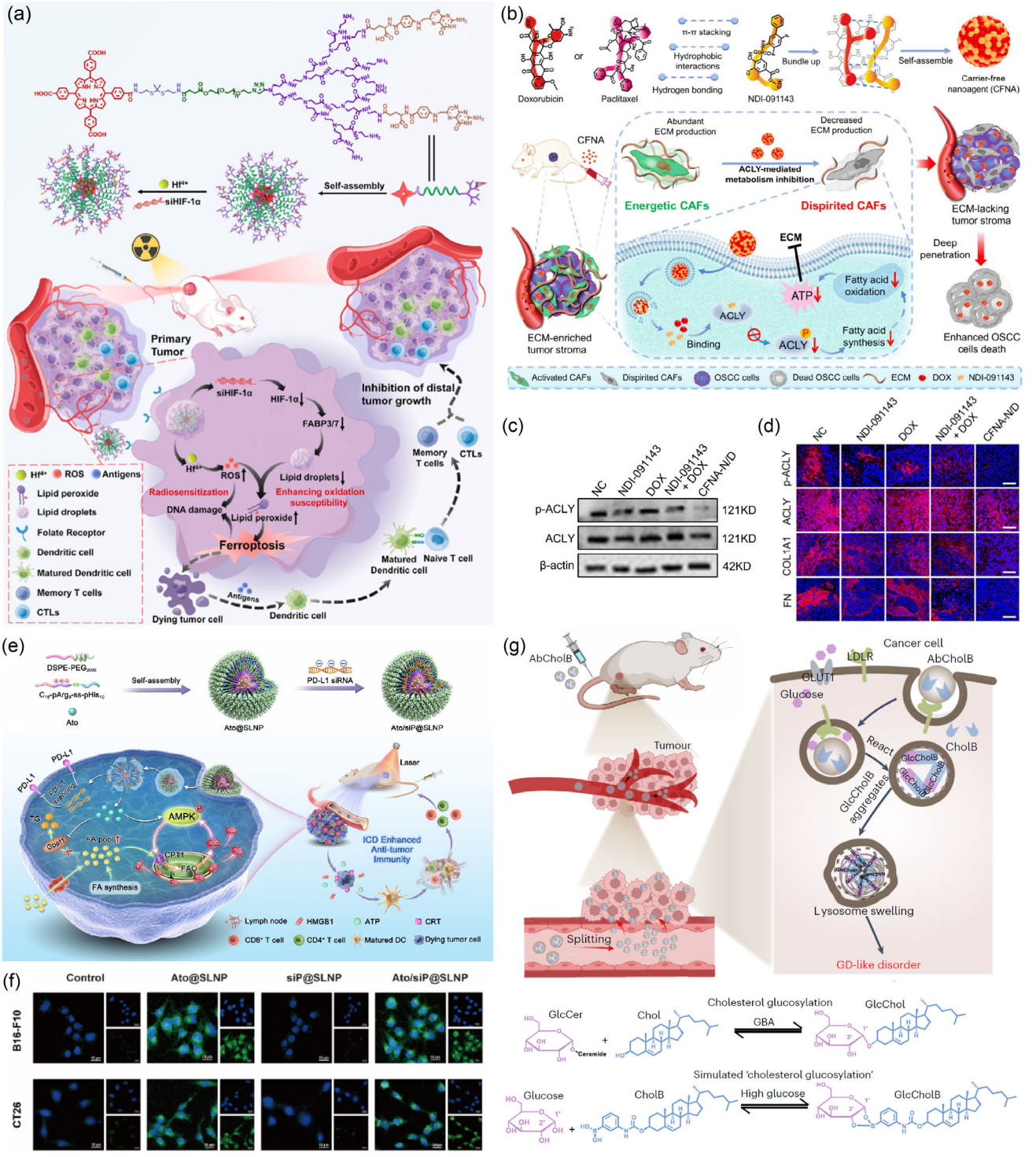

Figure 6. Nanomedicines for regulating lipid metabolism in cancer cells. a) Schematic of TCPP@Hf-TK-PEG-PAMAM-FA@siHIF-1α nanoassemblies for in situ reprogramming of LD biogenesis and low-dose radiation-activated ferroptosis immunotherapy. Reproduced with permission.[51] Copyright 2023, American Chemical Society. b) Disruption of tumor stromal barriers via ACLY inhibition in CAFs using CFNA, reducing ECM secretion and enhancing chemotherapeutic penetration. c) WB of ACLY and p-ACLY in CAFs treated with NDI-091 143, DOX, their combination, or CFNAN/D. d) IF staining of p-ACLY, ACLY, COL1A1, and FN in tumor sections across treatment groups. Reproduced with permission.[47] Copyright 2024, American Chemical Society. e) Self-assembled lipopeptide nanoplexes for self-amplifying ROS production and enhanced PD-L1 silencing efficacy. Ato activates AMPK and suppresses mitochondrial FAO, increasing ROS and sustaining a feedback loop. f) Intracellular ROS detected by CLSM at 6 h post-treatment. Reproduced with permission.[197] Copyright 2022, Elsevier. g) Mechanism of AbCholB-induced cholesterol glucosylation initiating Gaucher disease-like disorder in cancer cells by exploiting glucose and lipid avidity. Reproduced with permission.[208] Copyright 2023, Springer Nature.

cytokine secretion by effector T cells. Clinical studies show that targeting PGE_2 with celecoxib enhances ICB therapies in metastatic lung and melanoma cancers.[185] However, systemic combination therapies have not achieved optimal synergy due to different pharmacokinetic profiles. Additionally, the spatial separation of molecular targets, with COX-2 located in the cytoplasm of cancer cells and PD-1 on the surface of CD8+ T cells, further limits therapeutic effectiveness. To address these problems, Feng et al.[186] developed a pH and GSH dual-sensitive nanomedicine that improves immunotherapy by overcoming PGE_2-mediated immune suppression. The nanomedicine accumulates preferentially in tumors, where it extracellularly releases the PD-1/PD-L1 inhibitor BMS-202 in response to the TME, and intracellularly releases the COX-2 inhibitor celecoxib upon activation by GSH. Subsequently, celecoxib suppresses COX-2 activity and reduces PGE_2 levels, thereby reversing immunosuppression, while BMS-202 blocks the PD-1/PD-L1 axis to enhance antitumor immunity. This multistimuli nanoplatform addresses pharmacokinetic limits of metabolic modulators with tumor-specific activation, enabling controlled therapeutic release and metabolic reprogramming. It establishes a new framework for cancer therapy by integrating metabolic vulnerability with bio-responsive drug delivery.

