REVIEW

Reprogramming of Glucose Metabolism by Nanocarriers to Improve Cancer Immunotherapy: Recent Advances and Applications

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Abstract: Although immunotherapy has made significant progress in cancer treatment, its limited responsiveness has greatly hindered widespread clinical application. The Warburg effect in tumor cells creates a tumor microenvironment (TME) characterized by hypoxia, low glucose levels, and high lactate levels, which severely inhibits the antitumor immune response. Consequently, targeting glucose metabolism to reprogram the TME is considered an effective strategy for reversing immunosuppression and immune evasion. Numerous studies have been conducted on enhancing cancer immunotherapy efficacy through the delivery of glucose metabolism modulators via nanocarriers. This review provides a comprehensive overview of the glucose metabolic characteristics of tumors and their impacts on the immune system, as well as nanodelivery strategies targeting glucose metabolism to enhance immunotherapy. These strategies include inhibiting key glycolytic enzymes, blocking glucose and lactate transporters, and utilizing glucose oxidase and lactate oxidase. Furthermore, this article reviews recent advancements in synergistic antitumor therapy involving glucose metabolism-targeted therapy combined with other treatments, such as chemotherapy, radiotherapy (RT), phototherapy, and immunotherapy. Finally, we discuss the limitations and future prospects of nanotechnology targeting glucose metabolism therapy, hoping to provide new directions and ideas to improve cancer immunotherapy.

Keywords: nanoparticles, glycolysis, lactate metabolism, cancer immunotherapy, tumor microenvironment

Introduction

Immunotherapy has shown significant potential in cancer treatment and has revolutionized the landscape of cancer therapy. Among these, immune checkpoint blockade (ICB) therapies targeting co-inhibitory receptors on T cells have been the focus of extensive research, particularly those involving programmed death protein 1 (PD-1), programmed cell death ligand 1 (PD-L1), and cytotoxic T lymphocyte antigen 4 (CTLA-4).[1–3] However, only a minority of patients exhibit a favorable objective response, possibly due to weak antigen specificity and insufficient T-lymphocyte infiltration.[4,5] Additionally, cancer cells display high levels of heterogeneity and plasticity, enabling them to develop multiple mechanisms for immune escape, ultimately leading to unsatisfactory clinical outcomes.[6] Tumors can also induce the transition from an antitumor microenvironment to a protumor microenvironment by regulating metabolism. For example, hepatocellular carcinoma cells can upregulate hypoxia-inducing factor 1α (HIF1α) to induce the overexpression of hexokinase 2 (HK2), resulting in enhanced glycolytic metabolism and promoting the formation of a tumor immunosuppressive microenvironment (TIME).[7]

Graphical Abstract
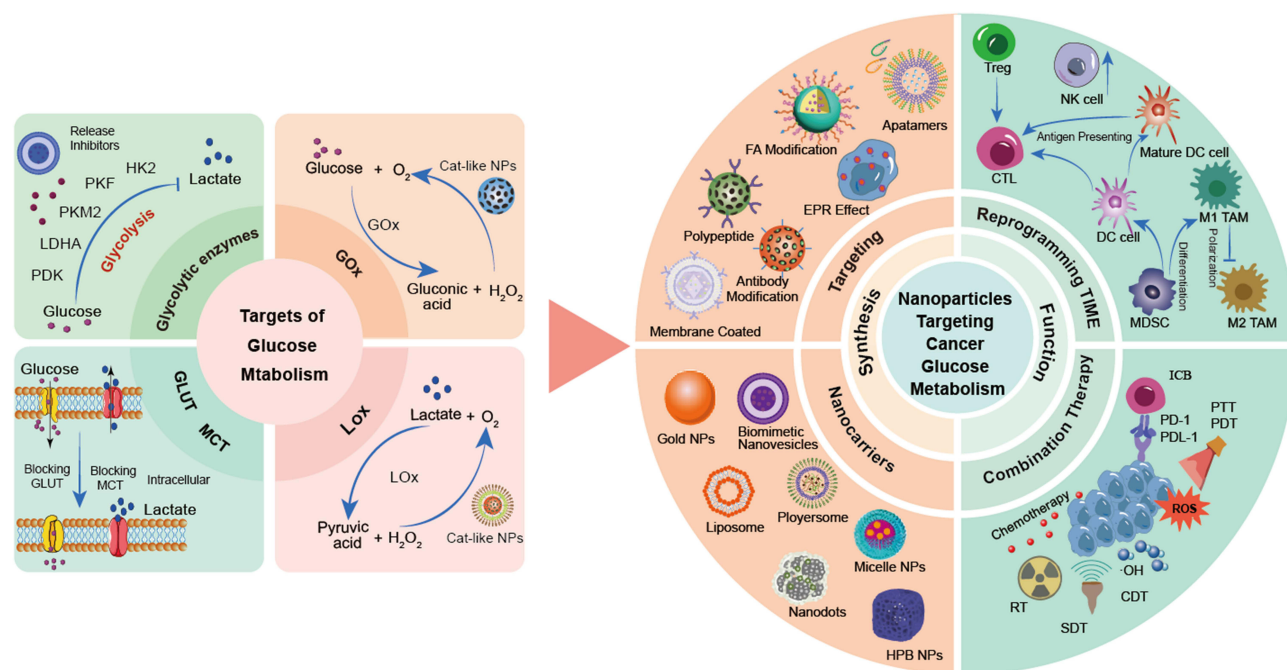
The specific glucose metabolism in tumors plays a pivotal role in shaping the TIME. Even under aerobic conditions, cancer cells rely primarily on glycolysis rather than oxidative phosphorylation (OXPHOS) to obtain energy, a phenomenon known as the Warburg effect.[8] Tumor competition for glucose limits the supply of glucose to T cells, hindering the antitumor immune response. Glycolysis creates a low-glucose, hypoxic, and acidic TME by converting glucose into lactate. The byproducts of glycolysis, such as lactate, impair the function of antitumor immune cells and facilitate the recruitment of immunosuppressive cells such as M2 macrophages and regulatory T cells (Tregs).[9] Alterations within the TME result in immunosuppression and facilitate immune evasion, thereby limiting the efficacy of immunotherapy and promoting tumor progression and metastasis. Consequently, an increasing number of studies have considered targeting glucose metabolism as a potential approach for enhancing immunotherapy. Reducing the glucose source of tumor cells and inhibiting key enzymes involved in glycolysis are effective strategies for reshaping the TME. Directly reducing lactate levels in the TME is also an important method for reversing the TIME.

In addition, the development of targeted delivery systems represents a revolutionary advancement in cancer therapy. A diverse array of nanocarriers, including polymer nanoparticles (NPs),[10] lipid-based materials,[11] metallic NPs,[12] and extracellular vesicles (EVs)[13] etc., have been utilized in anti-tumor therapy. One of the most prevalent applications involves the delivery of drugs through these nanocarriers, which leverage their specific targeting and responsive delivery capabilities to enhance the efficacy of anti-tumor treatments while minimizing adverse effects. Furthermore, more advanced functional nanocarriers have been developed, including nanovaccines designed to activate immune responses and improve the effectiveness of immunotherapy,[14] as well as nanozymes that regulate the TME by catalyzing H_2O_2.[15] Additionally, bionic nanocarriers have been engineered to overcome biological barriers,[16] and photothermal conversion nanomaterials facilitate precise ablation of deep tumors under near-infrared (NIR) light.[17] More importantly, there have been significant advancements in various targeted metabolic nanomedicines that enhance immunotherapy by inhibiting the Warburg effect.

Therefore, we conducted a comprehensive literature search and review utilizing various databases, including PubMed, ScienceDirect, Google Scholar, and Medline etc. The key terms employed in the search encompassed nanoparticles, glycolysis, lactate metabolism, tumor microenvironment, cancer, and immunotherapy etc. This review summarizes the

characteristics of tumor glycolytic metabolism and its role in immune regulation and tumor progression. Furthermore, this paper presents a comprehensive overview of various emerging strategies aimed at targeting glycolytic metabolic pathways to enhance immunotherapy, as well as recent advances in combining these strategies with other therapeutic approaches. Finally, the challenges and future possibilities of targeted therapies for glucose metabolism are also discussed.

Tumor Glucose Metabolism-Mediated Immunosuppression and Therapy Resistance

Characteristics of Glucose Metabolism in Cancer

Cancer cells often overexpress glucose transporters (GLUTs) to improve the efficiency of transporting glucose into the cell and obtaining sufficient energy.[18] Glucose is subsequently catalyzed to glucose 6-phosphate (G-6-P) via HK. G-6-P is converted to pyruvate by a range of enzymes, such as phosphofructokinase (PFK) and pyruvate kinase (PK). Under aerobic conditions, the anaerobic oxidation pathway of normal cells is inhibited, and pyruvate generates acetyl-CoA via pyruvate dehydrogenase (PDH) that finally enters the tricarboxylic acid (TCA) cycle to completely oxidize and produce abundant ATP, known as OXPHOS. However, in tumor cells, pyruvate preferentially enters the glycolysis pathway and is reduced to produce lactate by lactate dehydrogenase (LDH) (Figure 1).
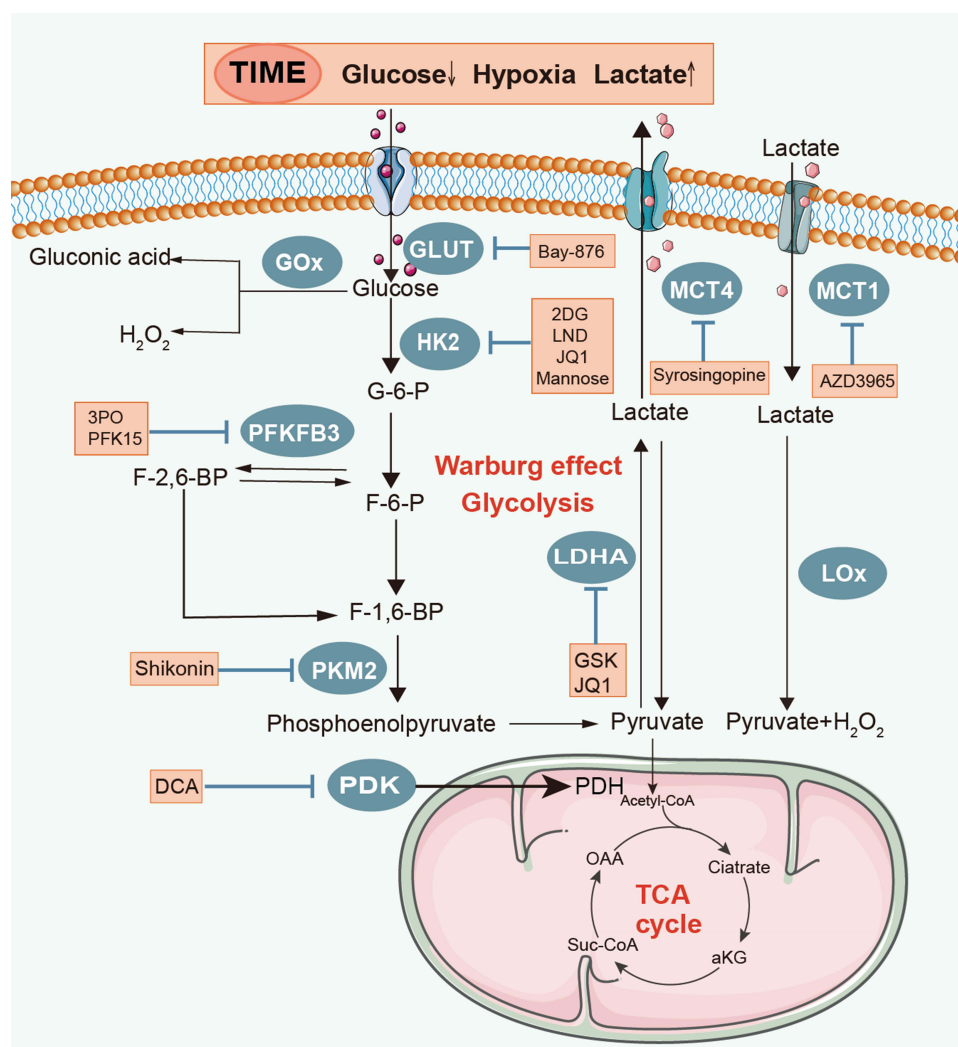

Figure 1 Key targets of glucose metabolism in cancer. Reprogramming TME by inhibiting glycolysis key enzymes (HK2, PFKFB3, PKM2, LDHA, PDK), and by oxidizing glucose (GOx) and lactate (LOx), blocking glucose (GLUT) and lactate transport (MCT).

Although aerobic glycolysis is the primary pathway in tumor cells, these cells can adjust their metabolic mode and adapt to the TME in response to different stresses. Hypoxia-induced tumor cells located far from blood vessels mainly undergo glycolysis, while oxygen-rich tumor cells located around blood vessels can obtain energy through OXPHOS.[19] Tumor cells can selectively express monocarboxylic acid transporter (MCT) 4 or MCT1, depending on different conditions. Oxygen-depleted tumor cells export lactate extracellularly in an MCT1-dependent manner, thereby mitigating lactate feedback inhibition and enhancing glycolysis.[20] Oxygen-rich breast cancer cells transport lactate into cells through MCT4 and serve as an energy source, allowing cancer cells to survive long-term glucose starvation and resist anti-PI3K/ mammalian target of rapamycin (mTOR) inhibitor therapy.[21]

In addition, Warburg reported that cancer cells consumed more glucose and other nutrients than did normal cells. Cancer cells possess higher enzymatic activity and glycolytic efficiency to obtain sufficient energy.[22,23] This idea was further validated by the discovery that highly glycolytic tumors were more aggressive.[24] Although a single glycolysis produces much less ATP than OXPHOS, the rate of ATP production is approximately 10–100 times that of OXPHOS.[25] This efficient and rapid ATP generation pathway and abundant intermediate products provide sufficient energy for tumor progression and migration. Uncontrollable proliferation of cancer cells leads to the accumulation of toxic metabolites, such as lactate, adenosine, and reactive oxygen species (ROS), resulting in a TME with high lactate levels, hypoxia and acidosis.[26] Excess lactate stabilizes HIF1α in the TME and further induces the production of proangiogenic cytokines. In addition, increased lactate levels promote endothelial cell production of CXCL8, which contributes to tumor progression and metastasis.[27] Metabolic alterations not only are extremely important for maintaining tumor growth and survival but also may trigger carcinogenic signals. For instance, neutrophils in the TME transmit the SPI1 mRNA through EVs, leading to increased expression of SPI1 in tumor cells, and SPI1 further drives the expression of glycolysis genes, promoting the progression of colon cancer.[28] Therefore, reprogramming glucose metabolism to reverse TME may be an effective anti-tumor approach.

