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REVIEW

Glucose Metabolism Intervention-Facilitated Nanomedicine Therapy

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Abstract: Ordinarily, cancer cells possess features of abnormally increased nutrient intake and metabolic pathways. The disorder of glucose metabolism is the most important among them. Therefore, starvation therapy targeting glucose metabolism specifically, which results in metabolic disorders, restricted synthesis, and inhibition of tumor growth, has been developed for cancer therapy. However, issues such as inadequate targeting effectiveness and drug tolerance impede their clinical transformation. In recent years, nanomaterial-assisted starvation treatment has made significant progress in addressing these challenges, whether as a monotherapy or in combination with other medications. Herein, representative researches on the construction of nanosystems conducting starvation therapy are introduced. Elaborate designs and interactions between different treatment mechanisms are meticulously mentioned. Not only are traditional treatments based on glucose oxidase involved, but also newly sprung small molecule agents targeting glucose metabolism. The obstacles and potential for advancing these anticancer therapies were also highlighted in this review.

Keywords: nanomedicine, starvation therapy, combined therapy, cancer metabolism

Introduction

As one of the most threatening health risks, cancer causes tens of millions of new cases and deaths each year.[1] Moreover, the incidence, and mortality of cancer are rising rapidly worldwide.[2] However, traditional oncology treatments, including surgical excision, chemotherapy, and radiotherapy, cannot eradicate malignancies.[3,4] Tumor metastasis and recurrence remain the major reasons for unfavorable prognosis, in which tumor metabolism displays an immense role.

Starvation therapy (ST) deprives critical nutrients and intervenes in tumor metabolism. It has gained the attention of scientists as an emerging treatment in past years. Malignant cells demand additional rates of catabolite absorption, transport, and usage than their normal counterparts. They remodel their metabolism to promote growth, proliferation, and even metastasis.[4,5] Since curing heterogeneous cancers based on distinctive genetic mutations has been proven to be complex and challenging, targeting the common metabolism phenotype shared by tumors is considered an extensive and sensitive anticancer strategy.[6]

The leading metabolic disorder is the Warburg Effect, indicating that cancer cells prefer aerobic glycolysis even when there is enough oxygen to maintain mitochondrial oxidative phosphorylation.[7] During the procedure, the uptake of glucose and lactate generation increased. This effect not only accelerates the pace of synthesizing adenosine triphosphate (ATP)[5] and anabolic processes[8] but also remodels the tumor microenvironment through H^+ ions.[9] Targeting glucose metabolism may gain major therapeutic benefits since glucose is the most abundant nutrient in circulation and the most frequent metabolic substrate utilized by malignant cells.[10] The restriction of key metabolic steps or the deprivation of intracellular glucose probably avoid the downregulation of mitochondrial aerobic respiration, block NADPH generation, and interrupt pentose phosphate synthesis, inhibiting tumor development.[11] Several medicines that target glycolytic

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enzymes and transporters are being investigated in preclinical investigations and clinical trials.[12,13] The brief glucose metabolism pathway and agents referred to in this review are shown in Figure 1.

Although ST has distinct advantages, several obstacles limit further clinical application. Different agents targeting glucose metabolism have their own limitations. For example, most small molecular drugs display poor solubility and short half-life, which limit their therapeutic efficacy.[14] Glucose oxidase (GOx) would be degraded by proteinase during circulation.[15] Meanwhile, despite malignant cells being profiled with a higher rate of metabolism, normal tissues share similar metabolic pathways. The off-target effect probably causes systemic adverse reactions. Immune cell differentiation would be impeded as well.[16] Besides, the compensation of other metabolites would lead to drug resistance to targeting a single nutrient and restrict the efficacy.[6,17] To address these concerns, nanomaterials have been constructed to facilitate ST.

Nanotechnology-assisted treatment techniques have received a great deal of interest in recent years. Employing the tumor-specific antigens[18] or specific cell membranes,[19] nanomedicines are able to accumulate in malignant regions to reduce systemic toxicity. Various material systems have been applied to optimize delivery efficiency,[20] improve targeting efficacy,[21] overcome biological barriers,[22] and increase the half-life of therapeutics.[23] More intriguingly, nanotechnology enables the simultaneous administration of multiple therapeutic agents for synergistic therapy. The pharmacodynamics and pharmacokinetics of diverse drugs can be coordinated in a nanodrug, thus increasing the therapeutic impact. Novel therapeutic alternatives based on the development of nanotechnologies, such as photothermal therapy (PTT),[24] photodynamic therapy (PDT),[25] chemodynamic therapy (CDT),[26] sonodynamic therapy (SDT),[27] and immunotherapy,[28] have popped up like mushrooms, offering a ray of hope in the fight against cancer. These benefits make up for the drawbacks of conventional ST intervention.