As a major type of stromal cell, CAFs have been widely identified as key promoters in producing ECM, which is a major obstacle for drug penetration. It is worth noting that CAFs are also highly glycolytic cells and have been found to exhibit increased lipid synthesis, with more stored lipids than normal fibroblasts, heavily relying on ACLY activity for their function.[187,188] Yu et al.[47] fabricated a carrier-free nanoagent (CFNA) using a self-assembling nanoparticle design, simply combining NDI-091143, an ACLY inhibitor, with DOX or paclitaxel (PTX) through multiple noncovalent interactions (Figure 6b). Once it reaches the tumor site rich in CAFs, NDI-091143-mediated ACLY inhibition in CAFs can block the de novo synthesis of FAs (Figure 6c), reducing the fatty acid-involved energy metabolic process. Due to a lack of sufficient energy, the energy-demanding CAFs become less active and are unable to produce abundant ECM (Figure 6d), thereby significantly improving drug perfusion and enhancing chemotherapy efficacy.

Lipid metabolism is crucial for the development, maturation, and activity of DCs. Abnormal lipid accumulation in tumor-infiltrating DCs (TIDCs) hampers their function, especially reducing their ability for cross-presentation and blocking T cell priming, which promotes tumor progression.[189–191] Thus, normalizing lipid levels in DCs can improve cancer vaccine effectiveness. TOFA, an acetyl-CoA carboxylase inhibitor, has been used to restore T cell-stimulating function by blocking fatty acid synthesis in DCs. Although targeted nanoparticles, such as those modified with anti-DEC205, anti-CD11c, or mannose, have been developed to target DCs, their efficiency may be lowered due to different receptor expression across various DCs subsets.[192,193] Drawing inspiration from the recognition of pathogen-associated molecular patterns on the surface of invading bacteria by DCs, Qin et al.[44] developed a nanovaccine, designated TPOP, aimed at modulating lipid metabolism of TIDCs directly at the site. TPOP comprises poly(lactic-co-glycolic acid) (PLGA) encapsulating TOFA (TOFA@PLGA) and is modified with bacterial outer membrane components (OMs) along with 2-distearoyl-sn-glycero-3-phosphoethanolamine-polyethylene glycol 2000-maleimide ($DSPE\text{-}PEG_{2000}$-MAL) to facilitate tumor antigen binding. The OMs on TPOP enhance TIDC uptake via PAMP-PRR binding. After injection, DOX-induced tumor cell death releases TAAs, which are captured by TPOP and presented by MHC-I on DCs. Subsequently, PLGA degradation releases TOFA, decreasing lipid accumulation in TIDCs and restoring cross-presentation. In mouse models of colorectal cancer and melanoma, TPOP combined with ICB effectively slowed tumor growth. Overall, this metabolic engineering platform reverses TIDC cross-presentation by modulating DC metabolism, presenting a safe and promising strategy to boost immune cell function through metabolic regulation.

4.3. Regulating Lipid Metabolism Homeostasis

Under TME conditions, lipids undergo breakdown into free fatty acids (FFAs), which are then utilized to generate ATP via the fatty acid oxidation (FAO) pathway. These FFAs also play roles in constructing biological membranes and serving as precursors in signal transduction processes.[194] Therefore, inhibiting the metabolism of FFAs represents a potentially effective strategy for combating tumors, as it interferes with critical metabolic pathways necessary for tumor cell survival, proliferation, and energy production. Cao et al.[195] proposed regulating FFAs metabolism using small interfering RNA (siRNA), which can silence target genes, including "undruggable" proteins. However, systemic siRNA delivery is challenging due to issues with charge, clearance, and membrane crossing; however, nanoparticles can overcome these barriers. Therefore, they developed a reduction-responsive platform for codelivering MGLL siRNA (siMGLL) and CB-2 siRNA (siCB-2) to treat pancreatic cancer. Inside PAC cells and TAMs, high GSH triggers the release of siRNA, silencing MGLL and CB-2, reducing FFAs production, and shifting TAMs from an M2 to an M1 phenotype, thus inhibiting PAC growth in xenograft and orthotopic models.

Notably, ROS are generated as byproducts during FAO. Moreover, in cancer cells, dysregulated lipid metabolism ensures a sufficient supply of fatty acid substrates, thereby sustaining ROS production from FAO without limitation.[196] Therefore, Gao et al.[197] constructed a self-assembled nanoplex, C18-pArg8-ss-pHis10, to coencapsulate atorvastatin (Ato) and PD-L1 siRNA. Ato activates AMPK, boosting mitochondrial FAO and ROS in cancer cells. The ROS further activate AMPK, creating a positive feedback loop maintained by abundant FAs from dysregulated lipid metabolism, while Ato inhibits triglyceride synthesis (Figure 6e,f). This method enhances anticancer efficacy by regulating lipid metabolism and self-amplifying ROS, overcoming oxy-substrate deficiency limitations, broadening metabolic intervention in cancer therapy, and opening new redox-based therapeutic avenues.