Tumor Glucose Metabolism Mediates Immunosuppression and Treatment Resistance

The TME encompasses various immune cells, such as T cells, dendritic cells (DCs), natural killer (NK) cells, and macrophages. Tumor cells reprogram the TME to allow immune cells to develop in a direction that supports tumor progression. Mature T cells differentiate into $CD4^+$ and $CD8^+$ T cell subtypes, the latter of which can be further divided into Tregs and helper T cells. Due to the competition for glucose by cancer cells, the proliferation and effector function of T cells are inhibited.[29,30] The glucose content in the TME of degenerative tumors is higher than that in progressive tumors with immune evasion; as a consequence, degenerative tumors can exert an immune function by promoting $CD8^+$ T cell production of IFN-γ and cancer cell death[31] (Figure 2). Hypoxia also hinders the function of T cells. Although $CD8^+$ T cells can still differentiate into functional effector cells under continuous stimulation or hypoxia, the combination of both conditions leads to elevated levels of ROS and impaired mitochondrial function, thereby inhibiting T cells proliferation and antitumor activity.[32,33] A high lactate level is an important marker of the TME and inhibits the nuclear factor of activated T cells and mitogen activated protein kinase pathways.[34,35] A low pH activates V-domain immuno-globulin suppressor of T cells activation signaling.[36] Lactate can inhibit the survival, proliferation and function of $CD8^+$ T cells through the above mechanism. Additionally, T cells exhaustion exacerbates immunosuppression, specifically due to the continuous stimulation of T cells by antigens in the TME, resulting in a gradual loss of effector function and immune memory in T cells.[37] T cells exhaustion is characterized by reduced production of antitumor cytokines such as IL-2, TNF-α, and IFN-γ and increased the expression of inhibitory receptors such as PD-1, CTLA4, and TIM-3.[38]

Tregs possess immunosuppressive properties, enabling them to inhibit the activation and proliferation of effector T cells (Teffs), suppress antitumor and anti-inflammatory effects, and mediate immune evasion and therapy resistance. Moreover, Tregs may show superior adaptability to metabolic alterations and nutrient limitations compared to other T cells subsets. Teffs rely on OXPHOS for energy production, whereas Tregs exhibit decreased GLUT1 levels, reduced glucose uptake, and increased reliance on fatty acid (FAO) oxidation.[39] Additionally, Tregs can tolerate a TME with high lactate levels and a low pH through metabolic remodeling mediated by the Treg transcription factor Foxp3.[40] In short, Tregs can utilize FAO metabolism and the lactate pathway to maintain their proliferation and function. Furthermore, hypoxia promotes the recruitment of Tregs, and indoleamine 2,3-dioxygenase (IDO) and adenosine in the TME can facilitate Tregs proliferation and immunosuppressive functions.[41]
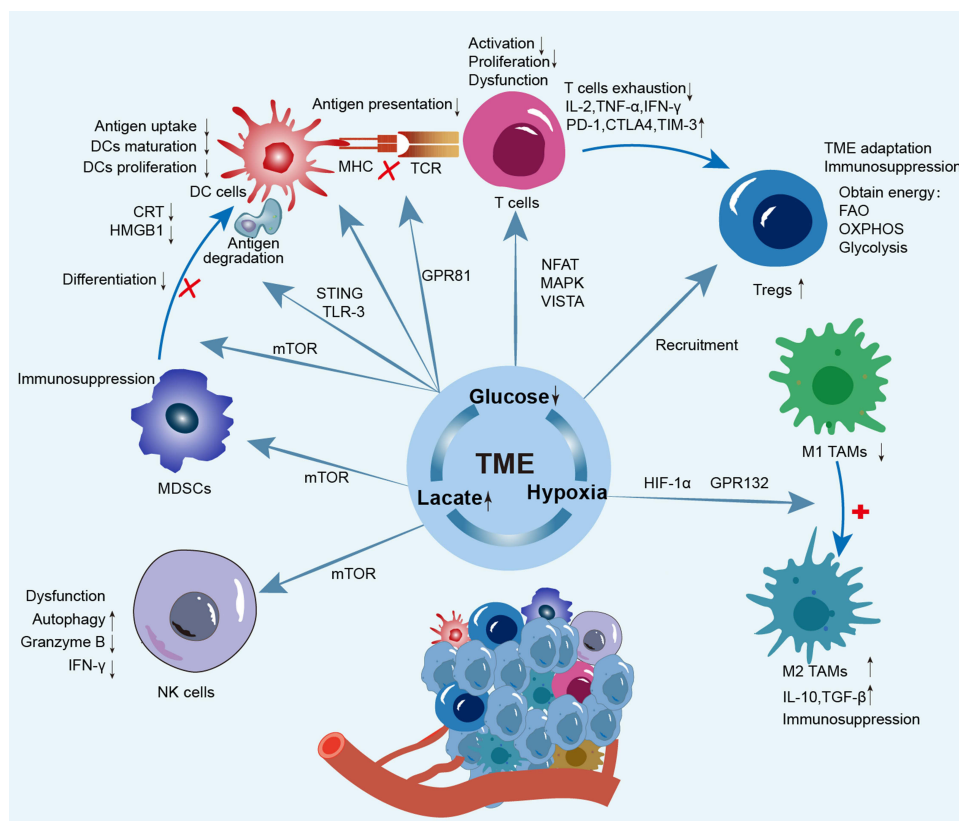
Figure 2 Immunosuppression mediated by TME. TME inhibits the differentiation, maturation, and antigen-presenting functions of DCs. This impairment leads to Teffs and NK cells dysfunction. In contrast, Tregs can utilize FAO and OXPHOS for energy production, which facilitates the recruitment of additional Tregs. Furthermore, the TME increases the proportion of MDSCs and promotes the polarization of M1 TAMs.

Abbreviations: GPR132, G protein-coupled receptor; MAPK, mitogen activated protein kinase; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells; STING, Stimulator of interferon genes; VEGFR, vascular endothelial growth factor receptor; VISTA, V-domain immunoglobulin suppressor of T-cell activation.

DCs are the most important antigen-presenting cells, which can trigger a specific cytotoxic T lymphocyte (CTL) antitumor immune response. Following tumor cell immunogenic cell death (ICD), the release of tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs) activate the immune response by promoting DCs maturation. Activation of DCs leads to an increased demand for glucose; however, the nutrient-restricted TME limits their antigen-presenting capacity.[42] Moreover, elevated levels of lactate, low pH, hypoxia and ROS resulting from tumor metabolism impair the antitumor effects mediated by DCs. On the one hand, lactate inhibits major histocompatibility complex (MHC) II presentation on the surface of DCs by activating G protein-coupled receptor 81.[43] On the other hand, lactate hampers cross-presentation by DCs through the inhibition of Toll-like receptor 3 and downstream IFN-I and stimulator of interferon genes signaling to accelerate antigen degradation.[43,44] An acidic TME can inhibit mTOR activity while promoting monocyte differentiation into DCs in a cytokine-dependent manner.[45] Hypoxia affects the differentiation process, as well as the antigen uptake and migration abilities of DCs.[46] The maturation of DCs is induced by high mobility group protein B1 (HMGB1), whose function is inhibited by the oxidation of ROS accumulated in the TME.[32]

Innate immunity is an important antitumor mechanism in which macrophages play a pivotal role. Tumor-associated macrophages (TAMs) can be categorized into two phenotypes: M1 and M2. The M1-like TAMs exhibit anti-inflammatory and antitumor effects, while the M2-like phenotype promotes angiogenesis and facilitates tumor progression and metastasis.[47] Tumor metabolites not only inhibit phagocytic activity but also induce the transformation of M1 macrophages to M2 macrophages, significantly compromising the antitumor potential of TAMs.[9] Hypoxia triggers A2A and A2B receptor activation, where adenosine binding to adenosine A2A receptors reduces M1-like polarization, and activating adenosine A2B receptors induces M2-like polarization.[48,49] Lactate stabilizes HIF-1α and induces the polarization of M2 TAMs through G protein-coupled receptor 132.[50,51] HIF-1α also modulates CD47 and CD24 signaling

in cancer cells, enabling the evasion of phagocytosis by liver cells.[47] Decreasing lactate levels or eliminating A2A expression can promote the polarization of M1 TAMs.[52]

MHCI molecules on target cells bind to NK cells suppressor receptors to avoid the self-destruction of NK cells.[53] Therefore, NK cells play an important role in clearing cancer cells by downregulating MHC molecules. As NK cells are activated, trophic receptors such as GLUT1, CD98, and CD71 are upregulated, resulting in increased glucose uptake and glycolysis efficiency.[54] However, the exhaustion of multiple nutrients in the TME inhibits the function of NK cells. Studies have shown that low glucose levels in the TME can interfere with IFN-γ and granzyme B expression by inhibiting mTORC1, and hypoxia can inhibit NK cells activated receptors.[55,56] Oxidative stress associated with lipid peroxidation can restrict glucose metabolism and cause NK cells dysfunction.[57] Furthermore, Tregs, M2 TAMs and myeloid-derived suppressor cells (MDSCs) secrete immunosuppressive factors such as IL-10 and TGF-β that hinder the activation and function of NK cells.

Tumor-associated MDSCs show enhanced FAO, hypoxia can induce MDSCs to express PD-L1 and recruit MDSCs to metastatic sites and induce MDSCs to differentiate into TAMs.[58–60] The upregulation of CD39 by hypoxia can induce AMP production, inhibit MDSCs differentiation to DCs, and promote MDSCs aggregation.[61] Alterations in the metabolism of tumors upregulate MDSCs, and MDSCs show good adaptability to energy depletion, hypoxia, and a high lactate level in the TME, which promotes cancer progression and immunosuppression.

In summary, the glucose metabolic reprogramming TME by tumor cells leads to the downregulation and impairment of the function of antitumor immune cells, including T cells, NK cells, and DCs. Simultaneously, more immunosuppressive cells, such as Tregs, M2 macrophages, and MDSCs, are recruited. The TIME allows tumor cells to evade immune surveillance and develop treatment resistance. Consequently, reconfiguring the TIME can markedly diminish therapeutic resistance and enhance the effectiveness of immunotherapy; furthermore, inhibiting tumor glycolysis represents a viable strategy for reprogramming TIME.

Strategies of Nanoparticles Targeting Glucose Metabolism for Cancer Immunotherapy

Given the critical role of glucose metabolism in tumor progression and immune evasion, numerous studies have concentrated on targeting glucose metabolism to enhance the efficacy of anti-tumor immunotherapy. With the ongoing development and application of nanomaterials, nanotechnology have also made remarkable progress in the delivery of glycolysis regulators. In comparison to conventional drugs, nanomaterials have garnered considerable attention due to their remarkable advantages: firstly, they substantially improve therapeutic efficacy while effectively minimizing side effects through precise targeting of tumor cells.[62] Secondly, nanomaterials facilitate the integration and assembly of multiple therapeutics, enabling coordinated approaches against tumors that involve various drugs or treatment modalities.[63] Furthermore, distinct nanomaterials exhibit unique characteristics: some can penetrate deeply into tumor tissues, others can release drugs under specific conditions, and certain types possess photothermal conversion capabilities or demonstrate enzyme-like activity—allowing researchers to leverage these properties to enhance the anti-tumor effects of NPs.[64–67] To inhibit glycolysis effectively, nano-systems can first target key glycolytic enzymes such as HK2, PFK, M2-type PK (PKM2), pyruvate dehydrogenase kinase (PDK), and LDH; additionally, they may obstruct glucose entry into cells and disrupt lactate shuttling by inhibiting transporters. Moreover, strategies that involve blocking the glucose supply for tumor cells via glucose oxidase (GOx) and reducing lactate accumulation by glucose oxidase (LOx) are also recognized as effective anti-tumor approaches (Figure 1, Table 1).

Nanoparticles Targeting Glycolysis-Related Enzymes for Cancer Immunotherapy
Nanoparticles Targeting Hexokinase (HK2)
HK2 functions as a crucial regulator of glycolysis, with its upregulation frequently observed in tumor cells.[107] The glucose analogue 2-deoxyglucose (2DG), recognized as the first developed inhibitor of HK2, undergoes phosphorylation by HK to yield 2-DG-6-phosphate.[108] 2-DG-6-phosphate subsequently inhibits both HK and G-6-P isomerase, ultimately leading to energy depletion and apoptosis in tumor cells.[109] Liu et al engineered targeted bionic nanovesicles (NVs)

Table 1 Strategies for Enhancing Cancer Immunotherapy by Targeting Glucose Metabolism with Nanoparticles

Targets	Nanoparticles	Nanocarriers	Targeted Drugs	Targeted Modification	ADJUVANT DRUGS	Immune Cells	Cytokines	Combination Therapies	Cell Lines	Ref
HK2	Haunt-Met@MS	PLGA polymers	2DG	/	Met	CD8$^+$TCM, CD8$^+$Teff↑, Tregs↓	IFN-γ, Gra-B, IL-15↑	PTT	CT26, B16F10	[68]
	PDG-NV	Nano-vesicles	2DG	Cancer cell membrane coated	DOX	CD4$^+$T, CD8$^+$T↑	IFN-γ, IL-2, perforin↑	Chemotherapy aPD-L1 ICB	TC-1	[69]
	LND/MCA	PLA polymers	LND	HA	Apatinib	/	/	aPD-1 ICB	B16F10	[70]
	IR-LND @Alb	Albumin polymers	LND	IR-68	/	CD3$^+$T, CD4$^+$T, CD8$^+$T↑	/	PDT	MB49, CT26	[71]
	TPP-LND@Lip	Liposome	LND	TPP+	/	/	/	Radiotherapy	A549, LLC, MB49	[72]
	Terbio	Carrier-free	LND	/	Ce6, SB505124	NK, DCs, CD8$^+$T↑, Treg↓	/	PDT, Immunotherapy	CT26	[73]
	M/LM-Lipo	Liposome	Mannose	/	Levamisole	DCs, CD8$^+$T↑, M2 TAMs↓	IFN-γ, Gra-B↑	Radiotherapy	4T1	[74]
PFK	PTX/PFK15-SLN@@[4T1-3T3]	Solid lipid NPs	PFK15	4T1and 3T3 cell membrane coated	PTX	CD4$^+$ T, CD8$^+$ T↑, M2 TAMs, Tregs↓	IFN-γ, TNF-α↑, TGF-β, CXCL 12↓	Chemotherapy	4T1, B16F10 Pan02	[75]
PKM2	SK/siR-NPs	DSPE-PEG$_{2K}$ PEI−PCL polymers	Shikonin	Folic acid	PD-L1 siRNA	DCs, CD8$^+$T, TCL, M1 TAMs↑, M2 TAMs, Tregs↓	IFN-γ, TNF-α↑	Immunotherapy	CT26	[76]
	SPI@hEL-RS17	Liposome	Shikonin	M1EVS	Met, IR820	DCs, CD4+T, CD8+T, M1 TAMs↑, M2 TAMs, MDSCs, Tregs↓	IFN-γ, TNF-α, IL-6, IL-1β↑, TGF-β↓	PTT	4T1, B16F10 A549	[77]
	Alum-CpG@Fe Shikonin NPs	Alum NPs	Shikonin	/	CpG ODN	DCs, NK, Ths, CTL, M1 TAMs ↑, M2 TAMs, Tregs↓	IFN-γ, TNF-α, IL-6↑	Immunotherapy	CT26	[78]
LDH	HPP-Ca @GSK	Metal-phenolic NPs	GSK	HA	IR780, CaCl2	DCs, CD8+T↑, Tregs↓	IFN-γ, TNF-α, IL-6, IL-12↑, IL-10↓	a-CTLA-4 ICB	4T1	[79]
	AMANC@M	Au@MSN NPs	CRISPR/Cas9	RBC-4T1 hybrid membrane coated	CPI-613	CD4+T, CD8+T↑, Tregs↓	IFN-γ, TNF-α, IL-6, IL-12↑, IL-11↓	PTT	4T1	[80]
	pCas9-sgLDHA /F3	Lipid NPs	sgLDHA	/	CRISPR/Cas9	IFN-γ+ T, Gra-B+T ↑	IFN-γ, Gra-B↑	aPD-L1 ICB	B16F10	[81]
	VNPsiLdha	vesicular CLAN NPs	SiLDHA	/	/	CD4+T, CD8+T, B cells, NK cells↑, Tregs↓	/	aPD-1 ICB	4T1, B16F10	[82]

(*Continued*)

Table 1 (Continued).

Targets	Nanoparticles	Nanocarriers	Targeted Drugs	Targeted Modification	ADJUVANT DRUGS	Immune Cells	Cytokines	Combination Therapies	Cell Lines	Ref
	SnSe@ ABS NSs	SnSe NSs	SnSe NSs	/	ABS	DCs, CD4+T, CD8+T↑, Tregs↓	IL-6, IL-12, IFN-γ↑, IL-10↓	PTT, aPD-L1 ICB	4T1	[83]
PDK	SMDN	MnFe2O4 NPs	DCA	/	/	CD4+T, CD8+T↑	IFN-γ, TNF-α↑	/	/	[84]
GLUT	DNA-PAE@ BAY-876	Polyβ-amino esterr	BAY-876	Apatamer	aptPD-L1, aptCTLA-4	DCs, CD4+T, CD8+T, M1 TAMs↑, M2 TAMs↓	IFN-γ, TNF-α, Gra-B, CXCL10↑, IL−10↓	PD-L1, aCTLA-4 ICB	4T1, HC11, B16F10	[85]
MCT	AZD-UPS NPsPs	PDPA polymer	AZD3965	/	/	CD8+ T↑	/	aPD-1 ICB	TC-1, B16F10	[86]
	HMONs@HCPT-BSA-PEI-CDMPEG@siMCT-4	HMONs	siMCT-4	Positively charged poly (ether imide)	HCPT	CD4+T, CD8+T, NK, B cells, M1 TAMs↑, M2 TAMs, Tregs, MDSCs↓	TNF-α, IFN-γ↑, Arg1, TGF-β↓	Chemotherapy	4T1, B16F10	[87]
GOx	mEHGZ	ZIF-8	GOx	CRT over-expressed membrane coated	Hemin, Epirubicin	DCs, CD8+ T↑	IFN-γ, TNF-α, IL-6 ↑	CDT, aPD-L1 ICB	4T1	[88]
	γ-PGA@ GOx@ Mn, Cu-CDs	Mn, Cu-CDs	GOx	γ-PGA	/	DCs, CTL↑	IFN-γ ↑	PTT/PDT, aPD-1 ICB	4T1	[89]
	GOx-Mn/HA	Mn-based NPs	GOx	HA	Mn2+	DCs, CD4+T, CD8+T, M1 TAMs↑, M2 TAM↓↓	IL-1α, IL-1β, IFN-γ, TN F-α↑	CDT, aPD-L1 ICB	4T1	[90]
	LMGC	Liquid Metal NPs	GOx	/	CaCO3	/	/	PTT	CT26	[91]
	CMSN-GOx	Mesoporous silica NPs	GOx	cancer cell membrane coated	/	DCs, CD4+T, CD8+T↑, Tregs↓	IFN-γ ↑	aPD-1 ICB	CT26	[92]
	PCP-Mn-DTA@GOx@1-MT	MOF NPs	GOx	/	1-MT	DCs, NK, BC, CTL, TEM↑, Tregs, TCM↓,	/	CDT, Immunotherapy	4T1, CT 26	[93]
	FeS-Gox @PTX	FeS Nanodots	GOx	/	PTX	DCs, CD8+T, TCL↑, Tregs↓	IFN-g↑	CDT, PTT, Chemotherapy	4T1, CT 26	[94]
	DOX/ASA@PEG-Au@ HMnMSNs	Gold NPs	GOxAuNPs	/	DOX, aspirin	CD4+T, CD8+T↑	IL-6, IL-12p70, IFN-γ, TNF-α↑	CDT, Chemotherapy, Immunotherapy	4T1	[95]
LOx	mCuLP	mPDA NPs	LOx	/	CuCl2	DCs, CTL, CD8+T, M1 TAMs↑, M2 TAMs ↓	TNF-α↑	PTT	4T1	[96]