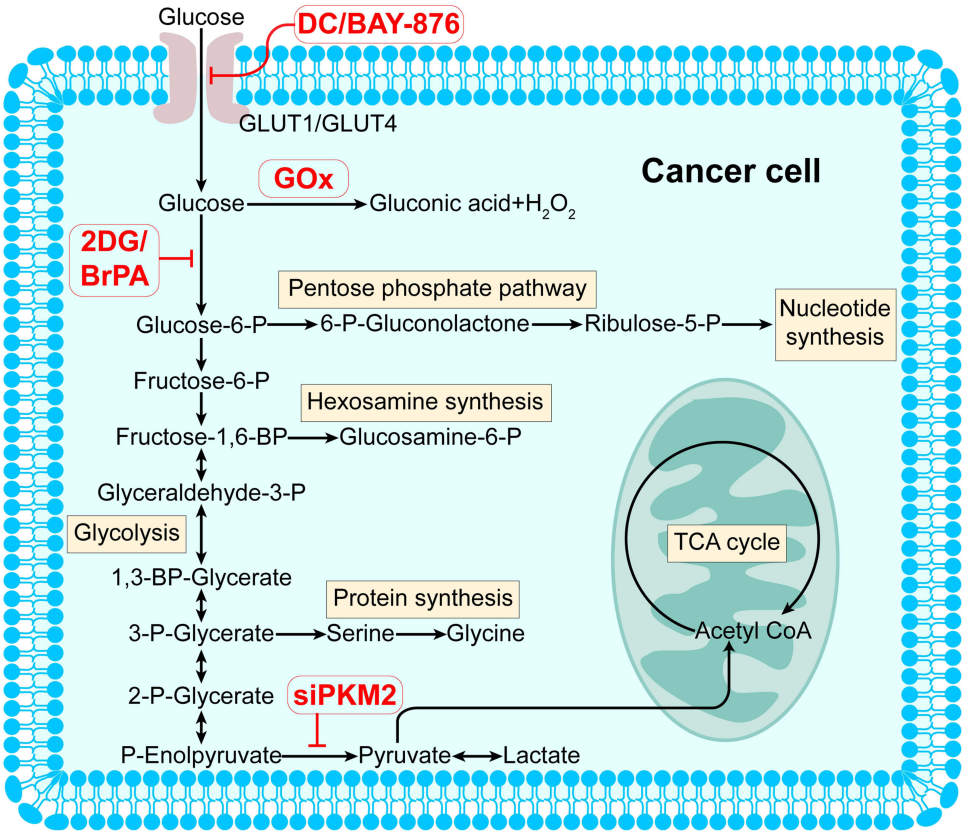

Figure 1 Glucose metabolism adaptation in cancer cells and drugs targeting glucose metabolism processes that included in the review. Malignant cells exhibit high anabolic rates. They prefer consuming large amounts of glucose for energy supplement and synthesis of biological essentials, including nucleotides, amino acids, and lipids. Agents disrupting glucose metabolism are predicted to result in a lack of energy and resources required for cell proliferation, leading to the death of neoplasm cells.
Abbreviations: DC, diclofenac; BAY-876, an inhibitor for glucose transporter 1; GLUT, glucose transporter; GOx, glucose oxidase; 2DG, 2-deoxy-d-glucose; BrPA, bromopyruvate; H_2O_2, hydrogen peroxide; siPKM2, an siRNA against pyruvate kinase isozyme M2; TCA cycle, tricarboxylic acid cycle; CoA, coenzyme A.

Here, we looked at studies that included methods consuming glucose[29] or limiting glucose uptake[30] and anabolic processes (Figure 2).[31] Interventions on glucose metabolism without the use of GOx that are rarely mentioned before are also involved. The design concepts of these formulations, as well as their anticancer effects, are highlighted.

Mechanisms of Agents Targeting Glucose Metabolism

Malignant cells tend to increase the import and usage of glucose to synthesize ATP rapidly. Moreover, the metabolic products from aerobic glycolysis can further flue the tricarboxylic acid cycle and the pentose phosphate pathway. Glucose metabolism is involved in the synthesis of hexosamine, amino acids, as well as lipids.[6] As the most prominent and well-studied metabolic disorder, glucose metabolism has been targeted by lots of agents. Enzymes, small molecule drugs, and even siRNAs have been applied in glucose metabolism blockage.

The most widely utilized molecule to block glucose metabolism is GOx. It serves as an efficient biocatalyst for the oxidation of glucose to gluconic acid and hydrogen peroxide (H_2O_2) with the assistance of oxygen (O_2),[32] as shown in the following reaction:

$$\text{Glucose} + O_2 + H_2O \xrightarrow{\text{GOx}} \text{Gluconic acid} + H_2O_2$$