Furthermore, increased ROS levels trigger ICD, which boosts the antitumor efficacy of PD-L1 silencing. In addition to pharmacological and genetic strategies, intrinsically active materials represent promising alternatives for modulating tumor lipid metabolism. For instance, supramolecular β-cyclodextrins naturally recognize and sequester cholesterol through host–guest interactions. Inspired by this mechanism, Zhou et al.[198]

engineered a class of supramolecular nanotraps based on heptakis(2,3,6-tri-O-methyl)-β-cyclodextrin (TMCD) for specific targeting of lipid molecules. Experimental data demonstrated that these nanotraps could effectively bind, extract, and lower levels of cholesterol and phosphatidylcholine (PC), thereby disturbing lipid metabolism homeostasis. Additionally, these nanotraps prompted pyroptosis in some tumor cells by activating NOD-like receptor signaling pathways and NLRP3 inflammasomes, which were triggered by lysosomal stress, ultimately inducing significant antitumor effects.

On the other hand, some researchers strongly claim that nutrient starvation methods, like lipid reduction, offer little advantage. Few clinical trials have shown significant benefits for patients,[199,200] with malnutrition affects up to 80% of cases.[201,202] Nutrient deprivation tends to mainly harm normal cells rather than cancer cells, as cancer cells have a greater ability to acquire nutrients.[203,204] Additionally, nutrient scarcity can drive mutations in cancer cells, enhancing their metabolic and predatory capabilities, which leads to a more aggressive phenotype.[205–207] In this context, the strategy of providing tumor cells with excessive nutrients has also been examined as a way to damage them. Inspired by Gaucher disease, which causes the accumulation of cholesteryl–glucoside in lysosomes and results in cell damage, Yue et al.[208] developed a biomimetic AbCholB nanoparticle designed to mimic lipoprotein-carried cholesterol and selectively induce Gaucher disease-like cytotoxicity in cancer cells. Composed of phenylboronic acid-modified cholesterol and albumin, AbCholB is internalized and trafficked to lysosomes. There, the cholesterol derivative reacts with glucose to form a cholesteryl–glucoside-like structure that resists degradation and aggregates into microscale crystals, resulting in glucose-dependent lysosomal dysfunction (Figure 6g). Notably, AbCholB exhibits favorable biosafety due to the reduced nutrient competition and uptake in normal cells. This study presents a novel therapeutic strategy that exploits the high metabolic demand of tumor cells to disrupt lysosomal function and induce metabolic catastrophe selectively.

5. Amino Acid Metabolism-Regulated Nanomedicines

Amino acids play a key role in biosynthesis, energy production, and maintaining cellular redox balance. Cancer cells, compared to normal cells, need more amino acids to support rapid growth and energy needs. Importantly, glutamate, cysteine, and glycine are vital for making glutathione, which protects cancer cells from oxidative damage. Besides their roles within tumors, amino acids also influence antitumor immune responses. Specifically, IDO and TDO can increase the intratumoral production and accumulation of immunosuppressive amino acid metabolites, thereby creating an immunosuppressive environment. Therefore, targeting amino acid metabolism in tumors can disrupt energy flow and redox stability while also reducing TME immunosuppression, enhancing the effectiveness of cancer immunotherapy. In this section, we summarize the recent advances in nanoplatforms engineered to reprogram amino acid metabolism for cancer treatment.

5.1. Regulating Glutamine Metabolism

Tumor-dependent glutamine metabolism is essential for cancer cell survival, but targeting this pathway with metabolic inhibitors presents challenges, such as compensatory metabolic responses and limited delivery efficiency. For example, although DON was tested in several clinical trials, those efforts were ultimately halted due to significant toxicity, especially in the gastrointestinal tract.[2] Therefore, delivering DON with nanotechnology, combined with other therapeutic approaches, would be an effective strategy. Xie et al.[62] developed a multifunctional nanomedicine, designated as CTTPA-G, which is capable of transporting and releasing a type I aggregation-induced emission (AIE) photosensitizer, TTPA, along with DON. CTTPA-G effectively fulfills the glucose and glutamine requirements of T cells, improves the hypoxic environment of tumors, and reprograms the metabolism of both tumor and immune cells, thereby inducing the ICD of tumor cells. Then the induced ICD promotes dendritic cell maturation and efficiently inhibits tumor growth. The metabolic competition between cancer and immune cells creates a therapeutic window through their different metabolic dependencies. By analyzing the inherent heterogeneity and dynamic plasticity of tumor versus immune cell metabolism, researchers develop precision metabolic targeting strategies to selectively reprogram immune-metabolic networks.

Glutamine is also closely linked to redox homeostasis, which can help maintain the redox balance in tumor cells.[209] In tumor cells, the solute carrier family 7-member 11 (SLC7A11/XCT) transporter mediates the uptake of cystine, which, along with glutamate and glycine, facilitates GSH synthesis. Based on these findings, Chen et al.[210] developed a platform by integrating Pt−Pd nanoflowers with DON (Pt−Pd@DON) for synergistic electrodynamic immunotherapy. In this system, DON inhibits GSH production, preventing ROS elimination under an electric field, which induces tumor cell death and triggers an ICD effect. The induced ICD then initiates a protective immune response for long-term tumor suppression in vivo.

Besides inhibiting glutamine metabolism enzymes, blocking glutamine uptake can also disrupt the nutrient supply to tumor cells. As reported, pancreatic cancer cells increase glucose uptake and utilization through KRAS mutations and boost glutamine and glutamic acid metabolism via the $KRAS^{G12D}$ mutation.[80,211] Thus, targeting both glucose and glutamine addiction offers a promising therapeutic strategy for pancreatic cancer. Wang et al.[212] fabricated BAY-876 (GLUT1 inhibitor) and V-9302 (ASCT2 inhibitor) coloaded human serum albumin (HSA) nanoparticles (BAY-876/V-9302@HSA NPs) that simultaneously inhibit the glucose transporter GLUT1 and the glutamine transporter ASCT2 in pancreatic cancer cells. This dual inhibition disrupts the energy supply to tumor cells, which further induces oxidative stress and reduces GSH production. The resulting imbalance leads to an overproduction of ROS, which activates caspase-1 and GSDMD, ultimately triggering pyroptotic cell death (**Figure 7**a). By encapsulating multiple metabolic inhibitors, this strategy could prevent tumor cells from activating compensatory pathways, offering a novel therapeutic approach targeting cancer metabolism.