	n(LOx)	PEGMA polymer	LOx	/	/	CD4+T, CD8+T, NKs↑, Tregs↓	IFN-γ↑	aPD-L1 ICB	4T1, B16F10	[97]
	PNDPL	PtBi NpS	LOx	/	NLG919	DCs, CD4+T, CD8+T↑, Tregs↓	TNF-α, IL-6, INF-γ↑	PTT	4T1	[98]
	PMOL	MOF NPs	LOx	/	Oxaliplatin	DCs, CD8+T, M1 TAMs↑, M2 TAM, Tregs↓	TNF-α, IL-6, IL-12p70, IFN-γ↑	Chemotherapy	4T	[99]
	HPB-S-PP@LOx/ siPD-L1	HPB NPs	LOx	/	SiPD-1	CD8+T↑, Tregs↓	IL-2, TNF-α↑, IL-10↓	Immunotherapy	4T1	[100]
	LOX-MnO2 @Gelel	H-MnO2 Nanoshells	LOx	HA	/	CTL, M1 TAMs↑, M2 TAMs, Tregs↓	TNF-α, IFN-γ↑	aPD-1 ICB	HCC	[101]
HK2 LDH	DHCRJ	HCR Polymer	JQ1	HA	DOX	DCs, CTLs↑, M2 TAMs, MDSCs, Tregs↓	/	Chemotherapy	4T1	[102]
	HCJSP	HCP Polymer	JQ1	HA	Pyropheophorbide-a	DCs, CD4+T, CD8+T↑, Tregs↓	IFN-γ↑	PDT	Panc02	[103]
HK2 LDH PKM2	Man-LF NPs	Lactoferrin NPs	Shikonin, JQ1	Mannose	Mannose	DCs, CD8+T, M1 TAMs↑, M2 TAMs, Tregs↓	IFN-γ, TNF-α↑, TGF-β↓	/	CT26	[74]
HK2 GLUT	D/B/CQ@ZIF-8@CS	ZIF-8	BAY-876, 2DG	Chondroitin sulfate coated	Chloroquine	CD4+T, CD8+T↑, MDSCs, M2 TAMs ↓	IFN-γ, TNF-α↑, IL-10, TGF-β↓	aCTLA-4 ICB	4T1	[104]
HK2 MCT	L@S/L	Liposome	Sy, LND	/	/	M1 TAMs, NK↑, M2 TAMs, Tregs↓	IFN-γ, TNF-α↑	/	4T1	[87]
HK2 GOx	NM-si	Gold Nanoclusters	HK2 SiRNAGOx	HA	CatalasePTX	CD8+T↑, Tregs↓	/	Chemotherapy	4T1	[105]
PFK LOx	PMLR	HMnO2 NPs	3PO, LOx		/	TCL, CD8+Gra-B+T, CD8 +IFN-γ+T↑, M2 TAMs↓	IFN-γ, IL-6↑	aPD-L1 ICB	B16F10	[106]

Abbreviations: /, the original article did not mention or report the relevant content;↓, Reduced level;↑, Elevated level; 4RM, RBC-4T1 hybrid membrane; ABS, 4-(2-aminoethyl), benzenesulfonamide; Au@MSN NPs, gold-mesoporous silica NPs; CLAN, cationic lipid-assisted NPs; DHCRJ, DOX@HA-CA)2-RRL/JQ1; DSPE-PEG2K, 1,2-distearoyl-sn-glycero-3-phosphoetha-nolamine-N-[(polyethyleneglycol)-2000]; HA, hyaluronic acid; HCC, hepatocellular carcinoma; HCR, hyaluronic acid (HA-CA)-ROS responsive linker(RRL); HCP, HA-CD and AD-SS-PPa polymers; HMONs, hollow mesoporous organosilica NPs; Mn,Cu-CDs, Mn,Cu-doped carbon dots; PDPA, (poly (dipropylaminoethylmetha-crylate); PEGMA, poly(ethylene glycol) methyl ether acrylate; PEI−PCL, polyethyleneimine−poly (epsilon-caprolactone); PLGA, Poly (D, L-lactic-co-glycolide); Tcm, Central Memory T cell; Tem, effector memory T cells; γ-PGA, Poly(γ-glutamic acid).

derived from genetically modified non-small cell lung cancer cell lines that overexpress PD-1. These P-NVs were loaded with 2DG and (DOX), referred to as PDG-NVs.[69] The homologous targeting capability of P-NVs facilitates effective binding between PD-1 on the P-NVs and PD-L1 on cancer cells. Notably, PDG-NVs significantly downregulated the expression of PD-L1 by interfering with its glycosylation via 2DG; concurrently, the presence of PD-1 protein on NVs disrupted the PD-1/PD-L1 axis within cancer cells, effectively enhancing anti-tumor immune responses. Luo et al developed PLGA microspheres co-loaded with hollow gold nanoshells (HAuNS) and metformin, termed HAuNS-Met @MS.[68] This nanosystem enables sustained pulsed release of metformin for over three weeks, contributing to enhanced anti-tumor effects.[110] When combined with 2DG, HAuNS-Met@M can inhibit glycolysis while reducing heat stress responses in tumor cells; it also enhances photothermal therapy (PTT) induced ICD, reverses heat tolerance in tumor cells, and improves their sensitivity to photothermal treatment.

Lonidamine (LND), an indazole derivative, effectively suppresses aerobic glycolysis by modifying mitochondrial ultrastructure and inhibiting HK2 activity.[71] It has entered clinical trials for various cancers, including breast cancer.[111] Jiang et al developed a high-fidelity spatio-temporal delivery strategy utilizing apatinib-loaded nanomedicine in conjunction with LND-loaded formulation.[70] Specifically, apatinib-loaded nanodurg initially targets tumor endothelial cells to selectively block the vascular endothelial growth factor receptor, facilitating vascular normalization therapy that promotes T cells infiltration. Subsequently, LND-loaded nanodurgexhibits delayed accumulation at tumors while reprogramming glucose metabolism to activate T cells against malignancies. Zhao et al designed a straightforward self-assembled nanoparticle named TerBio without additional carriers, synthesized through intermolecular interactions among LND, chlorine e6 (Ce6), and SB505124[73] (Figure 3). SB505124 effectively inhibits TGF-β signaling pathways while synergizing with metabolic modulation from LND to counteract immunosuppression.[106] Furthermore, both liposomes loaded with mannose and polymeric NPs containing JQ1 significantly inhibited HK2 activity, leading to successful suppression of glycolysis.[74,102,103] In summary, the targeted delivery of HK2 inhibitors via NPs effectively reprogrammed the TME and mitigated immunosuppression, demonstrating promising anti-tumor potential.

Nanoparticles Targeting Phosphofructokinase (PFK)

PFK, an enzyme crucial for regulating the rate of glycolysis, catalyzes the conversion of fructose-6-phosphate (F-6-P) to fructose-1,6-diphosphate. Furthermore, F-6-P can be converted into fructose-2,6-bisphosphate by fructose-2-kinase 6-phosphate/fructose-2,6-diphosphatase 3 (PFKFB3), recognized as the most potent allosteric activator of PFK. The overexpression of PFKFB3 has been observed to meet the metabolic needs of aggressive tumors, such as prostate cancer, colon cancer, and breast cancer.[112] 3-pyridine-1-(4-pyridine-2-propenyl-1-1) (3PO) and its derivative PFK15 are selective inhibitors of PFKFB3, effectively inhibiting glycolysis and consequently reducing lactic acid production.[113,114]

To more effectively counteract acidic TME, Gao et al encapsulated both 3PO and LOx within hollow manganese dioxide (HMnO$_2$) NPs[115] (Figure 4). The compound 3PO successfully inhibits lactic acid and ATP production by obstructing glycolysis; concurrently, LOx oxidizes lactic acid to generate H$_2$O$_2$. This hydrogen peroxide is subsequently catalyzed by the catalytic-like activity of PMLR NPs to produce O$_2$—thereby accelerating lactic acid consumption and
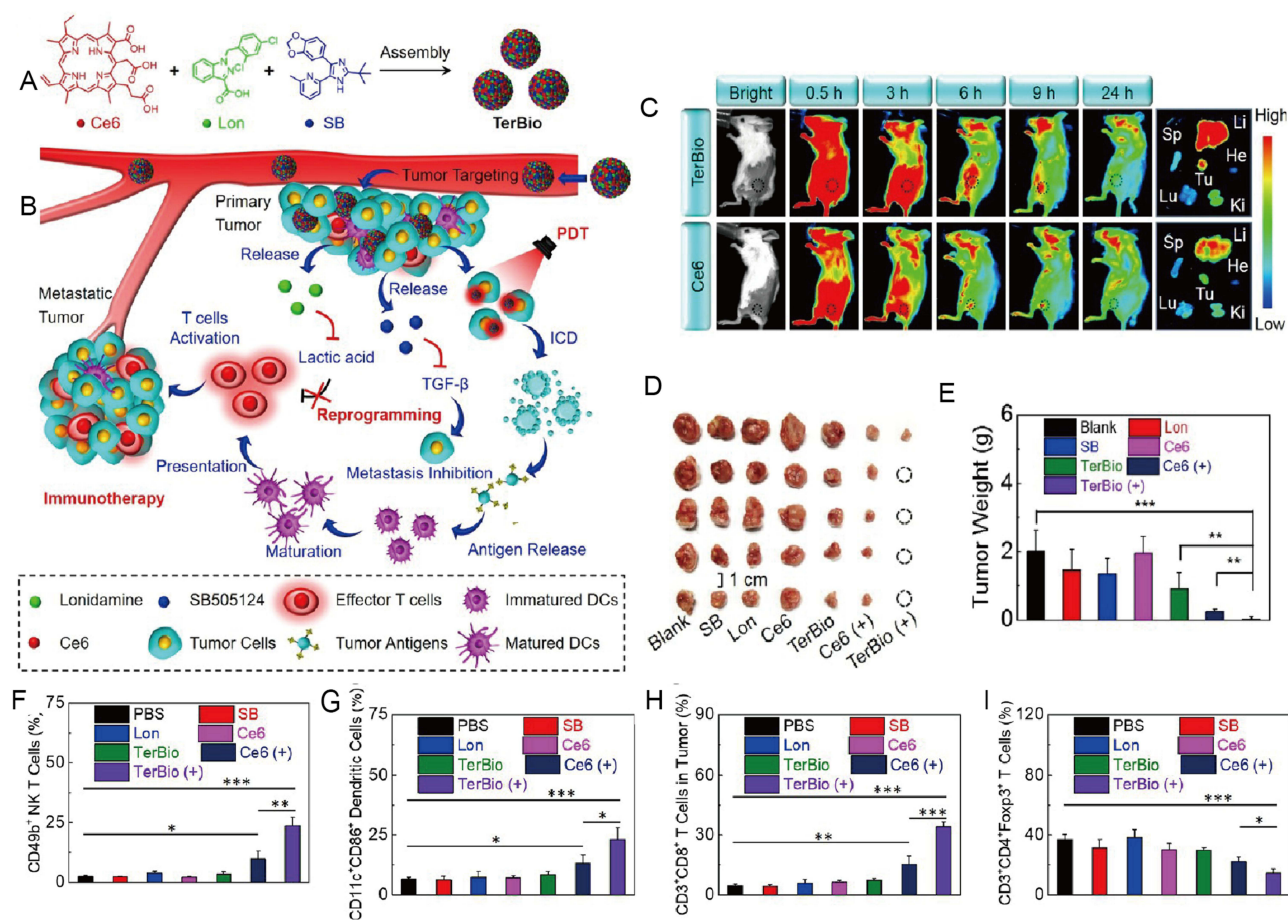
Figure 3 Nanosystem targets HK2 to reprogram TME and enhance immunotherapy. (**A**) Schematic illustration of the self-assembly of TerBio nanosystem and (**B**) its antitumor mechanism. (**C**) True real-time and in vitro fluorescence images of major organs and tumor tissues after intravenous Ce6 or TerBio administration, He, Li, Sp, Lu, Ki, and Tu stand for heart, liver, spleen, lung, kidney, and tumor respectively. (**D**) Tumor tissue and (**E**) average tumor weight in the presence or absence of light exposure. Flow cytometry (FCM) quantitative analysis of (**F**) CD49b$^+$ NK cells, (**G**) CD11c$^+$CD86$^+$ DCs, (**H**) CD3$^+$CD8$^+$ T cells and (**I**) CD3$^+$ CD4$^+$ Foxp3$^+$ T regulatory cells in tumor tissues after different treatments. *p < 0.05, **p < 0.01, and ***p < 0.001 were tested via a Student's *t* test. Adapted with permission from Zhao L-P, Zheng R-R, Kong R-J, et al. Self-delivery ternary bioregulators for photodynamic amplified immunotherapy by tumor microenvironment reprogramming. *ACS Nano.* 2022;16(1):1182–1197. Copyright © 2022 American Chemical Society.[73]

enhancing sensitivity to 3PO. This strategy not only targets lactic acid production but also promotes its depletion effectively reversing TIME dynamics while significantly improving ICB therapy efficacy.

TME is a complex, network-like system in which multiple pathways targeting the same objective are essential. However, directing attention to different targets within the TME also represents an innovative strategy. Cancer-associated fibroblasts (CAFs), as the predominant stromal cells in tumors, provide metabolites to tumor cells through glycolysis and collaboratively shape the TIME alongside these cells.[116] Zang et al encapsulated liposomes within hybrid cell membranes derived from 4T1 and CAF-like NIH3T3 cells, thereby facilitating homologous targeting of both tumor and CAF cells.[75] The solid lipid NPs were loaded with the chemotherapeutic agent paclitaxel (PTX) and PFK15, achieving a synergistic integration of chemotherapy and immunotherapy. These findings suggest that inhibiting PFK, a pivotal enzyme in glycolysis, constitutes an effective approach to enhance immunotherapy; furthermore, simultaneous targeting of multiple entities or pathways may yield more pronounced anti-tumor effects.

Nanoparticles Targeting Pyruvate Kinases (PKM2)