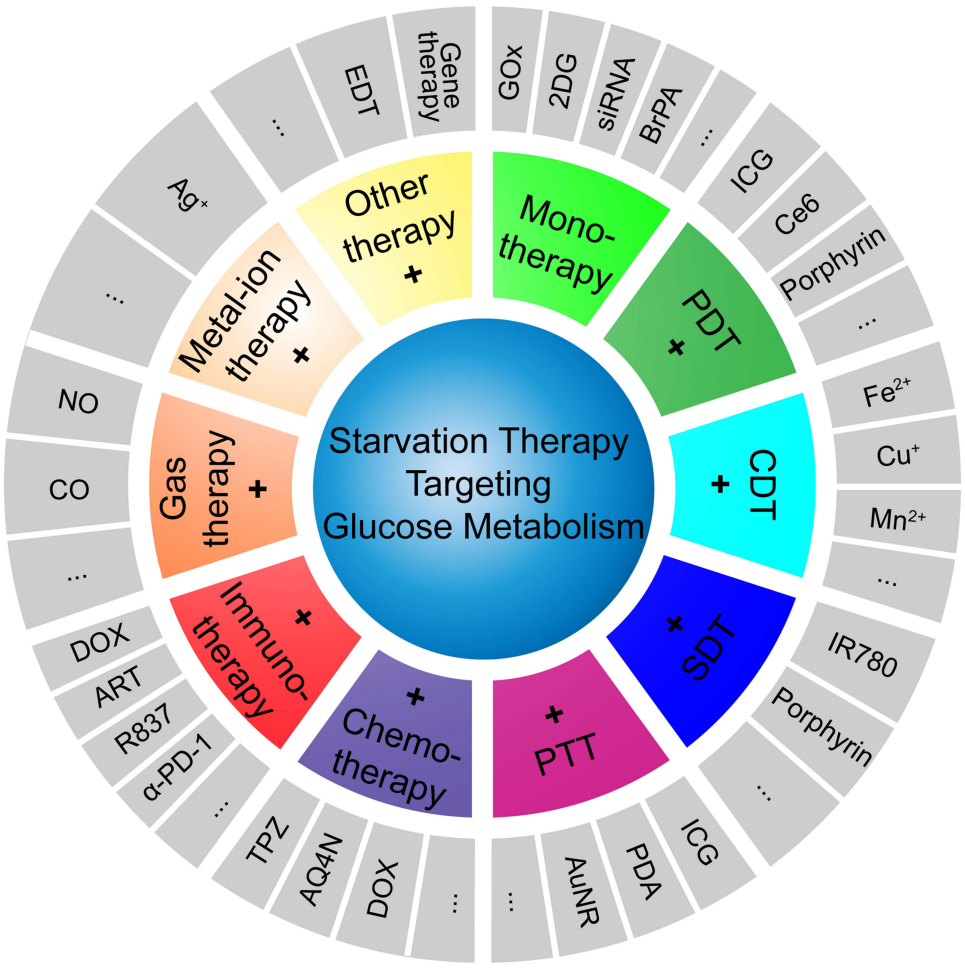

Figure 2 Schematic illustration of nanomaterial-assisted cancer starvation therapy targeting glucose metabolism.

Abbreviations: PDT, photodynamic therapy; CDT, chemodynamic therapy; SDT, sonodynamic therapy; PTT, photothermal therapy; GOx, glucose oxidase; 2DG, 2-deoxy-d-glucose; siRNA, small interfering ribonucleic acid; BrPA, bromopyruvate; ICG, indocyanine green; Ce6, chlorene6; IR780, a heptamethine cyanine molecule; PDA, polydopamine; AuNR, gold nanorod; DOX, doxorubicin; AQ4N, banoxantrone dihydrochloride; TPZ, tirapazamine; α-PD-1, anti-programmed death protein 1, an immune checkpoint-blocking antibody; R837, an immunostimulatory; ART, artemisinin; CO, carbon monoxide; NO, nitric oxide; EDT, electrodynamic therapy.

By depleting glucose in the tumor area, tumor cells would thus be devoid of nutrients, grow slowly, or even die. Aside from starving tumor cells, GOx has the potential of increasing acidity, hypoxia, and H_2O_2 level in the tumor microenvironment (TME). Several nanodrugs made up of components responding to specific environments have been constructed using this property.

Besides GOx, there are plenty of drugs interfering with glycolysis under investigation,[6] which target glucose transporter 1 (GLUT1), pyruvate kinase isozyme M2 (PKM2), hexokinase (HK), 6-phosphofructo 2-kinase-fructose-2,6-biphosphatase 3 (PFKFB3) and so on.[13,33] As the initial stage in cellular glucose metabolism, GLUT1 possesses the ability to transfer glucose into cells for subsequent reactions.[34] It has also been considered an ideal biomarker for solid tumor prognosis and survival.[35] Therefore, blocking GLUT1 by diclofenac or BAY-876 can greatly reduce the amount of glucose available in tumor cells. In addition to GLUT1, HK has been targeted by several nanomaterials as well. Catalyzing the conversion of glucose to glucose-6-phosphate, the rate-limiting process in glycolysis, HK is crucial in sustaining the high glucose catabolic rate required for tumor cells to flourish.[36] Pharmacological suppression of HK2 inhibits tumor development and restores tumor cell sensitivity to therapies.[37] Some pharmaceuticals have been included in nanomaterials to interrupt the function of HK, such as 2-deoxy-d-glucose (2DG)[38] and bromopyruvate.[39] Even small interfering ribonucleic acid (siRNA) targeting PKM2 has been utilized to sabotage glycolysis by knocking down PKM2, which is overexpressed in rapidly proliferating cancer cells.[40] PKM2 is regarded to be crucial not only in producing ATP and pyruvates but also in regulating the expression of genes involved in multiple steps of cell survival.[41] Inhibition of this enzyme potentially brings about novel glycolysis inhibition concepts by altering metabolic flux. To sum up, the applications of distinctive medications disrupting glucose metabolism have made the field bloom (Table 1).