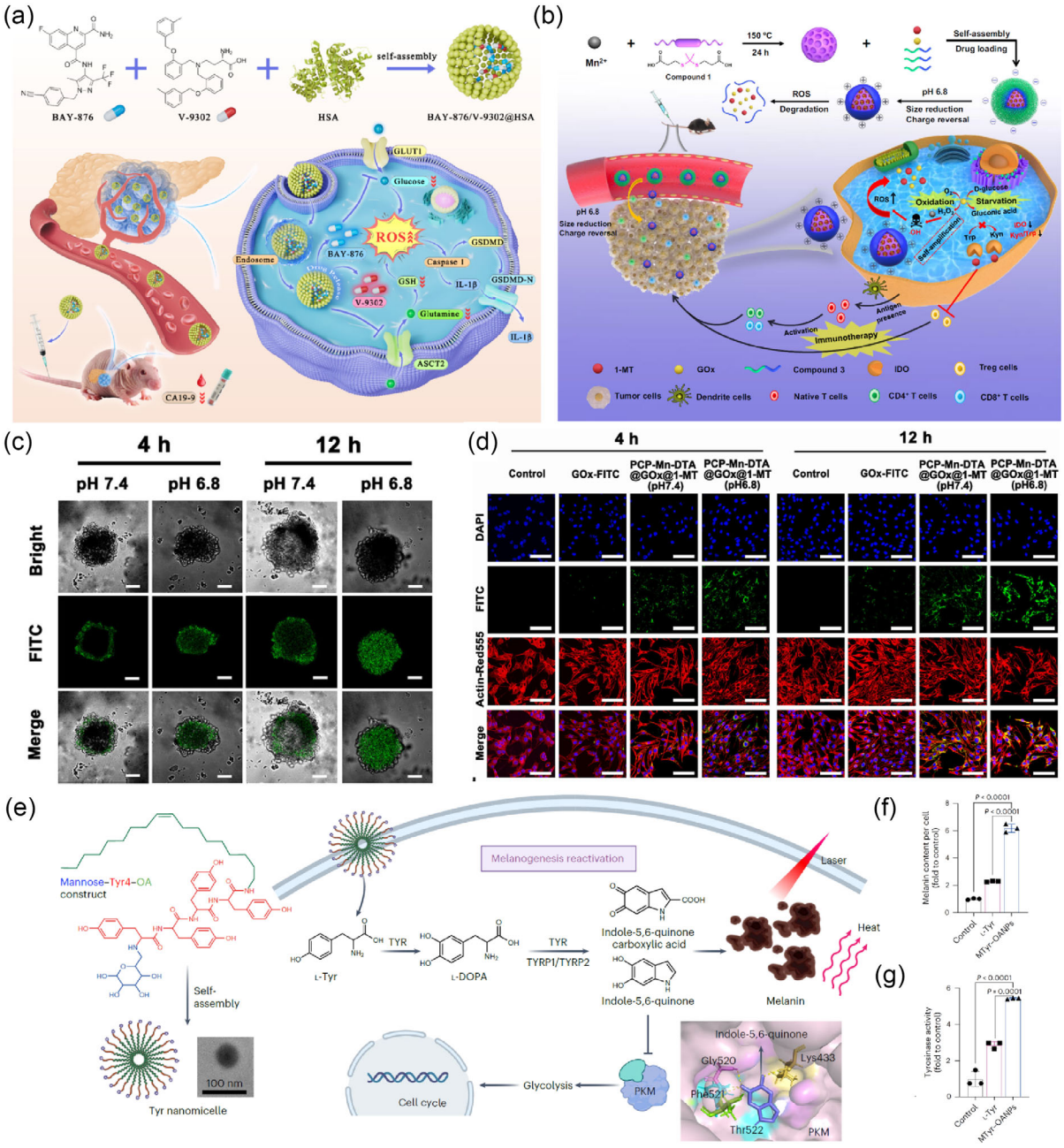

Figure 7. Nanomedicines for regulating amino acid metabolism in cancer cells. a) Mechanism of BAY-876/V-9302@HSA-induced pyroptosis for pancreatic cancer therapy via dual glucose and glutamine deprivation. Reproduced with permission.[212] Copyright 2024, American Chemical Society. b) Schematic of PCP-Mn-DTA@GOx@1-MT nanosystem for synergistic starvation, oxidative and immunotherapy. c,d) Penetration (c) and endocytosis (d) of FITC-labeled PCP-Mn-DTA@GOx@1-MT in B16F10 MCSs after incubation at pH 6.8 or 7.4 for 4 h and 12 h. Nuclei and cytoskeleton were stained with DAPI (blue) and ActinRed555 (red), respectively. Reproduced with permission.[215] Copyright 2022, Springer Nature. e) MTyr–OANPs elevate tyrosine levels in melanoma, reactivating melanin synthesis. The intermediate indole-5,6-quinone inhibits PKM and glycolysis, inducing cell cycle arrest. Endogenous melanin also enables PTT. f) Intracellular melanin levels. g) Tyrosinase activity in B16F10 cells after 48 h coculture with MTyr–OANPs. Reproduced with permission.[92] Copyright 2024, Springer Nature.