Fructose-1,6-diphosphate is catalyzed by a series of enzymes to produce phosphoenolpyruvate, which produces pyruvate via PK. PK is the third rate-limiting enzyme of glycolysis, and (PKM2 is often overexpressed in tumors. Shikonin (SK) is the primary active component isolated from the roots of the traditional Chinese herb Zicao. SK can not only
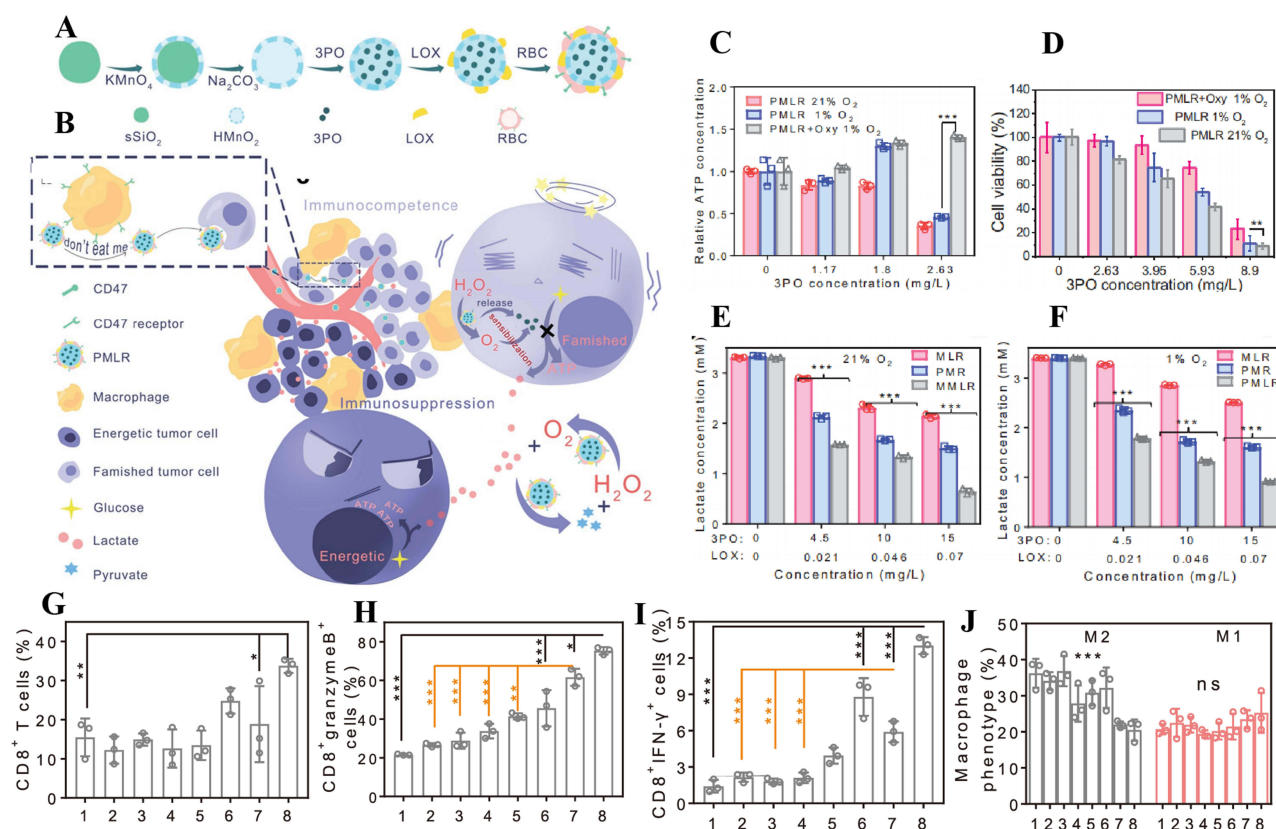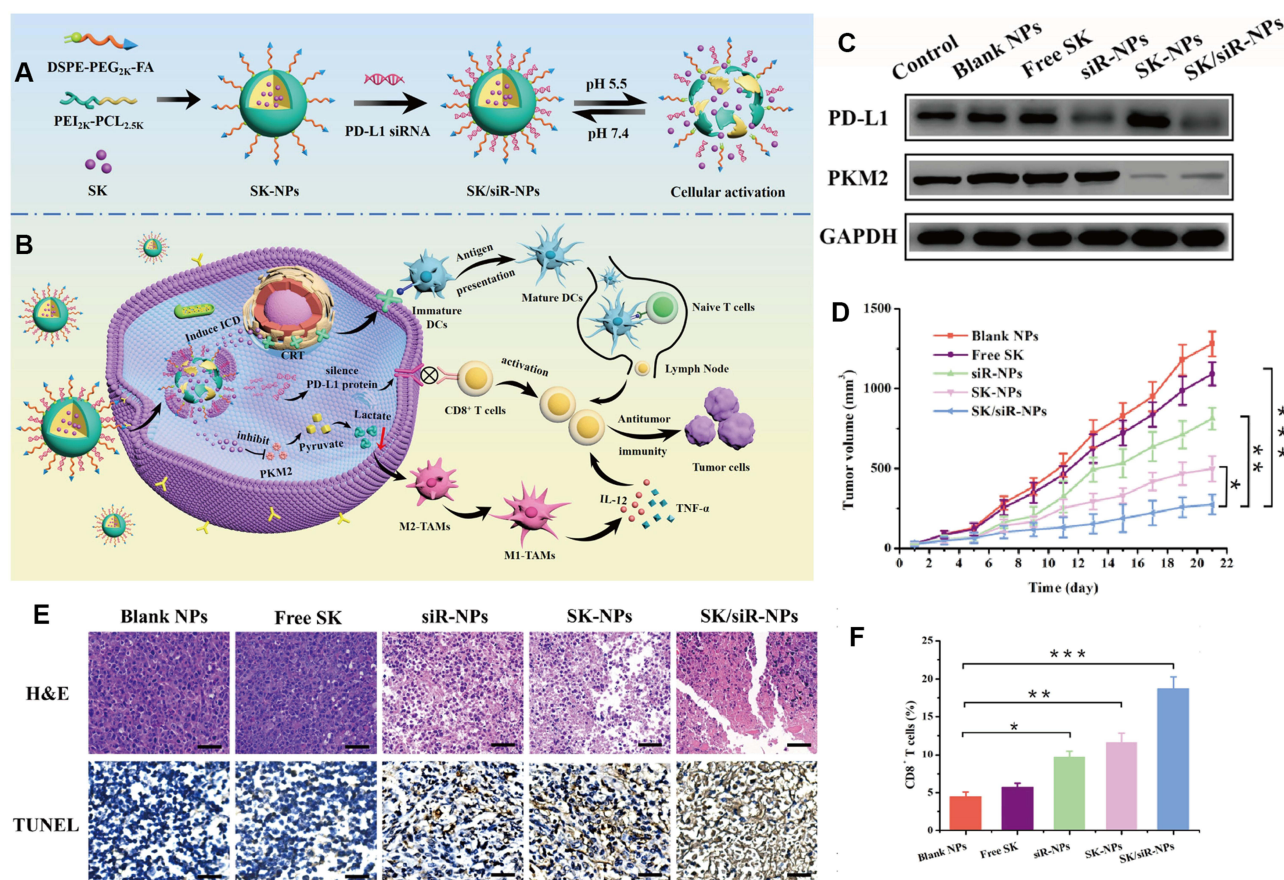
Figure 4 Nanosystem targets PFK to reprogram TME and enhance immunotherapy. (**A**) Schematic of PMLR nanosystem construction and (**B**) lactate exhaustion process via 3PO-mediated inhibition of production and LOx-mediated oxidation. (**C**) ATP inhibition and (**D**) cytotoxicity of PMLR NPs in B16F10 cells under normoxia or hypoxia. Lactate consumption effect of PMLR NPs under (**E**) normoxia or (**F**) hypoxia. Quantitative analyses of the (**G**) CD3$^+$CD8$^+$ T cells, (**H**) CD3$^+$CD8$^+$GranzymeB$^+$ T cells, (**I**) CD3$^+$CD8$^+$IFN-γ$^+$ T cells and (**J**) M2 macrophages according to the corresponding FCM data. *p < 0.05, **p < 0.01, ***p < 0.001. Adapted from Gao F, Tang Y, Liu W, et al. Intra/extracellular lactic acid exhaustion for synergistic metabolic therapy and immunotherapy of tumors. *Adv Mater.* 2019;31(51):1904639. © 2019 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.[115]

downregulate the expression of PKM2 and inhibit glycolysis and lactate production but also promote the production of ROS, induce necroptosis and ICD, and inhibit NF-κB regulated gene products, thus inhibiting tumor progression.[117]

Li et al utilized NPs to co-deliver SK and PD-L1 knockdown siRNAs (SK/SIR-NPs) to explore the roles of SK in regulating the TME and enhancing the efficacy of immunotherapy[76] (Figure 5). SK/SIR-NPs have been shown to diminish the production of lactic acid and ATP by down-regulating PKM2 expression, while simultaneously enhancing anti-tumor immunotherapy when combined with PD-1 knockdown. Naturally derived components tend to have more potential side effects. To improve the safety and therapeutic efficacy of SK, Li's team modified liposomes using M1 macrophage EVs and *RS* 17 peptide.[77] The innate homing capability of M1 EVs, along with the selective binding affinity of RS17 peptide to CD47 on tumor cells, allows these NPs to accurately target tumor cells.[118] Furthermore, the NPs are also equipped with photosensitizer IR 820 to exert PTT effect and augment anti-tumor immunotherapy in conjunction with SK.

The initiation and progression of tumors are influenced by various components within the TIME, rendering single-target therapies less effective and prone to drug resistance. Given that mannose and lactoferrin can specifically bind to overexpressed mannose receptors and low-density lipoprotein receptor-associated proteins found in cancer cells as well as TAMs, Wang et al developed a mannose-lactoferrin nanoparticle (Man-LF NP) encapsulating both SK and JQ1 for simultaneous targeting of tumor cells and TAMs within TIME.[119] JQ1 functions as a bromodomain inhibitor that targets terminal exo-motifs, effectively inhibiting HK-2, LDH, and PD-1 expression.[120,121] SK and JQ1 synergistically inhibit multiple key steps of glycolysis and promote TAMs repolarization towards M1 phenotype, thereby reversing TIME.

Nevertheless, the limited specificity and low cross-expression of antigens, coupled with the TIME, pose significant challenges to the efficacy of immunotherapy. Enhancing in situ ICD to generate autologous tumor cell lysates for antigen

Figure 5 Nanosystem targets PKM to reprogram TME and enhance immunotherapy. (**A**) Schematic illustration of the self-assembly of SK/siR-NPs nanosystem and (**B**) its antitumor mechanism. (**C**) Western blot analysis of the expression of PD-L1 and PKM2 after different treatments. (**D**) Tumor volume curve in different groups. (**E**) HE and TUNEL staining of tumor tissue after different treatments (scale bar, 10μm). (**F**) Qualitative analysis of CD8+ T cells infiltration in tumors by FCM. *p < 0.05, **p < 0.01, ***p < 0.001. Adapted with permission from Li J, Zhao M, Sun M, et al. Multifunctional nanoparticles boost cancer immunotherapy based on modulating the immunosuppressive tumor microenvironment. *ACS Appl Mater Interfaces*. 2020;12(45):50734–50747. Copyright © 2020 American Chemical Society.[76]

release and presentation can effectively trigger a cascade immune response and reverse the TIME. Consequently, Shi et al simultaneously induced necrotic apoptosis and ferroptosis by loading Fe^{2+} and SK onto alum NPs to elicit robust ICD.[78] Ferroptosis is not influenced by common tumor-associated mutations in apoptotic proteins, while necrotic apoptosis represents a more potent form of ICD compared to traditional apoptosis, significantly enhancing immunogenicity.[122] Furthermore, immunoadjuvant cytosine guanine dinucleotide (CpG) oligodeoxynucleotides (ODNs) and inorganic aluminum salts further enhance the antitumor efficacy of the glycolysis inhibitor SK. This treatment strategy activates an immune response through multiple dimensions and steps, demonstrating remarkable efficacy in inhibiting tumor growth, recurrence, and metastasis. These PKM2-targeted therapeutic strategies improve the delivery of NPs via EVs, lactoferrin, peptides, and various modifications, while also enhancing ICD and amplifying anti-tumor immune responses through the use of immune adjuvants, PTT, and ferroptosis.

Nanoparticles Targeting Lactate Dehydrogenase (LDHA)

LDHA plays a pivotal role as an enzyme in glycolysis, facilitating the conversion of pyruvate to lactic acid. The overexpression of LDHA in tumor cells can result in the infiltration of TAMs, thereby promoting immune evasion and therapeutic resistance.[123] GSK2837808A (GSK) has established a TME characterized by elevated glucose levels and reduced lactate concentrations through the inhibition of LDHA and restriction of glucose consumption. Yan et al demonstrated significant anti-tumor effects by combining GSK, an LDHA inhibitor, with sonodynamic therapy (SDT).[79] The HPP-Ca@GSK nanoplatform was concurrently integrated with PEG-IR 780, CaCl2, and GSK, effectively

reversing the TME while addressing calcium overload and ultrasound-mediated ROS-induced mitochondrial damage. By integrating these components, a robust ICD is induced that enhances the antitumor immune efficacy of anti-CTLA-4 therapy. Although small molecule inhibitors often exhibit poor stability, nanomaterials can alleviate this limitation. Two-dimensional tin selenide nanosheets (SnSe NSs) also demonstrate commendable LDH-like enzymatic activity under challenging conditions; they are capable of converting lactic acid back to pyruvate while effectively inhibiting glycolysis.[83,124,125] Moreover, SnSe NSs can successfully reverse acidic TME by delivering carbonic anhydrase inhibitors.[126–128] Furthermore, SnSe NSs possess remarkable photothermal properties that induce excessive ROS production upon NIRlight irradiation leading to apoptosis in tumor cells.

In addition to utilizing nanocarriers loaded with LDHA inhibitors, silencing or editing the LDHA gene represents another viable strategy. Zhang et al restructured the TME by silencing the LDHA gene utilizing cationic lipid-assisted NPs delivery methods.[82] Ju's team employed lipid NPs for delivering CRISPR/Cas9 plasmid DNA targeting LDHA, which effectively edited tumor cell genomes and inhibited LDHA expression.[81] She et al achieved dual inhibition of both glycolysis and TCA cycle activity by combining CRISPR/Cas9 technology with CPI-Z2 treatment[80] (Figure 6). CPI-Z2 downregulates mitochondrial TCA cycling activity while inducing ROS production via inhibition of pyruvate dehydrogenase complex and α-ketoglutarate dehydrogenase complex pathways. This ROS catalyzes L-arginine into nitric oxide, subsequently reducing drug resistance by
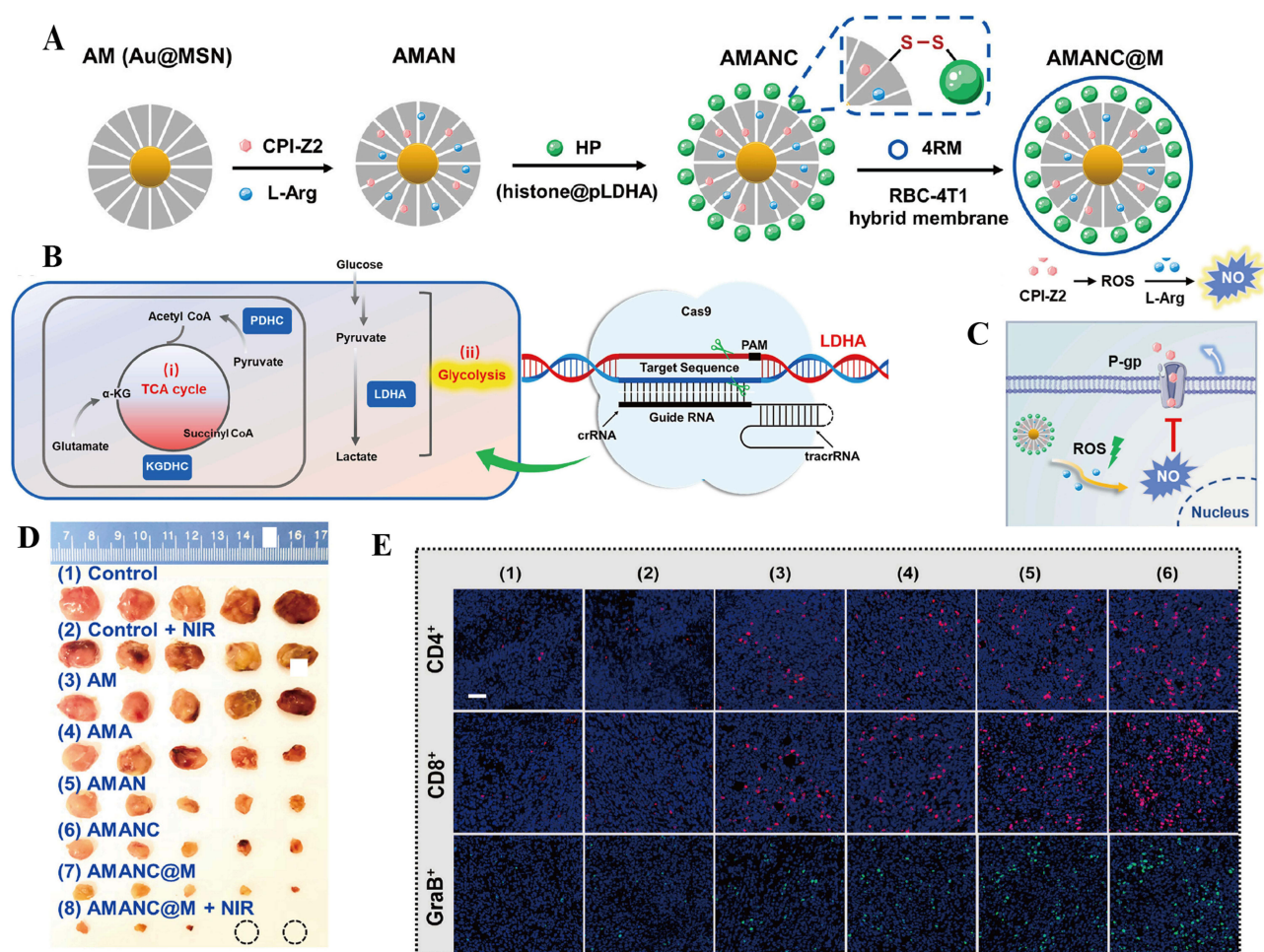

Figure 6 Nanosystem targets LDH to reprogram TME and enhance immunotherapy. (**A**) Schematic illustration of the synthesis of AMANC@M nanosystem. (**B**) AMANC@M blocks the energy supply of tumor cells. (i) Glycolytic inhibition by knocking down LDHA using CRISPR/Cas9 technology. (ii) TCA inhibition induced by CPI-Z2. (**C**) Schematic diagram of inhibition of P-gp to alleviate chemotherapy resistance via increasing NO mediated by CPI-Z2. (**D**) Tumor picture of mouse after different treatments. (**E**) immunofluorescence staining images of CD4+ T cells (red), CD8+ T cells (red), and granzyme B (green) in the tumor tissues (scale bar, 50μm).
Notes: (1) control (PBS), (2) AM, (3) AMA, (4) AMAN, (5) AMANC, (6) AMANC@M. Adapted from *J Control Release*, volume 366, She W, Li H, Wang Z, et al. Site-specific controlled-release nanoparticles for immune reprogramming via dual metabolic inhibition against triple-negative breast cancer. 204–220. Copyright 2024, with permission from Elsevier.[80]

inhibiting P-glycoprotein.[129–131] Furthermore, AMANC@M NPs were coated with erythrocyte-4 T1 hybrid membranes to enhance their targeting ability towards tumors while improving blood circulation stability. Collectively, these various nanodelivery strategies underscore that inhibiting LDHA constitutes an effective target for augmenting the efficacy of immunotherapy.