Monotherapy Targeting Glucose Metabolism

A great many nanodrugs have been developed for glucose-based starvation monotherapy. A number of nanosystems carrying GOx have been synthetized to enhance ST by avoiding hazardous side effects and preventing degradation by proteinases.[42–44] To ensure long-lasting catalytic activity, Yang et al devised a nanovehicle to load GOx coordinated with folic acid and Zn^{2+} termed GOx@PDA.[45] The nanodrug was further modified with a polydopamine (PDA) shell. Because of the protection of the PDA shell, GOx in the core was prevented from passing through the capsule membrane, while free glucose substrates could be transported. Therefore, even under harsh conditions, GOx activity was maintained. Furthermore, the authors incorporated GOx@PDA with microneedles (MNs) made of hyaluronic acid (HA) and polyvinylpyrrolidone, which allowed GOx@PDA to penetrate the skin for precise delivery to melanoma. Interestingly, the in vivo inhibition ratio of mice bearing B16F10 tumors was up to 91%.

Unfortunately, ST alone may induce medication resistance for elevated hypoxia or the supplementary of other metabolic pathways.[46] Autophagy triggered by metabolizing pressure is another factor weakening starvation therapy efficacy.[47] To inhibit that, several autophagy inhibitors have been applied in nanomedicine.[48,49] A nanoparticle co-delivering GOx and the autophagy inhibitor 3-methyladenine (3-MA) has been reported.[50] Aside from GOx, a variety of medicines that interfere with glycolysis are being investigated. Yang et al synthesized black phosphorus (BP)-based 2D nanosheets modified with polyethylene glycol (PEG)-NH_2 (Figure 3).[38] Regrettably, instead of loading 2DGs on BPs, the two substances were administered separately. The extracellular lactate produced by glycolysis was dramatically reduced as a result of competitively restricting glucose absorption by GLUT1 and noncompetitively decreasing glucose phosphorylation by HK.[51] The levels of lactate dehydrogenase A (LDHA), HK2, and MYC were lowered, and the ATP level was cut in half. The antineoplastic impact on tumor-bearing mice was considerable, owing to the restriction of lysosomal degradation and autophagic flux driven by BP nanosheets and ST. If BP nanosheets were to be employed as carriers as in other articles,[52] follow-up research to adjust the ratio of 2DGs to BPs and load 2DGs onto BP nanosheets would likely boost the treatment efficiency even more.

Combined Therapy Targeting Glucose Metabolism

Although several nanomedicines conducting ST alone achieved curative effect, it is a pity that ST alone is difficult to eliminate the tumor. The abundant capillary supplying glucose and other nutrients compensating for the lack of glucose metabolism would result in poor efficacy and drug resistance.[46] Besides, combined therapy is known to minimize

Table 1 Summary of Nanodrugs Targeting Glucose Metabolism

Therapies	Drugs Used for Starvation Therapy	Other Synergistic Therapeutic Agents	Ref.
Starvation therapy	GOx	–	[43–45]
		MnO_2	[199]
		Met	[42,200]
		3-MA	[50]
	siPKM2	-	[40]
	2DG	BP nanosheets	[38]
	BrPA	-	[39]
Starvation therapy/ photodynamic therapy	GOx	Porphyrin; CAT	[99,101]
		PCN-224; CAT	[100]
		Ce6	[96]
		Ce6; CeO_2	[201]
		Ce6; MnO_2	[94,95,97]
		ICG; $DMMnSiO_3$	[202]
		ICG; Fe-PDAP	[140]
		UCNP	[106]
		MnPc	[203]
		Ce6; CPPO; PFC	[104]
Starvation therapy/ chemodynamic therapy	GOx	Fe_3O_4	[112]
		Fe^{3+}- and tannic acid MPN	[111]
		Hb	[204]
		Ferrocene	[205]
		Pd@Pt nanosheets	[206]
		Ferric MOF	[110]
		Cu	[207]
		Cu^{2+}; TCPP; MnO_2	[208]
		$Cu_{2-x}Se$	[209]
		FePt; MnO_2	[210]
		Fe^{2+}/Fe^{3+}; perfluoropentane	[211]
		Fe_3O_4; PFC	[109]
		$Fe(OH)_3$; CaO_2	[29]
		Fe_3O_4; MnO_2	[84]
Starvation therapy/ sonodynamic therapy	GOx	HMME; IR780	[122]
		PCN-224; Pt	[126]
		PMnC	[123]
		HMME; CAT	[124,125]
Starvation therapy/ photothermal therapy	GOx	PB	[212]
		Gallium Indium eutectic liquid metal	[137]
		ICG	[213]
		Melanin; MnO_2	[136]
		Bi_2Se_3; PFC	[135]
		PDA; CQ	[134]
		AuNR	[133]
	DC	AuNR	[151]
	siPKM2	ICG	[155]
	2DG	DPQ	[31]

(*Continued*)

Table 1 (Continued).