5.2. Regulating Tryptophan Metabolism

Tryptophan is a vital amino acid that plays a role in several biological functions, including protein synthesis, neurotransmitter production, and immune system regulation. Its metabolism is mediated by enzymes like indoleamine IDO and TDO. In tumor cells and different immune cells, including MDSCs, TAMs, and suppressive DCs, the expression of tryptophan-degrading enzymes is upregulated, leading to increased tryptophan consumption within the TME, which depletes its availability and

impairs the antitumor activity of T cells.[127,128,213] Moreover, IDO and TDO convert tryptophan into kynurenine, a metabolite that inhibits the activation and proliferation of tumor-specific T cells and recruits immunosuppressive Tregs and MDSC, thereby promoting immune suppression and tumor immune evasion.[127,128] As a result, inhibiting IDO has become a promising approach to counteract tumor-induced immune suppression. So far, several IDO inhibitors have been developed, including indoximod, navoximod (also known as NLG919), HTI-1090, and IDO1 siRNA (IDO1 gene silencing).[214] Although these inhibitors demonstrate potential in reversing the immune suppression of cancer, they remain linked to the risk of immune-related issues.[214] Fortunately, nanotechnology offers a significant advantage by enhancing cancer immunotherapy while minimizing these toxicities. Li et al.[128] developed a nanomedicine that combines the ICD inducer epirubicin and the IDO1 inhibitor NLG919 for tumor chemo-immunotherapy. Epirubicin induces robust ICD in tumor cells, initiating a potent immune response. Moreover, by inhibiting IDO1, the conversion of L-tryptophan to kynurenine is decreased, which limits the recruitment of immunosuppressive cells and helps modify the tumor immune microenvironment. By simultaneously potentiating the immune response and reprogramming the immunosuppressive niche, this dual approach significantly improves chemo-immunotherapy outcomes.

Furthermore, to achieve the specific release of metabolic regulators, Dai et al.[215] developed a pH/ROS dual-sensitive nanosystem, which is capable of codelivering GOx and 1-methyltryptophan (1-MT) to target tumor environments, facilitating starvation, oxidative stress, and immune modulation through IDO inhibition (Figure 7b). Unlike earlier approaches, the release mechanism here is triggered explicitly by the slightly acidic TME (around pH 6.8) and elevated intracellular ROS levels within cancer cells (Figure 7c,d). The enzymatic activity of GOx consumes glucose, producing H_2O_2, which, in the presence of Mn^{2+}, undergoes Fenton-like reactions to generate highly damaging •OH. This cascade results in the disassembly of the MOF, releasing 1-MT and enhancing anticancer effects. Leveraging immune activation and suppression of immune resistance, this nanotherapeutic demonstrates potent antitumor efficacy.

5.3. Regulating L-Arginine Metabolism

Arginine is an endogenous alkali that neutralizes acids and plays a vital role in synthesizing key metabolites like nitric oxide (NO), polyamines, amino acids, and pyrimidines, all vital for cell survival and proliferation.[216] In the TME, arginine plays a vital role in enhancing antitumor immune responses, particularly by aiding T cell differentiation and activation.[217] However, arginine deficiency in the TME arises from both limited supply and excessive consumption.[218,219] Research indicates that arginine depletion greatly decreases T cell proliferation and IFN-γ production, weakening immune response. In contrast, supplementing with arginine helps recover T cell proliferation, differentiation, and memory development, and also boosts CD4+ T cell levels populations.[220,221] Despite its therapeutic potential, reaching the effective oral dose of arginine (150 g per 75 kg patient) is nearly impossible, and direct intratumoral administration faces obstacles like enzymatic degradation and the rapid diffusion of hydrophilic arginine in the TME.[222] Therefore, Zang et al.[222] engineered a small-molecule-tagged arginine to facilitate self-assembly, resulting in a high drug-loading capacity. Terephthalaldehyde (Ter), an aromatic aldehyde, was employed to modify arginine, creating acid-sensitive imine bonds that enhance the hydrophobic properties. The self-assembled nanoarginine (ArgNPs) can penetrate the TME via the EPR effect and release arginine in response to acidity. Combining ArgNPs with anti-PD-L1 therapy significantly increases tumor-infiltrating T cells, decreases MDSCs, and promotes proinflammatory M1-like macrophages. Local modulation of TME metabolism via this straightforward strategy demonstrates translational promise, potentially mitigating current barriers to ICB therapy efficacy.

Recent findings highlight that maintaining the M1-like macrophage phenotype after repolarization depends on increased levels of inducible NO synthase, which converts L-arginine into NO, thereby preventing the shift to M2-like phenotype by inducing mitochondrial dysfunction.[223] Hence, Zheng et al.[224] further incorporated toll-like receptor 7/8 agonist resiquimod (R848) into arginine NPs to form R848@Arg. R848 initially repolarized the macrophages, and then intracellular NO can be produced from released arginine through the upregulation of inducible NO synthase. Mechanistically, NO blocks the negative feedback of repolarized macrophages by causing mitochondrial dysfunction, thereby maintaining the M1-like phenotype in the TME.

5.4. Regulating Cysteine Metabolism

Cysteine, an amino acid containing sulfur, is essential for cellular metabolic processes. It is transported into cells via the Xc^- amino acid antiporter and is mainly used for synthesizing cysteine-derived biomolecules, reprogramming sulfur and carbon metabolism, and facilitating posttranslational protein modifications. Notably, the synthesis of GSH and thioredoxin (TXN), both essential redox systems, heavily depends on cysteine. Depleting cellular cysteine or blocking its extracellular supply can disrupt redox balance and promote lipid peroxidation. Consequently, nanomedicines targeting cysteine transporter proteins have shown promising therapeutic potential. For example, Li et al.[54] developed a mesoporous silica-based nanoplatform codelivering FePt NPs and siRNA targeting xCT to deplete cysteine and induce ferroptosis in breast cancer cells. Nanomedicine accumulates in tumors, where FePt induces ferroptosis and siRNA suppresses xCT, preventing cystine uptake, leading to cysteine depletion and redox imbalance, thereby increasing tumor cell death. This study introduces a cysteine depletion-enabled ferroptosis therapy paradigm, advancing amino acid metabolism regulation in tumors. Notably, IFN-γ released through immune-stimulating methods suppresses the Xc^- antiporter, hindering GSH synthesis and triggering lethal LPO cascades in tumor cells. Song et al.[225] Engineered pH-activatable nanoparticles for tumor immunotherapy via ferroptosis induction. The system combines ionizable block copolymers with phenylboronate ester (PBE) dynamic bonds to deliver the GPX4 inhibitor RSL-3. At physiological pH (7.4), π–π stacking maintains a stable encapsulation of RSL-3 in hydrophobic cores, whereas in acidic endosomal conditions (5.8–6.2), PBE cleavage is triggered, leading to

payload release. Furthermore, protonating the ionizable core allows for acid-activated PDT, which attracts tumor-infiltrating T lymphocytes to secrete IFN-γ and enhances the sensitivity of tumor cells to RSL-3-induced ferroptosis.