JQ1 down-regulates the expression of oncogenes c-Myc and PD-L1 by inhibiting bromodomain and extraterminal protein 4.[121] The reduction in c-Myc levels subsequently leads to decreased expression of key glycolytic enzymes, including HK2 and LDHA.[120,132] Furthermore, polymeric NPs encapsulating JQ1 effectively mitigate the lactate-driven TIME, elicit a robust immune response, and overcome the immune resistance associated with chemotherapy and photodynamic therapy (PDT).[102,103]

Nanoparticles Targeting Pyruvate Dehydrogenase Kinase (PDK)

In addition to obstructing the glycolytic metabolic pathway, transitioning tumor cells from glycolysis to OXPHOS presents a novel strategy for metabolic therapy. PDK phosphorylates and inactivates PDH, thereby inhibiting the conversion of pyruvate into acetyl-CoA and preventing its entry into the TCA. Dichloroacetic acid (DCA), a small molecule inhibitor of PDK, facilitates this transition from glycolysis to OXPHOS; however, its bioavailability remains suboptimal.[133]

Consequently, Dai et al utilized $MnFe_2O_4$ NPs for targeted delivery of DCA to cancer cells, effectively reducing levels of immunosuppressive lactate and adenosine, thus reversing the TIME[84] (Figure 7). Furthermore, ultra-small $MnFe_2O_4$ NPs (6 nm) can efficiently penetrate mitochondria to degrade Glutathione (GSH) and H_2O_2, releasing oxygen and hydroxyl radicals (·OH). This process enhances DCA efficacy and promotes apoptosis in tumor cells. In conclusion, the inhibition of key glycolytic enzymes to reverse aberrant glycolytic metabolism can reinvigorate the immune response and enhance the effectiveness of various therapeutic approaches.
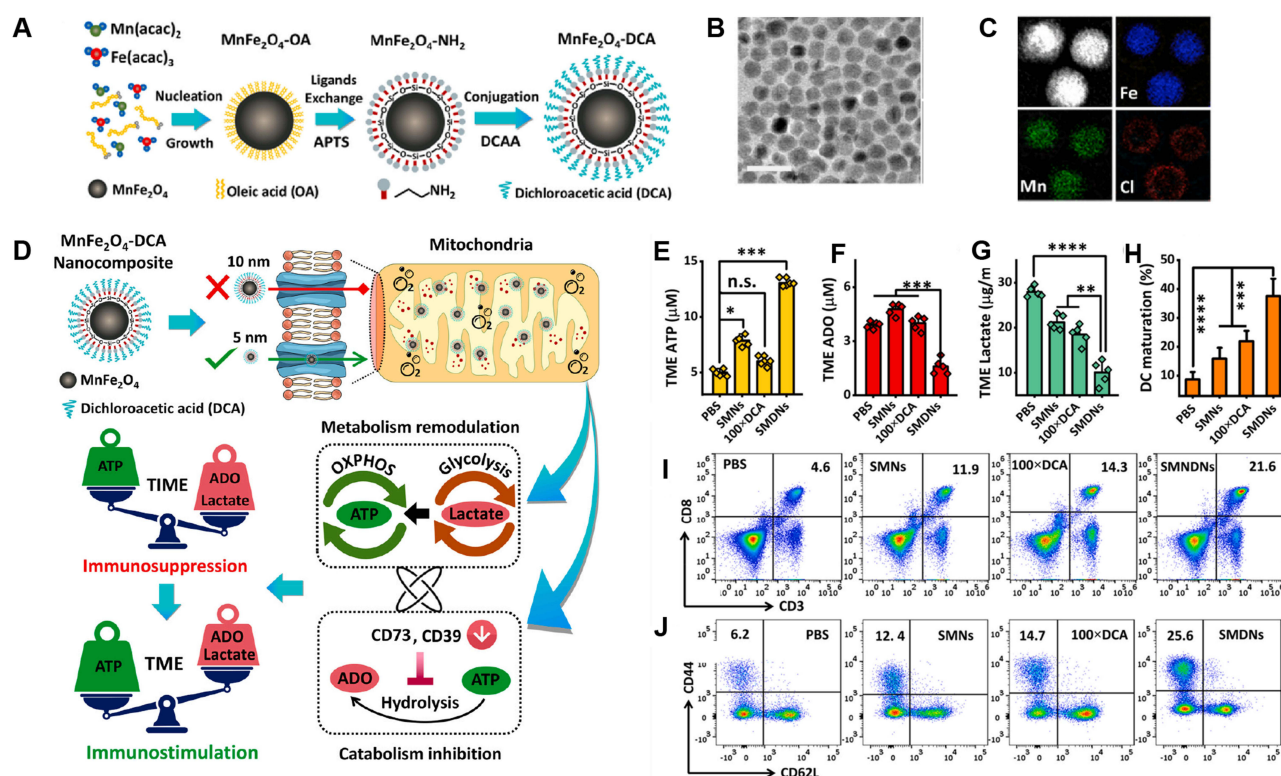

Figure 7 Nanosystem targets PDK to reprogram TME and enhance immunotherapy. (**A**) Schematic illustration of the preparation of SMDNs nanosystem. (**B**) TEM image, (**C**) dark field image and corresponding area-elemental mappings of SMDNs (scale bar, 10nm). (**D**) SMDNs reverses immunosuppression by converting glycolysis to OXPHOS and inhibiting ADO production. SMDNs activated the immune response by regulating (**E**) ATP, (**F**) ADO, and (**G**) lactate levels. The proportion of (**H**) mature DCs, (**I**) CD8+T cells, and (**J**) effector memory T cells with different treatments via FCM analysis. *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001. Adapted from *Biomaterials*, volume 284; Dai Z, Wang Q, Tang J, et al. A Sub-6 Nm MnFe2O4-dichloroacetic acid nanocomposite modulates tumor metabolism and catabolism for reversing tumor immunosuppressive microenvironment and boosting immunotherapy, page number: 121533. Copyright 2022, with permission from Elsevier.[84]

Nanoparticles Targeting Glucose and Lactate Transporters for Cancer Immunotherapy
Nanoparticles Targeting Glucose Transporters

The efficiency of glucose uptake and metabolism improves significantly to ensure a supply of nutrients and energy for the infinite proliferation of cancer cells. Blocking the intracellular glycolysis pathway may results in the adaptive upregulation of GLUT expression, particularly that of GLUT1, in tumors.[134] Consequently, targeting GLUT1-mediated glucose transport is considered an attractive antitumor therapeutic strategy. This strategy, which causes cancer cells death by blocking the supply of energy and nutrients, is called starvation therapy. Wu et al successfully constructed a "nanoenabled energy interrupter" (HZ@GD) by embedding a GLUT1 mRNA-cleaving DNAzyme into the nanocarrier zeolitic imidazolate framework-8 (ZIF-8) and then tethered it to hyaluronic acid to improve the effectiveness of starvation therapy.[135] The CD44-mediated active targeting mechanism promotes the uptake of HZ@GD by tumor cells, and the presence of hyaluronidase and an acidic pH allow Zn^{2+} and the DNAzyme to be released into the tumor cytoplasm. Zn^{2+} inhibits glycolysis by triggering a decrease in NAD+ levels and the inactivation of GAPDH, while the Zn^{2+}-activated DNAzyme reduces GLUT1 expression and decreases the glucose supply within tumor cells. Although HZ@GD has shown excellent tumor-suppressing effects, its impact on the immune system has not been assessed.

The effectiveness of ICB is often limited by increasing numbers of immunosuppressive cells and inhibitory cytokines in the TME and negative immune regulation mediated by CTLA-4. Ren et al addressed this challenge by introducing self-assembled aptamer polymers for targeted delivery of specific GLUT1 inhibitor BAY-876[116]. The supramolecular nanostructure (DNA-PAE @BAY-876) was designed by attaching BAY-876 to a nanocore DNA- polyβ-amino ester (PAE), which was formed by modifying PD-L1 and CTLA-4-antagonizing aptamers (aptPD-L1 and aptCTLA-4) with PAE (Figure 8). AptPD-L1 and aptCTLA-4 bind PD-L1 and CTLA-4 with high affinity and specificity to enhance immunotherapy. BAY-876 reduced the glycosylation of PD-L1 and enhanced the efficacy of aptPD-L1 by reducing lactate levels and negatively regulating the Glu-F6 -P-UDP-GlcNAc axis. Furthermore, DNA-PAE@BAY-876 has the potential to enhance the immune response and induce systemic immune memory, thereby preventing TNBC metastasis and recurrence.

The metabolic nanomodulator D/B/CQ@ZIF-8@CS was successfully constructed by encapsulating 2DG, BAY-876 and chloroquine within ZIF-8 NPs, followed by coating with chondroitin sulfate to improve the targeting of NPs.[104] 2DG and BAY-876 maximally block the supply of energy and nutrients to tumor cells, and indirectly increases the glucose supply to immune cells. As anticipated, the NPs activated an immune response characterized by the upregulation of T cells and the cytokines IFN-γ and TNF-α.

Nanoparticles Targeting Lactate Transporters

As mentioned earlier, rapid glycolysis in tumor cells leads to the production of plenty of lactate, which is transported out of the cell by MCT to form an acidic TME. MCT1 and MCT4 are the most important MCTs in cancer, and their overexpression is associated with a poor prognosis for various malignant tumors.[136] The efflux of lactate mediated by MCT4 helps to prevent intracellular acidification and alleviate the feedback inhibition of glycolysis caused by lactate accumulation in hypoxic cancer cells, while the influx of lactate mediated by MCT1 provides fuel for the respiration of oxygen-rich cancer cells.[86] In addition to inhibiting lactate production, inhibiting lactate transport by targeting MCT is also a promising antitumor therapy.

Blocking MCT1 inhibited lactate-fueled OXPHOS in oxygen-rich tumor cells and converted metabolism to glycolysis, which inhibited the energy metabolism of hypoxic tumor cells through competition for glucose. Additionally, blocking MCT1 inhibited glycolysis in hypoxic cancer cells by reducing the production of glycolytic intermediates, ultimately leading to the inhibited growth and proliferation of cancer cells. AZD-ultra-pH-sensitive (UPS) NPs are designed to selectively load the MCT1 inhibitor AZD3965 inside an UPS micelle via a microfluidic method.[86] These NPs are stable at pH 7.4 and can be quickly released in acidic environments. Additionally, AZD-UPS NPs combined with anti-PD-1 therapy significantly improved the immune response of CD8$^+$ T cells. However, MCT1 is more highly expressed in oxygen-rich tumor cells located near blood vessels, suggesting that drugs targeting MCT1 may penetrate more easily into tumors due to their closer proximity to blood vessels. However, Fischer et al reported that MCT1 is also expressed on normal cells, such as infiltrating CD8$^+$ T lymphocytes.[137] Consequently, MCT1-blocking therapy may
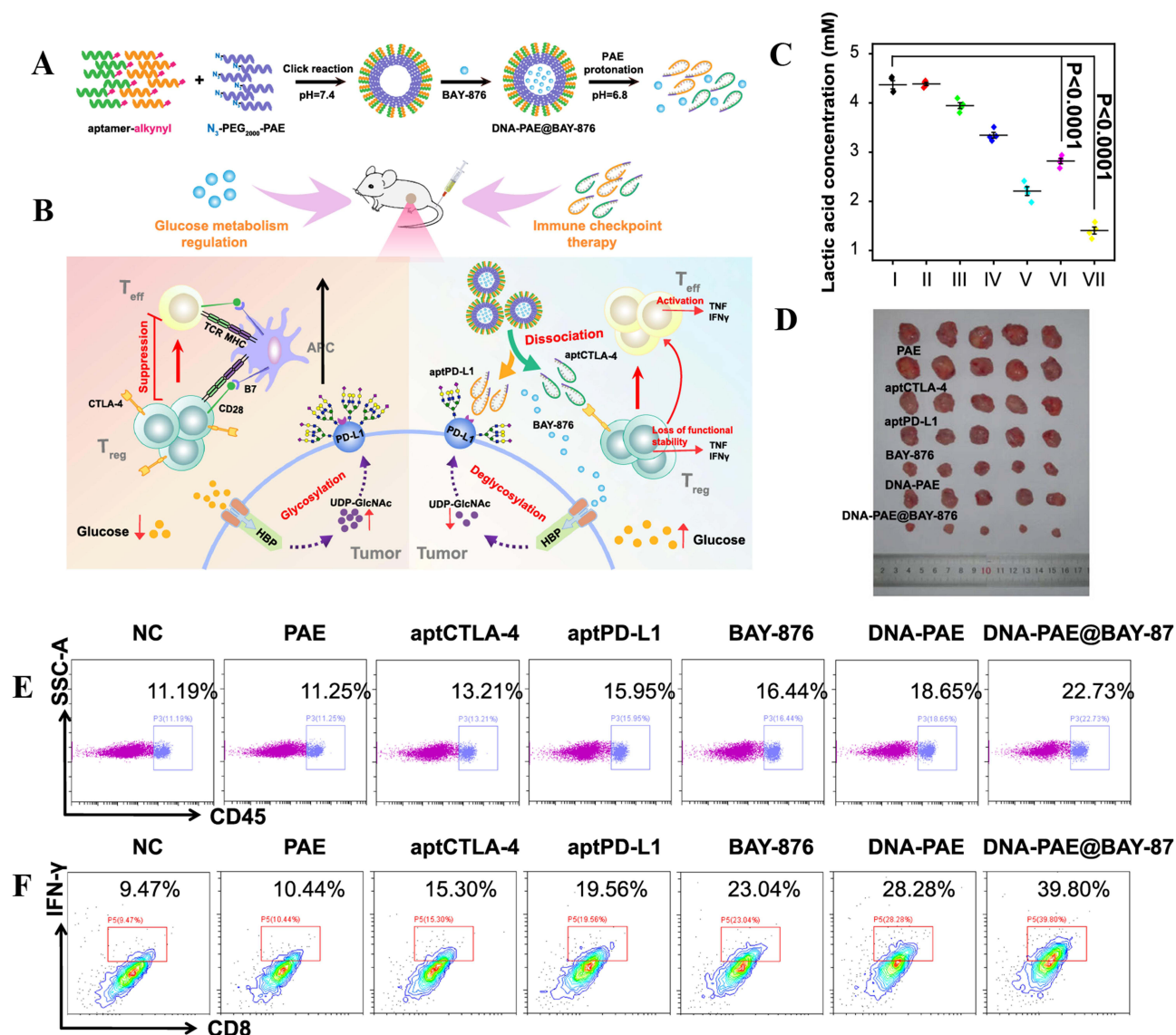
Figure 8 Nanosystem targets GLUT to reprogram TME and enhance immunotherapy. (**A**) Schematic illustration of the preparation of DNA-PAE@BAY-876 nanosystem and (**B**) the mechanism of reprogramming TIME. (**C**) ELISA analysis of the level of lactic acid following different treatments, I NC, (II) PAE, (III) aptCTLA-4, (IV) aptPD-L1, (V) BAY-876, (VI) DNA-PAE, (VII) DNA-PAE@BAY-876. (**D**)The comparative of mice tumors among the distinct treatment. FCM analysis of the (**E**) total immune cell population (CD45$^+$) and (**F**) IFN-γ^+CD8$^+$ T cells within the tumor tissues. Adapted from Ren X, Cheng Z, He J, et al. Inhibition of glycolysis-driven immunosuppression with a nano-assembly enhances response to immune checkpoint blockade therapy in triple negative breast cancer. *Nat Commun*. 2023;14(1):7021. Creative Commons.[85]

affect the immune activity of CD8$^+$ T lymphocytes. Therefore, enhancing nanoparticle targeting to cancer cells can potentially enhance the antitumor effects of MCT1 while minimizing adverse reactions.

Inhibition of MCT4 expression can lead to intracellular acidosis and the inhibition of glycolysis. Li et al loaded siMCT-4 and the chemotherapy drug hydroxycamptothecin (HCPT) with hollow mesoporous organosilica NPs modified with PEG-CDM and coated them with bovine serum albumin (Figure 9) 121. The NPs successfully silenced the expression of MCT-4, leading to intracellular lactate accumulation and promoting the necrosis and apoptosis of tumor cells. Tian et al proposed that a reprogrammed TME enhances immunotherapy efficacy by synergistically inhibiting lactate production and blocking lactate shuttling.[138] Syrosingopine, which inhibits MCT-4 expression, and the HK2 inhibitor LND were simultaneously encapsulated in PEGylated liposomes to form immune and metabolically regulated nanosheets (L@S/L). LND and syrosingopine synergically reduced extracellular lactate levels, increased the numbers of NK cells and M1-like TAMs, and upregulated IFN-γ and TNF-α, showing great potential for antitumor therapy. In

summary, these nanoplatforms reversed the TIME, significantly inhibiting tumor growth and progression. However, MCT4 is expressed in hypoxic tumor cells far from blood vessels, making it more difficult for MCT4-blocking drugs to reach therapeutic targets. Therefore, improving the penetration of NPs may further improve their antitumor effects.