Therapies	Drugs Used for Starvation Therapy	Other Synergistic Therapeutic Agents	Ref.
Starvation therapy/ chemotherapy	GOx	TPZ	[23,68,70,214,215]
		TPZ; CAT	[69]
		AQ4N	[71,72]
		DOX	[64]
		BDOX	[74]
		pDOX; Pd nanoparticles	[73]
		PTX	[61,216]
		CPT; MnO_2	[217]
	2DG	DOX	[65]
	BAY-876	DOX-Duplex	[30]
Starvation therapy/ gas therapy	GOx	L-Arg	[167,198]
		L-Arg; MnO_2	[165,166]
		Mn(CO)	[169,218]
Starvation therapy/ metal-ion therapy	GOx	AgNPs; ZIF-8	[175]
		AgNPs	[219]
Starvation therapy/ gene therapy	GOx	RTP801::p53	[177]
Starvation therapy/ electrodynamic therapy	GOx	pPt	[178]
Starvation therapy/ photodynamic therapy/ chemodynamic therapy	GOx	Ce6; MnO_2	[102]
Starvation therapy/ photodynamic therapy/ photothermal therapy	GOx	IR780	[139]
		MB; MnO_2	[138]
		ICG; CAT	[98]
		CPPO; ferric ion-linked porphyrin-MOF	[105]
Starvation therapy/ chemodynamic therapy/ chemotherapy	GOx	Pt; FcNV	[67]
		DOX; Mn	[63]
		Fe_3O_4; PTL	[220]
		Mil-101 (Fe); DOX	[119]
		Ferrocene; camptothecin prodrug	[75]
		Ferrocene; BA prodrug	[118]
Starvation therapy/ chemodynamic therapy/ photothermal therapy	GOx	TA; FeS_2	[221]
		NC	[222]
		$SrCuSi_4O_{10}$	[116]
		PB; MnO_2	[223]
		Hb; Fe^{3+}; PDA	[113]
		CuS	[114]
		$Cu_{3+x}(PO_4)_2$	[224]
Starvation therapy/ chemodynamic therapy/ magnetic hyperthermia therapy	GOx	HIONCs	[115]
Starvation therapy/ chemodynamic therapy/ sonodynamic therapy	GOx	Fe-MIL-88B-NH2; PFC-1	[117]
Starvation therapy/ chemodynamic therapy/ immunotherapy	GOx	IONP; ART	[85]
		Cu	[86]
Starvation therapy/ photothermal therapy/ chemotherapy	GOx	ICG; DOX; EGCG; IO	[143]
		PDA; TPZ	[142]
	GOx; Siram	PDA; DOX	[144]
Starvation therapy/ photothermal therapy/ immunotherapy	GOx	Au; R837	[146]
		$Cu_{0.3}Co_{2.7}O_4$; α-PD-1	[225]

(*Continued*)

Table 1 (Continued).

Therapies	Drugs Used for Starvation Therapy	Other Synergistic Therapeutic Agents	Ref.
Starvation therapy/ photothermal therapy/ gas therapy	GOx	BP nanosheets; MnO_2; L-Arg	[145]
Starvation therapy/ chemotherapy/ metal-ion therapy	GOx	TPZ; AgNPs	[173]
Starvation therapy/ chemodynamic therapy/ chemotherapy/ metal-ion therapy	GOx	TPZ; Fe^{3+}- and tannic acid MPN	[120]
Starvation therapy/ chemodynamic therapy/ chemotherapy/ immunotherapy	AuNP	Mn^{2+}; DOX; ASA	[90]