Bacteria-based metabolic therapy is recognized as a promising approach for cancer treatment. Wang et al.[226] Developed an L-cysteine-dependent bacteria–liposome hybrid through dual-screening directed evolution. The engineered strain shows a 36-fold increase in L-cystine uptake and a 23-fold rise in cysteine-degrading enzyme activity compared to wild-type bacteria. When conjugated with liposomes loaded with DMXAA (a potent vascular disruption agent), this biohybrid blocks tumor neovasculature while sustaining cystine catabolism. Local cysteine depletion disrupts redox balance, raising ROS levels to suppress various tumor models. This work pioneers a transformative therapeutic approach where metabolically rewired bacteria act as living drug factories, enabling tumor-specific metabolic disruption through continuous enzymatic catalysis.

Recent work by Cui et al. revealed that M2-like TAMs exhibit elevated lysosomal cysteine protease activity compared to other antigen-presenting cells (APCs). Blocking this enzyme enhanced antigen cross-presentation and $CD8^+$ T cell activation.[227] However, the therapeutic potential of the small-molecule cysteine protease inhibitor E64 is hampered by its low bioavailability, suboptimal pharmacokinetics, and poor membrane permeability.[228,229] To address these limitations, Qiao et al.[229] designed mesoporous silica nanoparticles coated with a cell membrane (ME@C) loaded with the cysteine protease inhibitor E64, modified with an artificial ligand for targeted delivery of E64 and TAAs to M2-like TAMs. Nanoparticles specifically target M2-like TAMs through CD302 receptor-mediated endocytosis. Inside lysosomes, E64 is released to inhibit cysteine proteases, boosting antigen cross-presentation and activating CD8+ T cells. This nanomedicine significantly improves tumor-targeted immunotherapy, exhibiting low toxicity and minimal inflammation in vivo, which highlights its promising potential for clinical application.

5.5. Regulating Tyrosine Metabolism

Metabolic pathways in tumors are often specific to cell types, and some specialized functions may not directly contribute to tumor growth. For instance, melanogenesis is considerably downregulated in melanomas compared to melanocytes. In this pathway, L-tyrosine (Tyr) is initially hydroxylated to L-dihydroxyphenylalanine (L-DOPA), which is then oxidized by tyrosinase to dopaquinone and ultimately forms melanin.[230] Chen et al.[92] developed a Tyr-based degradable nanosized micelle (MTyr–OANPs) designed to deliver Tyr to tumor cells and restore melanogenesis for melanoma therapy (Figure 7e). When entering tumor cells, a significant amount of Tyr released from MTyr–OANPs reactivates melanin synthesis (Figure 7f,g). During melanogenesis, the decrease in glycolysis caused by melanin intermediates halts the cell cycle. (Figure 7e). Additionally, leveraging the excellent photothermal conversion properties of endogenously produced melanin, PTT was used as a dual treatment strategy for tumors. This metabolism activation-based tumor therapy emphasizes that, besides inhibiting hyperactive metabolic pathways, reactivating hypoactive ones can also effectively suppress tumor growth. As a novel approach based on reverse-thinking logic, nutrient-driven metabolic reactivation has great potential for wide applications in cancer treatment.

5.6. Regulating Methionine Metabolism

As previously highlighted, tumor cells rely heavily on methionine because of its essential roles in epigenetic modifications and immunomodulation. To target this metabolic vulnerability, Ma et al.[231] engineered a multimodal methionine-depletion hydrogel that coencapsulates NPs loaded with the small-molecule inhibitors PF9366 and adenosine dialdehyde, along with the extracellular methionine uptake inhibitor JPH203. This combination treatment successfully inhibited tumor growth in mouse models of triple-negative breast cancer (TNBC), liver cancer, and colorectal cancer. Importantly, this strategy spares normal cellular methionine metabolism, thereby reducing off-target toxicity.

5.7. Regulating Leucine Metabolism

A recent study found that dihydrolipoamide S-acetyltransferase (DLAT), an enzyme involved in pyruvate metabolism, enhances leucine buildup by acetylating AUH at K109. This process inhibits leucine catabolism and helps sustain mTOR activation in hepatocellular carcinoma.[232] Wang et al. developed an AUHK109R-mRNA LNPs therapy that restores AUH function, effectively inhibiting leucine-driven tumor growth and mTOR signaling in vivo. The DLAT-mediated acetylation mechanism is associated with poor prognosis in HCC, establishing AUH-targeted LNPs as a novel therapeutic approach.

6. Nucleotide Metabolism-Regulated Nanomedicines

Cancer cells enhance nucleotide metabolism to sustain malignant behaviors, including rapid proliferation, chemoresistance, and metastatic dissemination. Clinically, nucleotide metabolism-targeting agents (e.g., antifolates, nucleoside analogs) constitute mainstay therapeutics across diverse malignancies. Paradoxically, recent studies reveal that extracellular ATP accumulation undergoes ectoenzymatic conversion to immunosuppressive adenosine, fostering an immune-evasive TME. Conversely, nucleotides such as cyclic GMP-AMP (cGAMP) activate the STING pathway, stimulating the production of IFNs to enhance antitumor immunity.[233,234] This dual role positions nucleotide metabolic reprogramming as a novel framework for immunotherapeutic approaches. This section summarizes recent developments in nanomedicines designed to control nucleotide metabolism for targeted cancer treatment.