Nanoparticles Targeting Glucose Oxidase (GOx) for Cancer Immunotherapy

Tumor cells need to consume more glucose to maintain growth, and thus starvation therapy has been proposed to block the energy supply to tumor cells. GOx is an endogenous oxidoreductase that blocks glycolysis and inhibiting the production of lactate and ATP via converting glucose into gluconic acid.[92,139] However, its efficacy has been severely limited by poor bioavailability and rapid inactivation when encountering biological barriers.[140] Additionally, the adverse effects associated with GOx, such as hypoglycemia and organ damage, have hindered its clinical application.[141,142] Nevertheless, the advent of nanomaterials effectively addresses the limitations associated with GOx. Therefore, mesoporous silica NPs (MSNs) have been utilized to deliver GOx to construct the CMSN-Gox NPs, which can effectively target tumor due to the cancer cell membrane enveloping the CMSN-GOx.[92] CMSN-GOx effectively induced an immune response and inhibited tumor growth. LMGC, an acidic TME-responsive spherical nanoparticle, was prepared by immobilizing GOx onto the surface of liquid metal (LM) nanocapsules, followed by modification with mineralized $CaCO_3$ and the copolymer PEG-PAsp.[143] Gox-induced glycolytic inhibition and Ca^{2+}-mediated mitochondrial dysfunction result in a significant reduction in ATP production. Upon NIR light irradiation, LM nanocapsules can effectively kill tumor cells via PTT.[91] Surprisingly, LMGC markedly reduces the expression of heat shock protein (HSP), enhancing the sensitivity of PTT and reversing tumor cell heat resistance.

However, glucose oxidation requires the participation of O_2, and a severely hypoxic TME limits this process.[144] A nanocarrier that can relieve the hypoxic TME must be designed to improve the catalytic efficiency and sustainability of GOx. Therefore, various nanocarriers with dual GOx and catalase activities have been developed to catalyze H_2O_2 to produce O_2, which improved the oxidation efficiency of GOx. For example, Zhang et al hybridized GOx with $MnCl_2 \cdot 4H_2O$ using a biomineralization method to synthesize GOx-Mn/HANPs, creating a virtuous cycle with dual enzyme activity.[90] Furthermore, cationic gold nanoclusters (CAuNCs) adsorbed GOx and catalase through electrostatic interactions, followed the NPs were further condensed with HK2 siRNA to create nanomotors NM-Si.[105] The CAT-catalyzed cascade of enzymatic reactions continued to generate oxygen bubbles, prompting nanomotors using H_2O_2 as fuel to move autonomously to tumor tissues with higher H_2O_2 concentrations.[105] NM-si significantly reduces tumor cell migration and invasion by downregulating the expression of HIF1α and HK2.[145]

GOx can also enhance the Fenton reaction by increasing the production of H_2O_2, which is catalyzed by Fe^{2+} to generate ·OH and enhance chemodynamic therapy (CDT).[88,146] GOx and ·OH work synergistically to promote ICD induction, facilitate DCs maturation, and enhance the antitumor immune response. Ren et al introduced PTX into FeSGOx through hydrophobic interactions to construct FGP NPs.[94] The photothermal effect of FGP can promote the activity of GOx and increase the production of ·OH. FGP serves as a cascade bioreactor that combines starvation therapy, CDT, PTT, and chemotherapy to amplify ICD induction and generate a potent antitumor immune response. Similarly, another biomimetic nanosystem, mEHGZ, was developed by loading epirubicin, GOx and hemin into porous ZIF-8 NPs.[147] The mEHGZ displayed outstanding tumor-targeting capabilities via the coating of tumor cell membranes with overexpressed CRT.[148] The Fe^{2+} in hemin reacts with H_2O_2 to produce abundant ·OH and Fe^{3+}, while Fe^{3+} oxidizes intracellular GSH. A decrease in GSH levels disrupts the redox balance, inhibits the clearance of ·OH, accelerates ROS production and enhances endoplasmic reticulum stress.[149–151] A metal–organic framework (MOF) nanoreactor was equipped with GOx and the IDO inhibitor 1-methyltryptophan (1-MT) to construct a nanoplatform[93] (Figure 10). Another nanoparticle was fabricated by loading DOX and aspirin onto PEG-modified manganese-doped hollow mesoporous silica-coated gold NPs.[95] The two NPs exhibited the enzymatic properties of GOx and catalase and increased ·OH levels through a Fenton-like reaction mediated by Mn^{2+}. These agents synergized with the immunomodifiers 1-MT and aspirin to counteract immunosuppression, and enhance the antitumor efficacy of the NPs.
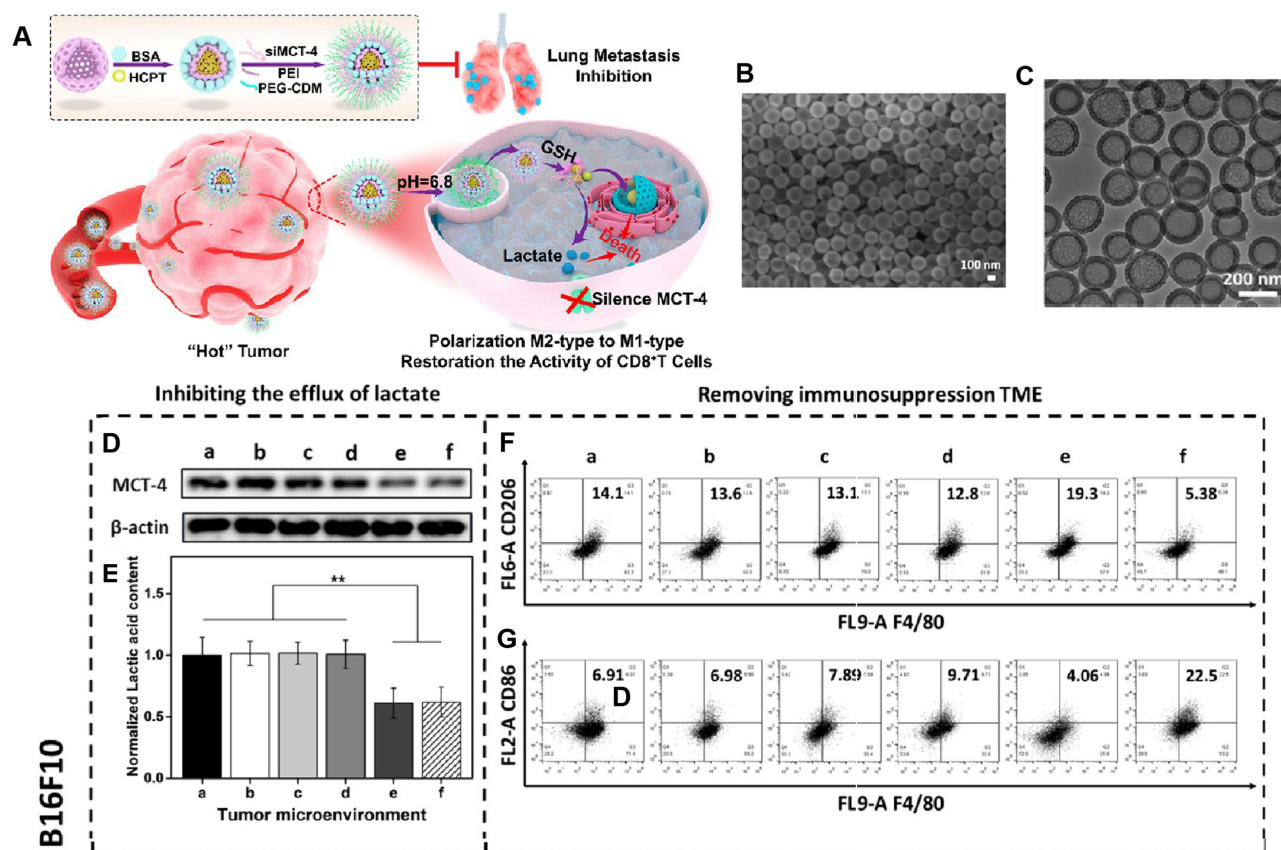
Figure 9 Nanosystem targets MCT to reprogram TME and enhance immunotherapy. (**A**) Schematic illustration of the preparation HMONs@HCPT-BSA-PEI-CDM-PEG @siMCT-4 nanosystem and the mechanism of reverse TIME. (**B**) SEM and (**C**) TEM images of HMONs. (**D**) MCT-4 expression in B16F10 tumor tissues by Western blotting. (**E**) Standardized lactate levels in TME, FCM analysis of (**F**) M2-TAMs (CD206$^+$) and (**G**) M1-TAMs (CD86$^+$) in tumor tissues. (a: Saline, b: HMONs-BSA-PEI-CDM-PEG, c: HCPT, d: HMONs@HCPT-BSA-PEI-CDM-PEG@siNC, e: HMONs@HCPT-BSA-PEI-CDM-PEG@siMCT-4+forskolin, f: HMONs@HCPT-BSA-PEI-CDM-PEG@siMCT-4). **p < 0.01. Adapted from Li K, Lin C, He Y, et al. Engineering of cascade-responsive nanoplatform to inhibit lactate efflux for enhanced tumor chemo-immunotherapy. *ACS Nano*. 2020;14(10):14164–14180. Copyright © 2020 American Chemical Society.[87]

Nanoparticles Targeting Lactate Oxidase (LOx) for Cancer Immunotherapy

The above studies have focused mainly on reducing lactate production, but strategies for direct lactate depletion have been quite compelling. LOx converts lactate to pyruvate and H_2O_2 to improve the TIME. Microbial-derived recombinant LOx was encapsulated in a thin polymer shell using a single enzyme encapsulation platform to construct n(LOx) NPs.[97] The n(LOx) NPs significantly reduced the level of lactate while promoting the continuous release of H_2O_2. H_2O_2 successfully activates nuclear factor κB signaling and promotes the secretion of antitumor cytokines, thereby activating T cells and guiding their migration into tumors.[99,152,153] Wang et al developed the biomimetic nanosystem PMOL, which encapsulates LOx and the chemotherapy drug oxaliplatin within MOFs.[99] The coating of a platelet membrane onto NPs enables specific tumor targeting. Oxaliplatin induces the apoptosis of tumor cells and triggers an ICD-mediated immune response while working in conjunction with LOx to distinctly suppress tumor growth.

Although the antitumor effects of Lox have been verified, its function is limited due to its instability and inhibition by the anoxic TME.[154] Hence, hollow Prussian blue (HPB) carriers were introduced to solve these problems. HPB has CAT-like activity and can catalyze H_2O_2 to provide oxygen for lactate consumption.[155] Furthermore, HPB can prevent the leakage of LOx and protect its activity. LOx was coated with HPB NPs and PD-L1 siRNA (siPD-L1) was loaded into the NPs by electrostatic adsorption to further explore the combination therapy of LOx and PD-1[100] (Figure 11). High GSH levels in tumor cells promote the cleavage of disulfide bonds, effectively releasing LOx and siPD-L1. The NPs mitigated hypoxia, enhanced lactate consumption and ROS production, and downregulated PD-L1 expression in cancer cells. MCuLP NPs were constructed by integrating LOx and Cu^{2+} onto pegylated mesoporous polydopamine (mPDA) NPs.[96] Upon the chelation of
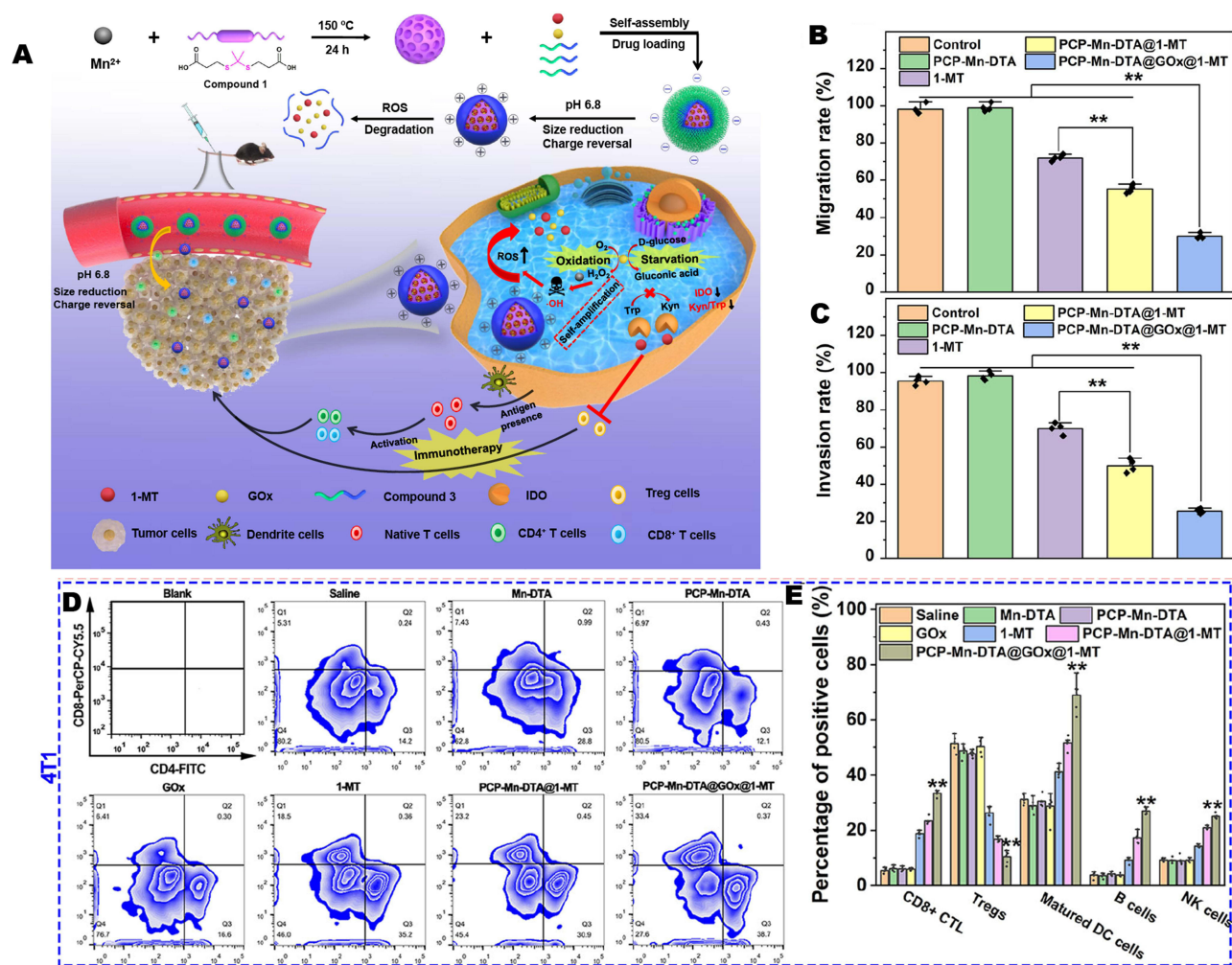
Figure 10 Nanosystem targets GOx to reprogram TME and enhance immunotherapy. (**A**) Schematic illustration of constructing PCP-Mn-DTA@GOx@1-MT nanosystem and its antitumor mechanism. Quantitative analysis of (**B**) migration and (**C**) invasion assays of B16F10 cells treated with this nanosystem. (**D**) FCM and Quantitative analysis on the populations of CD8$^+$ CTLs, Treg cells, NK cells, matured DCs, and B cells with different treatments. Adapted from Dai L, Yao M, Fu Z, et al. Multifunctional metal-organic framework-based nanoreactor for starvation/oxidation improved indoleamine 2,3-dioxygenase-blockade tumor immunotherapy. *Nat Commun*. 2022;13(1):2688. Creative Commons. **p < 0.01.[93]

Cu^{2+}, mPDA exhibits catalase-like properties and forms a closed loop with the catalytic activity of LOx,[156] leading to a significant reduction in the lactate concentration without increasing pyruvate levels, and thereby significantly enhancing immunosuppression. The mCuLP nanosystem also showed excellent photothermal conversion and stability,[157,158] with a limited impact on the activity of LOx. Furthermore, the PTT-induced apoptosis of tumor cells promotes the exposure of DAMPs (such as CRT and HMGB1), induces DCs maturation, and enhances T-cell-mediated killing of cancer cells. Xie et al designed PNDPL NPs by coating PtBi nanozymes and NLG919 with an amphiphilic polymer and linking LOx to the surface of nanomicelles through amide bonds.[98] Upon NIR light irradiation, PtBi nanozymes demonstrated efficient photothermal conversion and stability. An increase in temperature facilitated the release of PtBi nanozymes and NLG919 while also enhancing the Cat-like enzyme activity of PtBi nanozymes.[159,160] Furthermore, oxygen provided by PtBi nanozymes promotes lactate oxidation catalyzed by LOx, resulting in a significant reduction in lactate levels. In combination with metabolic immunoregulation and PTT, PNDPL enhances antitumor immunogenicity, induces powerful ICD, and achieves a robust immune response. Additionally, Chen et al reported that $HMnO_2$ NPs loaded with LOx overcame hypoxia and immunosuppression after the local thermal ablation of hepatocellular carcinoma.[101]