Abbreviations: GOx, glucose oxidase; Met, metformin; 3-MA, 3-methyladenine; siPKM2, an siRNA against pyruvate kinase M2 isoform; 2DG, 2-deoxy-d-glucose; BP, black phosphorus; BrPA, bromopyruvate; CAT, catalase; PCN-224, a kind of porphyrin metal-organic framework; Ce6, chlorene6; ICG, indocyanine green; DMMnSiO3, (Mn)-etched dendritic mesoporous silicon; Fe-PDAP, Fe-doped polydiaminopyridine; UCNP, upconversion nanoparticle; MnPc, manganese phthaleincyanide; CPPO, bis[2,4,5-trichloro-6-(pentyloxycarbonyl)phenyl] oxalate; PFC, perfluorohexane; MPN, mental polyphenol network; Hb, hemoglobin; MOF, metal-organic frameworks; TCPP, tetrakis(4-carboxy phenyl)porphyrin; HMME, hematoporphyrin monomethyl ether; IR780, a heptamethine cyanine molecule; PMnC, Mn(5,10,15,20-tetrakis (4-chlorophenyl) porphyrin)Cl; PB, prussian blue; CQ, chloroquine; AuNR, gold nanorod; DC, diclofenac; DPQ, a narrow-bandgap conjugated polymer synthesized by diketopyrolopyrrole and triazole [4,5-g]-quinoxaline; TPZ, tirapazamine; AQ4N, banoxantrone dihydrochloride; DOX, doxorubicin; BDOX, a hydrogen peroxide-activatable prodrug of doxorubicin; pDOX, an acidic environment-activatable prodrug of doxorubicin; PTX, paclitaxel; CPT, camptothecin; BAY-876, an inhibitor for glucose transporter 1; DOX-Duplex, an adenosine triphosphate-activatable doxorubicin stored in DNA; L-Arg, L-arginine; Mn(CO), manganese carbonyl; AgNP, silver nanoparticle; ZIF-8, zeolitic imidazolate framework-8; RTP801::p53, a hypoxia-activatable p53 plasmid; pPt, porous platinum nanospheres; MB, methylene blue; FcNV, ferrocene-containing nanovesicle; PTL, parthenolide; Mil-101 (Fe), a nanocarrier containing iron; BA, betulinic acid; TA, tannic acid; NC, nitrogen-doped carbon; PDA, polydopamine; HIONC, hollow iron oxide nanocatalyst; Fe-MIL-88B-NH2, a metal-organic framework with the catalytic activity of the Fenton-like reaction and served as the template of the nanoparticle; PFC-1, a hydrogen-bonded organic frameworks with drug release effect and photodynamic capacity; INOP, mesoporous iron oxide nanoparticles; ART, artemisinin; EGCG, (-)-epigallocatechin-3-gallate; IO, iron oxide; Siram, siramesine; R837, an immunostimulatory; α-PD-1, anti-programmed death protein 1, an immune checkpoint-blocking antibody; AuNP, gold nanoparticle; ASA, aspirin.

medicine dosage, reduce drug toxicity, and boost effectiveness.[53] Therefore, it is reasonable to combine ST with other treatment modalities.

Chemotherapy Based on Glucose Metabolism Intervention

Chemotherapy, as a traditional therapeutic approach, has proven to be beneficial in healing most human malignancies. Chemotherapy significantly extended the survival time of patients with specific chemosensitive tumors. Serving an essential role as adjuvant treatment combined with radical local treatments, the characteristics of chemotherapy are expanding and widely applied.[54,55] Nevertheless, it is challenging to cure tumors using chemotherapy individually due to a variety of factors, including the multidrug resistance (MDR) effect.[56] Additionally, chemotherapeutic side effects arising from nonselective cytotoxicity on normal cells are a barrier.[57] Hence, synergistic therapies are desired to improve chemotherapy therapeutic efficacy while lowering toxic side effects. Starvation could sensitize certain malignant cells to chemotherapy, probably because of attenuated chemoresistance, while switching normal cells to a defensive mode.[58,59] Although fasting has been used in conjunction with chemotherapy in clinical studies, intolerability and nonspecificity might impede its further applications.[60] To cope with this, platforms incorporating starvation agents and chemotherapeutic medicines have been devised.[61–64] Lately, Yang et al designed Lip-(2DG+DOX) to co-encapsulate 2DG and doxorubicin (DOX) hydrochloride (Figure 4).[65] Cancer cells, such as HeLa, 4T1, and B16 cells, were considerably injured by the pharmacological action of 2DG and DOX, resulting in mitochondrial depolarization and an increase in reactive oxygen species (ROS), but normal cells were less impacted. The differential metabolism-regulated pathways increased tumor mortality while sparing other tissues. What is more intriguing is that limiting glucose metabolism potentially helped with MDR by reducing medication efflux via P-glycoprotein (P-gp), an ATP-binding cassette transporter.[66] The concrete mechanism of conquering MDR was reported by Chen et al, engineering a nanovesicle containing ferrocene, GOx, and Pt (GOx&Pt@FcNV).[67] The therapeutic technique reduced the expression of P-gp by about 41%, which led to improved therapeutic efficacy. It illustrated that combining a chemotherapeutic medication with