6.1. Regulating the Nucleotide Availability

MTX and 5-FU inhibit nucleotide synthesis through a competitive mechanism. For example, MTX targets DHFR, reducing tetrahydrofolate (THF) levels, which are essential for nucleotide production. Previous research indicates that adding histidine enhances the cytotoxic effects of MTX by depleting THF in tumor

cells, suggesting that histidine supplementation could be a valuable addition to MTX-based therapies.[235] Unfortunately, these drugs lack the ability to selectively target tumor sites, which may result in systemic toxicity. To address this, Wang et al.[236] Developed a ferrous ion-chelated histidine nanoparticle (FHM) that not only delivers MTX directly to tumor sites, reducing systemic toxicity through the EPR effect, but also enhances the cytotoxicity of MTX via histidine metabolism. Within tumor cells, MTX blocks essential enzymes such as DHFR, aminoimidazole carboxamide adenosine ribonucleotide transformylase, and thymidylate synthase (TYMS), thereby disrupting 1C metabolism, along with purine and pyrimidine production. Simultaneously, histidine metabolism reduces intracellular THF levels, which further enhances the inhibition of 1C metabolism. When combined with FMD treatments, FHM nanoparticles effectively inhibit the growth of three tumor types. Notably, using a 95% reduced MTX dose (12.5 mg kg^{-1}) in combination therapy effectively inhibited the growth of two murine tumor models without apparent systemic toxicity.

6.2. Regulating Immunosuppressive Nucleotide

ADO accumulates to abnormally high levels in the TME, acting as a metabolic checkpoint that allows tumors to evade immune surveillance. This process results from the hydrolysis of extracellular ATP by ectonucleotidases CD39 and CD73, which are overexpressed under hypoxic conditions.[133] Subsequently, ADO binds to adenosine receptors such as A2AR and A2BR on both tumor and immune cells, triggering multiple immunosuppressive effects that further help the tumor evade the immune system. Specifically, ADO activates epithelial-mesenchymal transition (EMT), inhibits apoptosis, and promotes metastasis. Additionally, it not only impairs DC antigen presentation and suppresses T cell activation and cytotoxicity but also promotes the conversion of naïve T cells into immunosuppressive Tregs, favors M2 macrophage polarization, and enhances MDSC aggregation.[133] Thus, eliminating the immunosuppressive effects of ADO is critical for improving cancer immunotherapy.

Ectonucleotidase inhibitors, primarily nucleotide derivatives like ARL67156 (ARL), adenosine 5′-(α,β-methylene)diphosphate, and PSB12379, function by preventing ATP breakdown into ADO.[237] However, rapid blood clearance prevents these highly hydrophilic small-molecule nucleotide derivatives from achieving therapeutic tumor concentrations.[238] Delivery systems, like liposomes, can overcome this limitation.[239] Despite this, achieving targeted release of these compounds within tumors remains challenging. Stimuli-responsive drug delivery systems offer a promising solution for disease-specific targeting and reducing off-target toxicity. Mao et al.[240] developed ROS-generating nanoparticles loaded with the CD39/CD73 inhibitor ARL and a photosensitizer IR700. Upon light irradiation, these particles induced PDT, resulting in cancer cell destruction and the release of ATP. At the same time, ROS generated by irradiation reversed the nanoparticle charge, enabling responsive ARL release and preventing ATP conversion to ADO. This nanomedicine effectively induced ICD, enhanced DC maturation, and promoted T cell activation through tumor antigen cross-presentation. Significantly, it triggered immune responses in the patient-derived organotypic tumor spheroid model.

While ectonucleotidase inhibitors can be effective, their use may lead to off-target toxicity because A2AR is widely distributed in various tissues organs.[241] Additionally, targeting A2AR alone

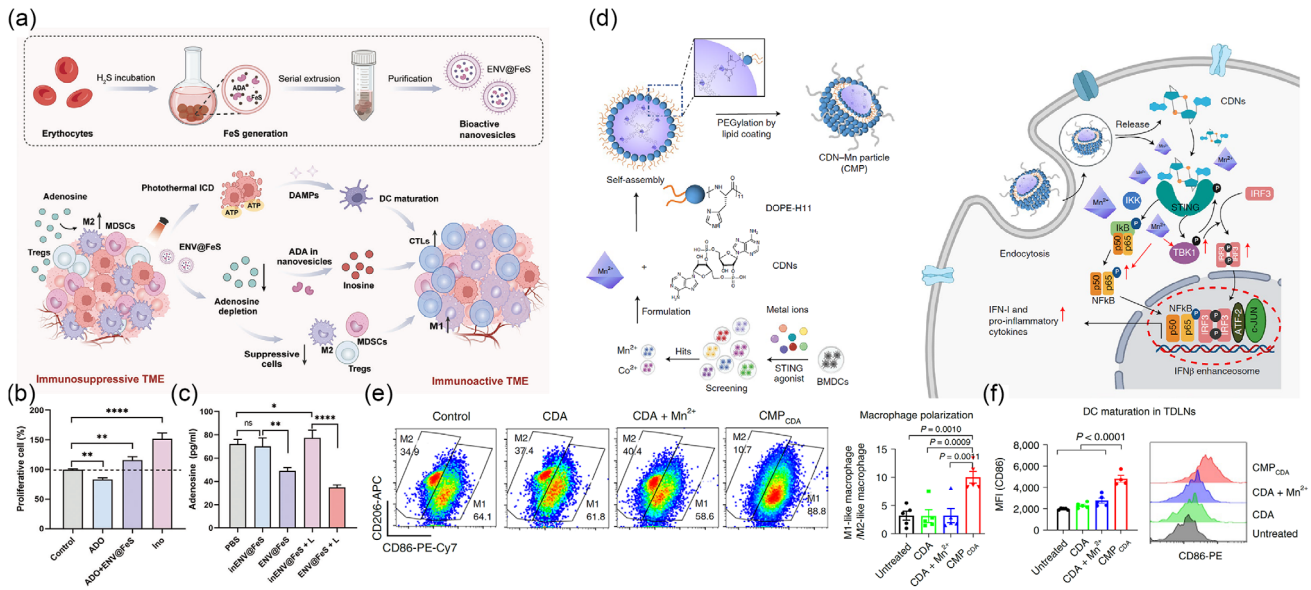

Figure 8. Nanomedicines for regulating nucleotide metabolism in cancer cells. a) Mechanism of ENV@FeS nanovesicles for alleviating adenosine-mediated immunosuppression via adenosine depletion in the TME. b) T cell proliferation after treatment with adenosine or inosine, measured by CCK-8 assay. c) Adenosine levels in 4T1 cell supernatants after ENV@FeS treatment, detected by ELISA. Reproduced with permission.[242] Copyright 2024, Wiley. d) Schematic of CDN–manganese particles amplifying STING activation for local and systemic metalloimmunotherapy. e) Proportion of M1 and M2 macrophages in the TME. f) CD86 expression on DCs in tumor-draining lymph nodes. Reproduced with permission.[244] Copyright 2021, Springer Nature.