GOx/LOx facilitates the production of H_2O_2, making the incorporation of nanomaterials with catalase-like activity advantageous for alleviating hypoxia and enhancing glucose and lactic acid oxidation. Furthermore, employing
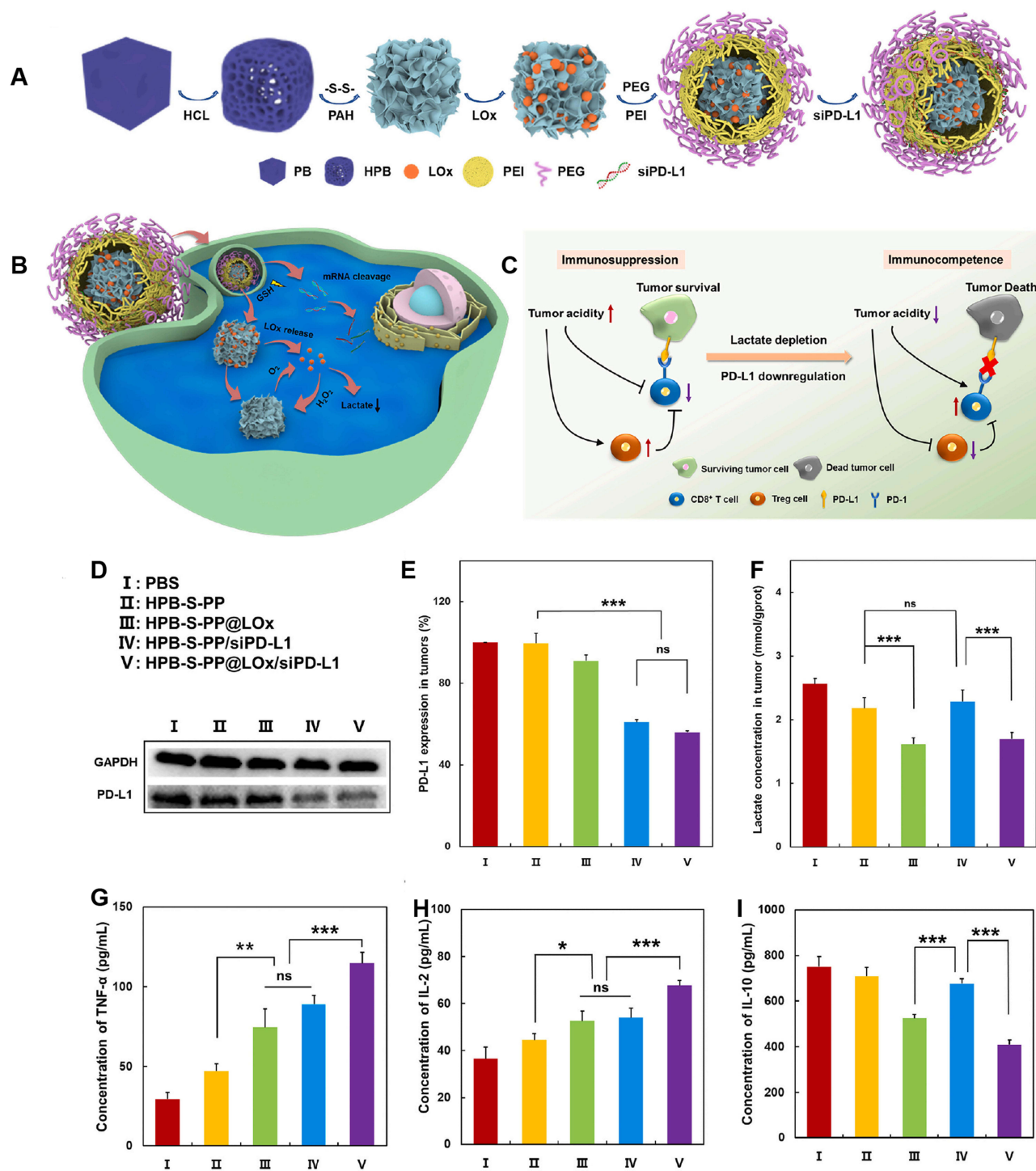
Figure 11 Nanosystem targets LOx to reprogram TME and enhance immunotherapy. (**A**) Schematic illustration of constructing HPB-S-PP@LOx/siPD-L1 nanosystem. (**B**) Lox-mediated downregulation of lactate to (**C**) enhance the effect of PD-1/PDL-1 blocking therapy by up-regulation of CD8^{+} T cells and down-regulation of Tregs. (**D**) Western blot analysis of PDL-1 expression in resected tumors after different treatments. Quantitative analysis of (**E**) the expression of PDL-1, (**F**) the levels of lactate, (**G**) TNF-α, (**H**) IL-2 and (**I**) IL-10 after different treatments. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. Adapted from *Biomater Adv*, volume 150, Tang Y, Chang Q, Chen G, et al. Tumor immunosuppression relief via acidity modulation combined PD-L1 siRNA for enhanced immunotherapy. 213425. Copyright 2023, with permission from Elservier.[100]

nanoenzyme capable of catalyzing the Fenton reaction in conjunction with GOx provides a dual benefit. Gox/LOx regulates lactate metabolism while supplying substrates for the Fenton reaction, whereas nano-enzyme contributes to tumor suppression through its catalytic role in CDT.

Combination Therapy with Nanoparticles Reprogramming Glucose Metabolism

With ongoing research into cancer therapies yielding promising results, more effective approaches are being developed for combating tumors effectively, including chemotherapy, PTT/PDT, ICB, RT, SDT, CDT and more. Unfortunately, tumor resistance to treatment is a significant issue that cannot be ignored, as it seriously hinders the effectiveness of tumor treatment. The glucose metabolism of tumor cells and the reprogrammed immune microenvironment are important factors in tumor resistance. Glucose metabolism-targeted therapy has the potential to enhance the immune response, reverse drug resistance, and improve antitumor therapeutic effects. Nanosystem represent a powerful strategy for the synergistic integration of multiple therapeutic modalities. On one hand, nanomaterials can encapsulate various drugs with distinct properties; on the other hand, they often exhibit inherent therapeutic effects themselves. Moreover, glycolytic metabolism therapy has been demonstrated to enhance the efficacy of diverse anti-tumor treatments, thereby achieving a synergistic effect characterized by "1+1>2" (Figure 12).

Combination with Chemotherapy

Chemotherapy is a systemic antitumor therapy that has been widely applied in clinical practice. However, patients often have to discontinue treatment due to drug resistance and unacceptable side effects. Drug resistance is a main adaptive regulatory mechanism in aggressive tumors, but its specific mechanism is not fully understood. Currently, the evidence suggests that the TME affects the accumulation/retention of chemotherapy drugs within tumor cells, which is considered a contributing factor to clinical chemotherapy failure. First, an acidic pH reduces the uptake of drugs by cancer cells; for example, the uptake of DOX by MCF-7 cells at pH 6.8 is significantly lower than that at pH 7.4.[161] Second, the low pH and hypoxia of the TME enhance P-gp activity, which promotes drug transport out of cells, reducing its ability to kill
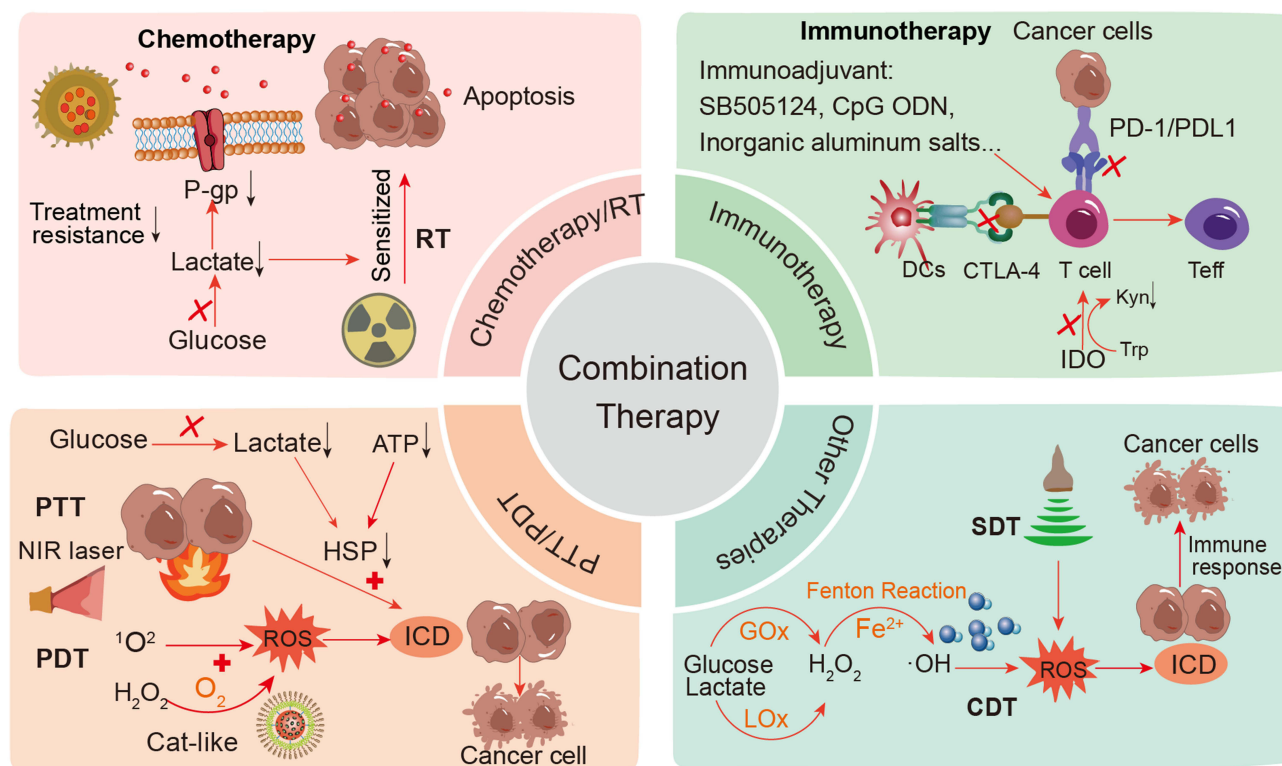

Figure 12 Combination therapy with reprogramming glucose metabolism nanoparticles. Inhibition of glycolysis reduces lactate levels and enhances the susceptibility of tumor cells to chemotherapy and RT. Furthermore, the reduction in lactate inhibits P-gp from effluxing chemotherapy drugs out of the cell. Reprogramming of glycolysis has synergistic antitumor effects with ICB (PD-1/PDL-1, CTLA-4, IDO) or immune adjuvants. Additionally, glycolytic inhibition can augment the efficacy of PTT by down-regulating HSP, and improve the effectiveness of PDT by alleviating hypoxia or increasing oxygen production. Glycolytic modulators can facilitate Fenton reaction to enhance CDT, as well as boost ICD induced by SDT, thereby synergistically enhancing immune response.

cancer cells.[162] The aforementioned nanomaterials targeting key nodes of glucose metabolism can reprogram the TME, improve hypoxia and acidity in the TME, and effectively alleviate chemotherapeutic resistance.

The combination of chemotherapeutic drugs with metabolic regulators synergistically enhances antitumor efficacy. The increases in CRT and HMGB-1 indicate that DOX@HA NPs has the ability to induce ICD during chemotherapy.[135] However, DOX@HA NPs loaded with the HK2 inhibitor JQ1 induced stronger ICD and amplified the antigen-presenting effect of DCs. Moreover, DOX can attract more CD8$^+$ T cells and activate more inflammatory cytokines in tumors.[163] Moreover, studies have revealed that 2DG promotes the activation of CD8$^+$T cells by downregulating the level of PD-L1.[164] Therefore, PDG-NV NPs carried DOX and 2DG enhance the potential of chemical immunotherapy.[69] PTX/PFK15-SLN@[4T1-3T3] NPs target both tumor cells and CAFs, inhibit glycolysis and decrease the supply of glycolytic metabolites derived from CAFs to cancer cells. This process significantly increases the sensitivity of cancer cells to PTX and enhances its antitumor effect. This finding was further verified by calculating the CI for the PTX and PFK15 combination.[75,165] The CI values at the IC50 in 4T1 cells (0.30±0.01) and 3T3 cells (0.48±0.03) were significantly less than 1, indicating a synergistic effect between these two drugs.[75] Similarly, other nanoplatforms co-equipped with chemotherapy drugs and regulators of glucose metabolism have also achieved superior antitumor effects.[87,94,99]

In addition, targeted drug delivery through nanomaterials can significantly reduce the concentration and frequency of administration. The starvation effect of 2DG can also decrease the toxicity of DOX toward normal cells and chemotherapy-induced side effects.[166] Furthermore, some NPs can be selectively decomposed and released under specific conditions; for example, GSH-responsive nanomaterials are released in weakly acidic TME and tumor cells with high levels of GSH, while the release of PTX is almost undetectable in normal cells with low GSH levels, thus preventing damage to normal cells to the greatest extent.[87] Although metabolic nanomedicine holds great potential for synergistic immunotherapy and chemotherapy, further exploration is necessary to understand the mechanism of synergistic therapy and the binding effect between different metabolic targets and various chemotherapeutic drugs.

Combination with Radiotherapy

RT is an important method for treating tumors. However, studies have indicated that RT can cause an increase in intracellular PD-L1 expression, leading to enhanced tumor resistance to DNA damage and significantly limiting the effectiveness.[167,168] LND has been demonstrated to reduce PD-L1 expression and reverse hypoxia by interfering with mitochondrial OXPHOS. Hence, Wang et al combined LND with triphenylphosphine cations (TPP+) to construct TPP-LND@Lip NPs.[72] These NPs effectively targeted the mitochondria through TPP+ and enhanced RT sensitivity and immune activity. The combination of TPP-LND@Lip and RT exhibited superior efficacy compared to PD-1 therapy. Furthermore, increased EVs secretion from cancer cells after RT can promote the polarization of M2-like TAMs and inhibit the immune response.[169] Shen et al developed the M/LM-Lipo NPs by utilizing mannose to interfere with glucose metabolism and reduce PD-L1 expression.[74] Additionally, levamisole hydrochloride not only facilitates the glycolysis of mannose but also induces mitochondrial degradation and autophagy in M2 macrophages. The combination of M/LM-Lipo and RT induces a robust immune response, alleviates RT resistance, and significantly inhibits local tumors, distant tumors, and metastatic tumors. However, research on the combination of RT with metabolic immunotherapy targeting glycolysis is limited, and further efforts are needed to fill these gaps in the field.

Combination with Immunotherapy

Immunotherapy exerts a crucial function in inhibiting tumor growth and metastasis by reactivating and sustaining the immune cycle and restoring the body's innate immune response. Treatments targeting the PD-1/PD-L1 pathway and anti-CTLA-4 therapy are the most extensively researched ICB therapies, with widespread clinical use and remarkable results. However, tumors have developed various defense mechanisms against the immune system. Intervening in glucose metabolism and reducing negative immune metabolites are important strategies for reversing immunosuppression and improving immune escape. Previous studies have shown that various NPs targeting glucose metabolism can alleviate immunosuppression and enhance the efficacy of anti-PD-1 therapy.[82,97] The combination of PMLR NPs equipped with LOx and 3PO, with α-PDL-1 induced the largest area of damage to tumor tissue and the highest survival rate in mice.[101] In addition, T cells and M1 TAMs were upregulated, and the secretion of the immune activators IFN-γ and IL-6 was

significantly increased. Nanomaterials targeting PD-1/PD-L1 have been developed to further validate the synergistic effect of ICB and glucose metabolism regulation therapy.

F-6-P is responsible for synthesizing UDP-GlcNAc through the action of glutamine fructose-6-phosphate amidotransferase, which serves as a crucial substrate in the glycosylation of numerous proteins and lipids.[170] The functionality of PD-1/PDL-1 relies on glycosylation; therefore, the enzymes that inhibit F-6-P production, including GLUTs, HK2, and GOx, can potentially diminish the immunosuppressive effect of PD-1/PDL-1. For instance, Li et al developed biomimetic NVs (PDG-NVs) derived from cancer cell membranes overexpressing PD-1.[69] PDG-NVs affect the glycosylation of PD-L1 via 2DG to inhibit glucose metabolism. Additionally, the binding of PD-1 on P-NVs to PDL-1 on cancer cells blocks the PD-1/PD-L1 axis. A nanosystem equipped with LOx/siPD-1 has been developed.[100] LOx reduces lactate levels and reprograms the TIME into an immunostimulatory state. It collaborates with siPD-1 to block the binding of PD-1 and PDL-1, thus enhancing the effect of immunotherapy. Ren et al combined the GLUT1 inhibitor BAY-876 with aptCTLA-4 and aptPD-L1 in a nanoplatform to establish an effective antitumor therapy system.[85] BAY-876 improves immunosuppression by inhibiting glucose competition and glycolysis in cancer cells. Additionally, it promotes the establishment of a strong and stable immune response through aptPD-L1 binding to PD-L1 and aptCTLA-4-mediated CTLA-4 blockade during therapy. In combination with a CTLA-4 checkpoint blocker, FGP NPs loaded with GOx and PTX promoted the upregulation of CD8$^+$ T cells and the downregulation of Tregs and enhanced the curative effect on local and distant tumors in mice.[94]

Additionally, IDO, a heme enzyme highly expressed in tumor cells, inhibits the proliferation of Teffs and induces the expansion of Tregs by catalyzing the conversion of tryptophan (Trp) to kynuridine (Kyn).[171,172] The IDO inhibitor 1-MT can improve immune tolerance, while starvation therapy with LOx can initiate and enhance the immune response. Nanocarriers can synergistically promote tumor cells apoptosis and inhibit tumor growth by combining GOx and 1-MT.[93] Similarly, targeted tumor therapy combining lactate depletion of LOx with the IDO inhibitor NLG919 has shown promising antitumor effects.[98] NLG919 blocks the Trp/Kyn metabolic pathway and mitigates the immunosuppressive effects of Kyn.[173] Furthermore, combination therapies involving other immunotherapy agents with glycolysis-targeted therapy have also been shown to enhance antitumor effects. For example, blocking the CD47-SIRPα signaling pathway, which is used in combination with the PKM2 inhibitor SK, promotes macrophage phagocytosis, and the TGF-β receptor inhibitor SB505124 is used in combination with the glycolysis regulator LND.[73,77] CpG ODN activates Toll-like receptor 9, which promotes DC maturation and MHC-II expression, thereby inducing both innate and adaptive immunity.[174] Additionally, the presence of inorganic aluminum salts in NPs allows the effective adsorption of antigens, and NPs act as an "antigen pool" that continuously releases antigens to initiate and prolong the adaptive immune response.[175] Immunoadjuvant CpG ODN and inorganic aluminum salts further enhance the antitumor efficacy of the glycolysis inhibitor SK. The effect of immunotherapy was enhanced through the integration of immune adjuvant CpG ODN, inorganic aluminum salt and SK on the same nanoparticle.[78]

Nevertheless, maintaining the long-term effectiveness of immunotherapy and addressing adverse reactions caused by prolonged use remain unresolved issues that require attention. Overall, significant advances in immunotherapy will be achieved through a greater understanding of these immune mechanisms and targeted interventions.