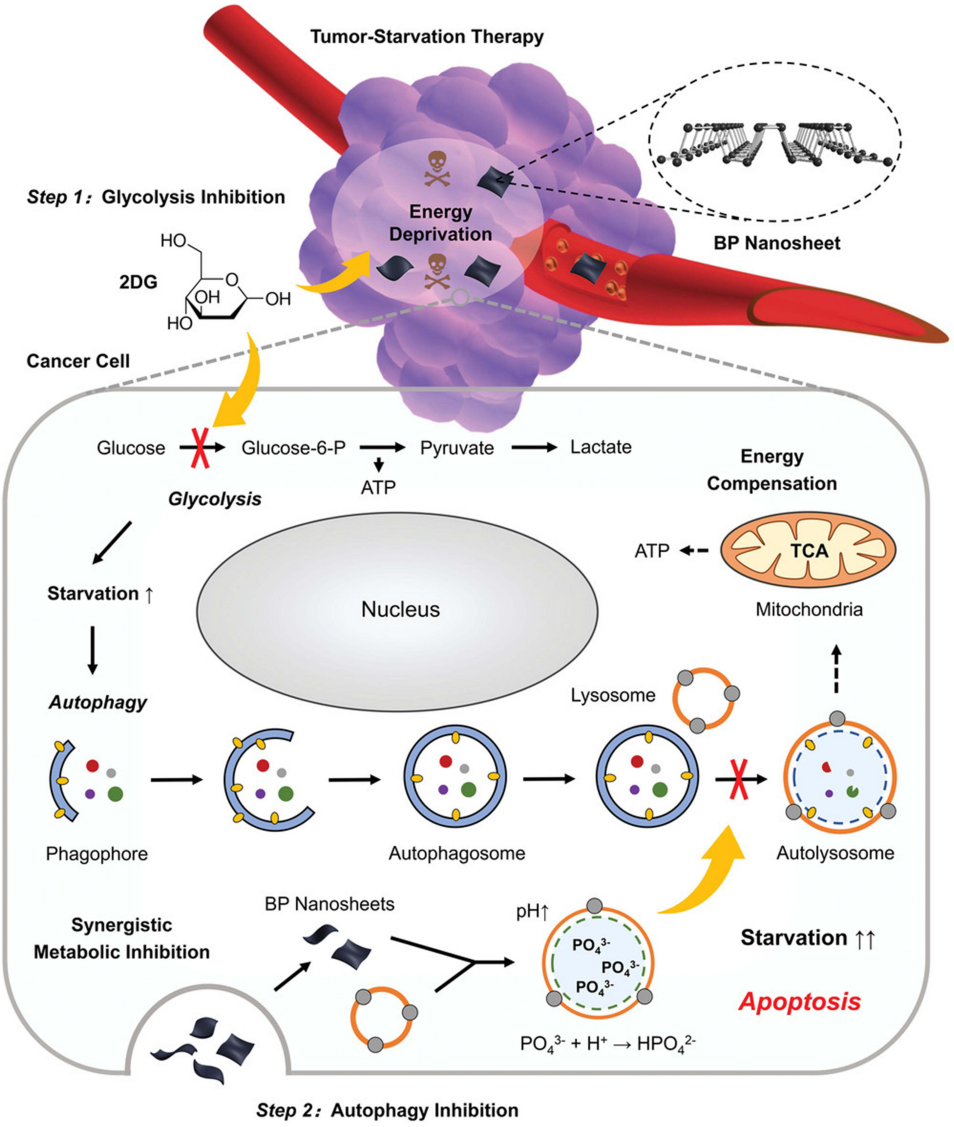

Figure 3 Schematic illustration for the mechanism of autophagy inhibition-augmented tumor-ST. Step 1: 2DG is applied to restrain glycolysis and initiate severe starvation of cancer cells. Step 2: BP nanosheet inhibits downstream protective autophagy, cuts off the compensatory nutrition supply and finally promotes apoptosis. Reproduced with permission from: Yang B, Ding L, Chen Y, Shi J. Augmenting Tumor-Starvation Therapy by Cancer Cell Autophagy Inhibition. *Adv Sci (Weinh)*. 2020;7(6):1902847. doi:10.1002/advs.201902847.[38] Copyright 2020 The Authors. Creative Commons Attribution License.

suppression of the MDR mechanism could result in considerable cytotoxicity. In these nanosystems, the role of drugs regulating glucose metabolism was eye-catching and irreplaceable.

Apart from MDR, starvation therapy is capable to induce prodrug-to-drug conversion for spatiotemporal precision. Several prodrugs have been identified, such as hypoxia-activated tirapazamine (TPZ)[68–70] and banoxantrone dihydrochloride (AQ4N),[71,72] pDOXs responding to acid,[73] and BDOX responding to H_2O_2.[74] In addition to generating products because of the distinctive environmental characteristics aggravated by GOx, prodrugs reacting with the original tumor microenvironment for precise release have been advanced.[75] By analogy, DOX-Duplex formed by loading DOX in deoxyribonucleic acid (DNA) segments enabled DOX to release in the presence of external ATP. Fortunately, ATP was overexpressed in tumor tissues for a high degree of anabolic processes. On account of the properties of DOX-Duplex, Jiang et al established a nanomedicine named BAY-876@(mPEG-SS-PEI-DSPE-DOX-Duplex) (short for P-B-D), delivering DOX-Duplex and BAY876 rationally (Figure 5).[30] The carrier, polyethylene glycol-disulfide bond-polyethylenimine-1,2-Distearoyl-sn-glycero-3-phosphoethanolamine, was manufactured with disulfide bonds reacting with