might not completely block ADO function due to the presence of multiple adenosine receptors.[242] Alternatively, directly targeting ADO metabolism in the TME offers a promising approach. Adenosine deaminase (ADA) irreversibly converts ADO to inosine (Ino), depleting ADO levels. Inosine has also been shown to modulate T cell growth and activation, making ADA a valuable tool for regulating ADO-mediated immunosuppression. Wang et al.[242] developed catalytic erythrocyte nanovesicles (ENV@FeS) enriched with ADA through serial extrusion. Nanomedicine can enhance blood circulation, regulate adenosine metabolism, and improve tumor photoimmunotherapy. FeS-mediated PTT kills tumor cells, induces ICD, and promotes DC maturation and tumor antigen presentation (**Figure 8**a). Meanwhile, ADA in ENV@FeS converts ADO to inosine, reversing its immunosuppressive effects on tumor-infiltrating immune cells and enhancing the antitumor immune response (Figure 8b,c). Intelligent nanovesicles like extracellular vesicles enable precise therapy through controllable physical stimuli,[243] such as light, heat, magnetic fields, and ultrasound, while reducing systemic immune risks due to their low toxicity. This strategy offers promising clinical potential in metabolism-regulating nanomedicine.

6.3. Activating Immune Responses via Nucleotide Signaling

Some nucleotides, such as cGAMP, are crucial for activating antitumor immunity. cGAMP is synthesized by cGAS upon cytosolic double-stranded DNA damage, subsequently activating STING-mediated immune responses.[233,234] It functions as a second messenger to trigger the STING pathway and stimulate IFNs, which have demonstrated promising antitumor effects in preclinical studies. However, traditional cyclic dinucleotide (CDN)-based STING agonists face challenges, including metabolic instability, low cellular permeability, and poor drug-like properties. To address this, Sun et al.[244] Investigated metal ion synergy with STING agonists and found that Mn^{2+} and Co^{2+} significantly enhance IFN-I activity. Then, developed a coordination nanoparticle (CMP) by self-assembling Mn^{2+} with CDN STING agonists, such as cyclic di-AMP (CDA) (Figure 8d). Administration of CMP-CDA via intratumoral or intravenous routes significantly boosts STING activation, reverses immune suppression in the TME, and demonstrates strong antitumor efficacy. As shown in Figure 8e,f, M1-like macrophages and mature DCs increase significantly. These findings indicate that metal ion-enhanced STING activation using coordination nanoparticles offers a promising strategy to overcome the limitations of traditional CDN-based therapies and may provide an effective approach to enhance antitumor immunity.

7. Conclusion and Perspectives

Reprogramming cancer metabolism is a key feature of tumor progression and offers a promising target for therapy. This review highlights innovative strategies in developing nanomedicines to modulate key metabolic pathways, including glucose, lactate, amino acids, lipids, and nucleotides. By utilizing nanotechnology, researchers have overcome traditional barriers, including low bioavailability, poor specificity, and off-target effects, of metabolic drugs, thereby enhancing therapeutic efficacy and reducing side effects on normal tissues and cells. Additionally, exploring metabolism-regulating nanomedicines also enables the controlled and targeted delivery of these agents, allowing for spatiotemporal drug release and synergistic combinations with other therapies, such as chemotherapy, phototherapy, and immunotherapy. These advancements are expected to provide extensive opportunities for designing multifunctional nanomedicines that improve cancer treatment outcomes and open new avenues for overcoming immune suppression and drug resistance.

Despite these achievements, challenges still exist. First, the metabolic adaptability of cancer cells presents a major obstacle, as tumors often develop compensatory pathways to escape single-pathway inhibitors. Therefore, future research should focus on developing nanomedicine platforms that can target multiple pathways and adapt dynamically. Additionally, nanomedicines have shown great promise in combining various metabolism-regulating agents with emerging modalities to produce synergistic effects. Second, creating nanomedicines that selectively target tumor metabolism while minimizing effects on normal tissues remains a key challenge. This requires designing nanomedicine delivery systems that can precisely reprogram tumors by identifying highly specific cell surface markers to distinguish cancer cells from normal ones. Furthermore, incorporating stimuli-responsive mechanisms, such as pH, redox, enzymes, light, ultrasound, or magnetic fields, can enable precise control over multistage metabolic modulation, thereby reducing off-target effects and enhancing therapeutic success. Third, understanding the dynamic interplay between tumor metabolism and the microenvironment is crucial for developing next-generation therapies, yet it remains an area that requires further research. Fourth, while considerable progress has been made in preclinical studies, moving to clinical applications involves overcoming hurdles like scalability, reproducibility, safety, and long-term effectiveness. Establishing standardized research protocols and comprehensive drug management strategies will be critical to fully realizing the potential of nanomedicine and expanding its clinical use. Ultimately, advancing this field requires interdisciplinary efforts that combine insights from oncology, nanotechnology, and systems biology. A more profound knowledge of tumor heterogeneity, patient-specific metabolic profiles, and biomarker discovery will be vital for customizing nanomedicine therapies for individual patients. Metabolically targeted nanomedicines, achieved through continuous innovation and strategic initiatives, hold the promise to transform cancer therapy and enhance patient outcomes globally.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

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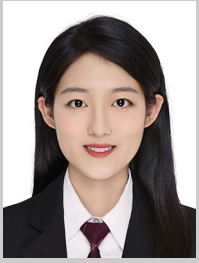

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