Combination with Phototherapy (PDT/PTT)

Phototherapy, which mainly includes PTT and PDT, has been applied to treat various tumors and has achieved certain curative effects. With active targeting and enhanced permeability and retention effects, nano photothermal transduction agents can selectively accumulate in tumors to reduce adverse reactions.[80,96,176] PTT converts NIR light energy into heat, causing a rapid increase in temperature within the target tissue, which can selectively kill local tumor cells.[177,178]

PTT can induce an ICD cascade reaction, which induces DCs maturation by releasing recognizable TAAs and DAMPs and further activates the immune response. In addition, PTT can improve the immunogenicity of tumor cells through photothermal effects; thus, PTT has become an important method for inducing in situ vaccines.[179] Mild PTT can also increase the permeability of T cells, effectively treat primary tumors, and inhibit tumor metastasis.[180] However, tumor cells develop thermal resistance by activating cytoprotective pathways during treatment.[181] Damaged tumor cells can dramatically increase glycolysis efficiency to produce sufficient ATP that promotes HSP synthesis, expression, and function.[182] HSPs can promote the repair of damaged proteins, thus compromising the efficacy of PTT.[182,183] Glycolysis inhibitors

overcome the thermal tolerance of PTT by blocking the energy supply of tumor cells. LM nanomaterials have a good photothermal conversion efficiency and low nonspecific toxicity. LM-loaded GOx and Ca^{2+} inhibit glycolysis and mitochondrial respiration, resulting in the substantial inhibition of ATP production and HSP expression and enhancing the tumor-killing effect of PTT.[143] Luo et al combined 2DG with Hauns-Met@M to treat tumors, 2DG blocked the energy supply by inhibiting glycolysis, significantly improved the sensitivity of tumor cells to PTT, and reversed heat tolerance.[68] At the same time, 2DG induced endoplasmic reticulum stress by inhibiting protein glycosylation, synergistically enhancing PTT-induced ICD, activating the immune response and inducing and enhancing long-term immune memory, which are conducive to the complete elimination of primary tumors. In addition, the heat generated through PTT can not only promote drug release from nanosystem but also improve enzyme activity and enhance metabolic immunotherapy.[98]

PDT promotes apoptosis via generating a large amount of cytotoxic ROS, thereby initiating the ICD cascade to enhance tumor immunogenicity and activate the immune response. However, the effectiveness of PDT is limited by immune resistance. Glycolytic regulators can reprogram the TIME and induce or promote ICD to activate the immune response. Therefore, researchers are highly interested in exploring the combined effects of these two approaches. For instance, pyropheophorbide-a can produce ROS and induce ICD under NIR irradiation. The nanoplatform HCJSP combined with JQ1 and pyropheophorbide-a improved the acidic and hypoxic TME by inhibiting HK2 and LDHA expression, and alleviated PDT-induced immune resistance.[103] Importantly, an appropriate light source, adequate photosensitizer and adequate O_2 are crucial factors for effective PDT.[184,185] However, the hypoxic nature of the TME significantly limits PDT efficacy. Liu et al constructed an automatic oxygen regulation nanomedicine (IR-LND@Alb) that could overcome this problem.[71] The photosensitizer IR-68 can be transported to mitochondria through organic anion transport peptides, and cooperate with LND to reduce the efficiency of OXPHOS by inhibiting mitochondrial complexes, thereby reducing endogenous oxygen consumption and enhancing the antitumor effect of PDT.[186] IR-LND@Alb NPs successfully inhibit HIF-a expression, reverse hypoxia, amplify ROS production, and promote tumor cell apoptosis and immune system activation.[71] In addition to reducing oxygen consumption, strategies to increase oxygen production have also been developed. Zhang et al designed self-oxygenated nanomaterials using Mn,Cu-doped CDs as a photosensitizer for PDT and promoted the endocytosis and retention of the NPs through the action of γ-PGA.[89] GOx oxidizes glucose to produce H_2O_2, which is catalyzed by Mn and Cu-CD to produce O_2. GOx and Mn,Cu-CD synergistically increased O_2 production and the singlet oxygen ($^1O_2$) content in tumors, greatly improving the efficiency of PDT. In conclusion, PTT/ PDT has overcome some shortcomings in the presence of nanotechnology and glycolysis regulators, showing broad application prospects. However, active explorations of more effective binding of NPs to PTT/PDT and glycolysis regulators are needed, including screening for photosensitizers, glycolysis targets and the design of nanosystem.

Combination with Other Therapies (SDT, CDT)

CDT can produce highly cytotoxic ·OH through Fenton or Fenton-like reactions in the presence of H_2O_2, independent of external stimuli or local O_2 levels.[187] Various nanomaterials that can catalyze Fenton reactions, such as FeS-GOx nanodots and gold NPs (Au@HMnMSNs), have been developed for targeted tumor therapy.[94,95] The Fenton reaction is more efficient under acidic conditions (pH 3.0–5.0), while a weakly acidic TME (pH 6.5–6.9) cannot fully increase the efficiency of the Fenton reaction.[188,189] Therefore, combination therapy with GOx and CDT can solve this problem effectively.[94,95,147,190] GOx catalyzes glucose to produce gluconic acid and H_2O_2, which not only provides a substrate for the Fenton reaction but also reduces the pH of the TME. This self-reinforcing Fenton reaction is sustainable and leads to robust ROS production, triggering an effective immune response via ICD. GOx starvation therapy combined with GOx-enhanced CDT is a highly effective antitumor strategy. LOx accelerates the Fenton reaction by oxidizing lactate to produce H_2O_2 and collaborates with CDT to promote tumor cell apoptosis.[191] Wang et al enhanced the efficacy of CDT by targeting lactate transport.[192] SiMCT-4 inhibited MCT4-mediated lactate efflux from cells through gene silencing, leading to a decrease in the intracellular pH and amplifying the tumor damage caused by CDT.

Nowadays, SDT has garnered significant attention due to the high tissue permeability and safety of ultrasound.[193] It activates and produces ROS via external ultrasound to induce tumor cell apoptosis.[194] Zhang et al designed a nanoplatform, PALF, that enhances SDT by regulating metabolism.[195] Under the action of the sonosensitizer PEG-Ce6 polyphenol, PALF significantly increased $^1O_2$ and cytotoxic ROS during ultrasound exposure, leading to therapeutic

cell death. LOx oxidizes lactate to reverse the immunosuppressive state and enhance SDT, while atovaquone improves the hypoxic TME by interfering with mitochondrial respiration to promote the effects of LOx and SDT. PALF activates an effective immune response, thereby inhibiting tumor proliferation and metastasis. Furthermore, the multifunctional metal–phenol nanomedicine HPP-Ca@GSK exerted synergistic antitumor effects on glucose metabolism and SDT.[79] GSK successfully reduced lactate levels by inhibiting LDHA, while ultrasound drove the sonosensitizer GIR780 to produce a large amount of ROS, which cooperated with calcium overload to induce mitochondrial damage. HPP-Ca @GSK increases the recruitment of effective immune cells and the secretion of proinflammatory cytokines and has good therapeutic effects on tumors. However, current research seems to focus more on how to generate excessive ROS to maximize its tumor-suppressive effect but less on the sustainability, drug resistance, and toxicity of ROS in normal cells.

Conclusions and Future Perspectives

Overall, the reprogramming of glucose metabolism in tumor cells plays a significant role in immunosuppression and immune evasion, thereby enabling these cells to better endure treatment-induced stress. Targeting glucose metabolism has the potential to reverse the TIME, enhance the efficacy of immunotherapy, and mitigate treatment resistance. In comparison to conventional pharmaceuticals, nanomaterials present several advantages: superior targeting capabilities, precise drug release mechanisms, enhanced permeability, and minimal adverse effects. The modulation of glucose metabolism through nanomaterials elicits a more pronounced anti-tumor immune response, positioning this approach as a promising strategy for cancer therapy. Furthermore, nanocarriers can simultaneously deliver drugs with diverse properties and therapeutic targets, facilitating synergistic and complementary effects across multiple therapeutic modalities while further augmenting anti-tumor efficacy.

Nevertheless, nanomaterials designed to target glucose metabolism for the enhancement of immunotherapy continue to face significant challenges. (1) the mechanisms underlying tumor development are highly complex; the metabolic network is intricately interconnected and exhibits considerable plasticity and flexibility, enabling tumor cells to potentially evade treatment through alternative metabolic bypasses. Furthermore, the administration of these drugs in humans may activate metabolic regulatory switches that disrupt normal cellular metabolic pathways, potentially leading to uncontrolled outcomes. This issue is particularly pronounced when drug targeting is suboptimal or when off-target effects result in unpredictable consequences. (2) While NPs can be sufficiently small to traverse physiological barriers for optimal tumor treatment, they also pose potential risks.[66] Studies have indicated that free radicals generated by NPs can inflict damage on cell membranes, organelles, and DNA.[196,197] Although current research suggests that nanomaterials do not exhibit greater toxicity than conventional drugs, their long-term biosafety and potential impacts remain inadequately assessed. Thus, further investigation into their transport mechanisms, metabolic processes, and transformation pathways is warranted. (3) Due to the inherent complexity of tumors, an increasing number of studies are opting for a combination of metabolic therapy with other treatment modalities that demonstrate superior outcomes compared to monotherapies.[76,145] However, whether such combinatorial approaches can achieve a synergistic effect remains questionable. Moreover, when integrating various targeted drugs into nanoparticle formulations, it is crucial to consider their properties and interactions in order to avert potential inefficiencies or adverse effects.

In summary, nanosystem target glucose metabolism to reprogram TIME, thereby reconfiguring the TIME and considerably enhancing the efficacy of immunotherapy. However, developing an optimal nanosystem presents a considerable challenge. (1) Primarily, it is crucial to select an appropriate nanocarrier that demonstrates high drug loading capacity, exceptional stability, and robust biocompatibility. Enhancing the drug loading capacity facilitates a reduction in the quantity of nanomaterials required, necessitating the selection of nanomaterials with high surface area-to-volume ratios while considering their physical and chemical properties. The modification of small molecules or the construction of biomimetic nanocapsules can avoid immune system clearance and enzyme degradation to improve their stability within circulation.[198,199] (2) Furthermore, strategies must be devised for the precise delivery of therapeutic agents to the tumor site; this may involve selecting targeted nanocarriers or modifying nanosystem with small molecules (hyaluronic acid, folic acid etc)., targeting peptides, antibodies, aptamers and cell membranes derived from various cell types.[76,85,92,200,201] Additionally, engineering nanosystem capable of disintegration under specific conditions—such as in the presence of high GSH or at acidic PH—can facilitate complete drug release within tumor cells for effective action.[135,202] (3) Leveraging the unique properties of

nanomaterials can significantly enhance therapeutic efficacy while minimizing required drug dosages. For instance, certain nanomaterials possess NIR or ultrasound stimuli responsive capabilities that allow for concurrent application of PTT, PDT or SDT.[79,98] Moreover, some nanomaterials exhibit catalytic functions—such as CAT and Fe^{2+}—which can convert O_2 to alleviate hypoxic conditions within tumors and initiate Fenton or Fenton-like reactions for improved anti-tumor effects through CDT.[93,94] (4) It is essential to select glycolysis inhibitors that have well-established efficacy and safety profiles. Initially, it is crucial to identify an appropriate glycolytic target, followed by developing a drug that demonstrates strong specificity towards this target. However, given that drugs may have potential adverse effects, innovative strategies could also involve silencing or editing genes associated with critical glycolytic enzymes.[81,82] (5) Ultimately, prioritizing the maximization of immune cascade activation and enhancement of immune responses is essential. This can be achieved by amplifying both the quantity and functionality of normal TME cells as well as immune cells through targeted glycolysis interventions. Furthermore, exploring various methods to induce ferroptosis, PDT, CDT, etc., can effectively trigger robust ICD and facilitate DAMPs release to promote antigen presentation.[78,95,103] Additionally, synergistic enhancement of immune responses and prolongation of anti-tumor immunity through adjunctive use of immune checkpoint inhibitors, antibodies and immune adjuvants represent viable strategies.[76,89,98] Nevertheless, in our pursuit of efficacy, it is essential to recognize that nanomaterials demonstrating enhanced superior properties and ease of synthesis are more likely to be integrated into clinical practice.

In summary, nanotechnology targeting glucose metabolism offers a revolutionary strategy for reprogramming TME and enhancing cancer immunotherapy. As research progresses, a deeper understanding of the role of glucose metabolism in tumor biology is expected to drive further innovation. We believe that continued research efforts will ultimately optimize nanosystem targeting glucose metabolism, thereby improving clinical anti-tumor therapy and benefiting patients.

Abbreviations

OH, Hydroxyl radicals; 1-MT, 1-methyltryptophan; $^1O_2$, Singlet oxygen; 2DG, 2-deoxyD-glucose; 3PO, 3-pyridine-1-(4-pyridine-2-propenyl-1-1); APA, Apatinib; CAFs, Cancer-associated fibroblasts; CDT, Chemodynamic therapy; Ce6, Chlorine e6; CpG ODN, Cytosine guanine dinucleotide oligodeoxynucleotide; CRT, Calreticulin; CTL, Cytotoxic T lymphocyte; CTLA-4, Cytotoxic T lymphocyte-associated antigen-4; DAMPs, Damage-associated molecular patterns; DCA, Dichloroacetate; DCs, Dendritic cells; DOX, Doxorubicin; EVs, Extracellular vesicles; F-6-P, Fructose 6-phosphate; FAO, Fatty acid oxidation; FCM, Flow cytometry; G-6-P, Glucose 6-phosphate; GLUTs, Glucose transporters; GOx, Glucose oxidase; GSH, Glutathione; GSK, GSK2837808A; HCPT, Hydroxycamptothecin; HIF1α, Hypoxia-inducing factor 1α; HK2, Hexokinase 2; HMGB1, High mobility group protein B1; $HMnO_2$, hollow manganese dioxide; HPB, Hollow Prussian blue; HSP, Heat shock protein; ICB, Immune checkpoint blocking; ICD, Immunogenic cell death; IDO, Indoleamine 2,3-dioxygenase; Kyn, kynuridine; LDH, Lactate dehydrogenase; LM, Liquid metal; LND, Lonidamine; LOx, Lactate oxidase; MCT, Monocarboxylic acid transporter; MDSCs, Myeloid-derived suppressor cells; MHC, major histocompatibility complex; MOF, Metal–organic framework; mTOR, Mammalian target of rapamycin; mPDA, Pegylated mesoporous polydopamine; MSNs, Mesoporous silica nanoparticles; NIR, Near-infrared; NK, Natural killer; NPs, nanoparticles; NVs, Nanovesicles; OXPHOS, Oxidative phosphorylation; PAE, Polyβ-amino ester; PD-1, Programmed death-1; PD-L1, Programmed cell death 1 ligand 1; PDH, pyruvate dehydrogenase; PDK, Pyruvate dehydrogenase kinase; PDT, Photodynamic therapy; PEI, Poly (ether imide); PFK, Phosphofructokinase; PFKFB3, Fructose-2-kinase 6-phosphate/fructose-2, diphosphatase 3; P-gp, P-glycoprotein; PK, Pyruvate kinase; PKM2, Pyruvate kinase-M2; PTT, Photothermal therapy; PTX, Paclitaxel; ROS, Reactive oxygen species; RT, Radiotherapy; SDT, Sonodynamic therapy; SK, Shikonin; TAAs, Tumor-associated antigens; TAMs, Tumor-associated macrophages; TCA, Tricarboxylic acid; Teffs, Effector T cells; TIME, Tumor immunosuppressive microenvironment; TME, Tumor microenvironment; Tregs, Regulatory T cells; Trp, Tryptophan; TPP+, triphenylphosphine cations; UPS, Ultra-pH-sensitive; ZIF-8, Zeolitic imidazolate framework-8.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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