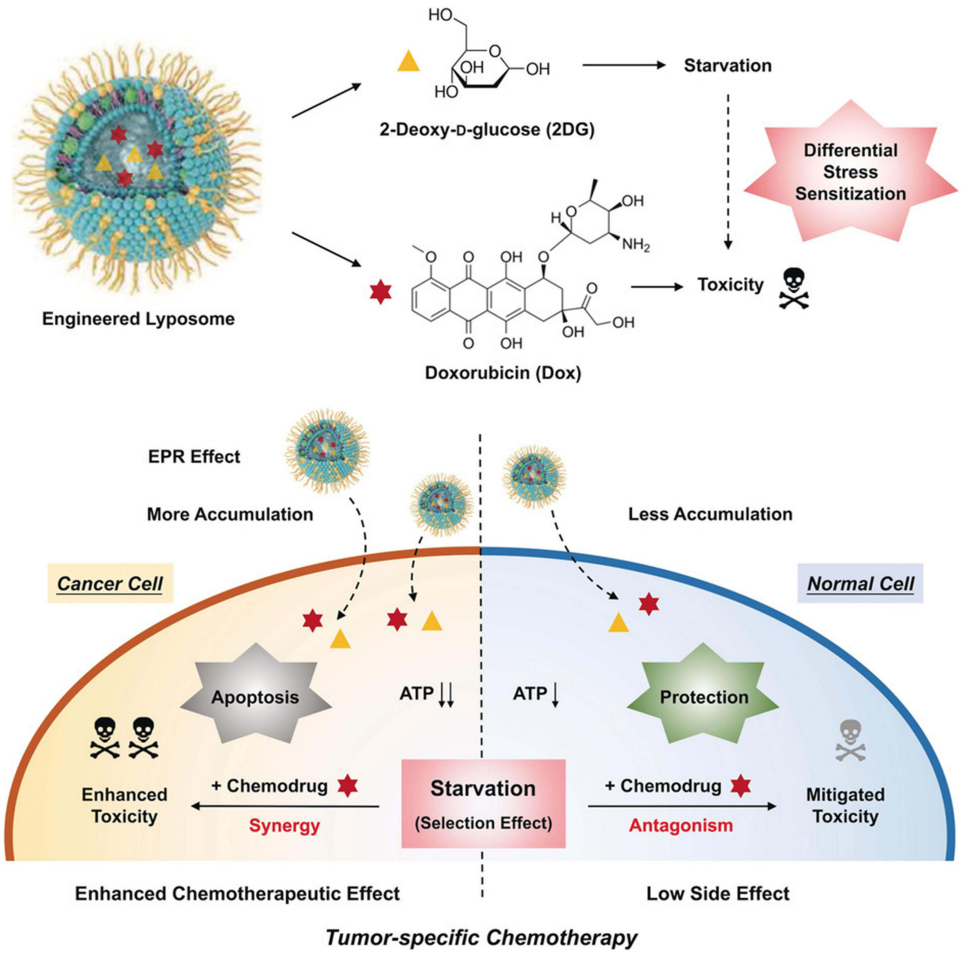

Figure 4 Schematic illustration of engineered liposome nanomedicines and their interaction with cancer cells and normal cells enabling differential stress sensitization of chemotherapy. Reproduced with permission from: Yang B, Chen Y, Shi J. Tumor-Specific Chemotherapy by Nanomedicine-Enabled Differential Stress Sensitization. *Angew Chem Int Ed Engl.* 2020;59(24):9693–9701. doi:10.1002/anie.202002306.[65] Copyright 2020, Wiley-VCH.

glutathione (GSH), leading to GSH deprivation and TME-triggered discharge of cargos. The double guarantee of ATP and GSH activation ensured precious release and minimal DOX side effects. As a chemical that inhibits GLUT1, BAY876 substantially reduced glucose absorption. The intracellular ATP level was reduced for at least 72 hours after one dose of DOX-Duplex therapy by depleting previously created ATP and preventing de novo production. Therefore, 4T1 cells underwent ferroptosis while normal tissues suffered little.

Immunotherapy Based on Glucose Metabolism Intervention

Immunotherapy, defined as harnessing antitumor immune responses to recognize and attack cancer cells, has been a fundamental strategy in a variety of solid and hematologic malignancies. Various types of immunotherapies, including cytokine therapy, adoptive cell therapy, checkpoint inhibitors (ICIs), oncolytic viruses, and cancer vaccines, have been developed.[76,77] While manipulating the immune system to reactivate the antitumor immune response, immunotherapy has its own set of side effects.[78,79] Moreover, the limited population benefited from checkpoint inhibitor-based immunotherapy restrictions its wider applications.[80] ST has brought about a novel method to enhance the efficiency of immunotherapy with other agents.

Another impediment to effective immunotherapy is the intrinsic immunosuppressive TME, including anti-inflammatory and protumor M2 macrophages secreting immunosuppressive cytokines.[81,82] Fortunately, ROS have been proven to repolarize tumor-associated macrophages (TAMs) from the M2 phenotype to the tumoricidal M1 phenotype.[83] As an agent to induce ROS, GOx has been included in nanodrugs to remodel the TME and promote immune reactivity.[84,85]

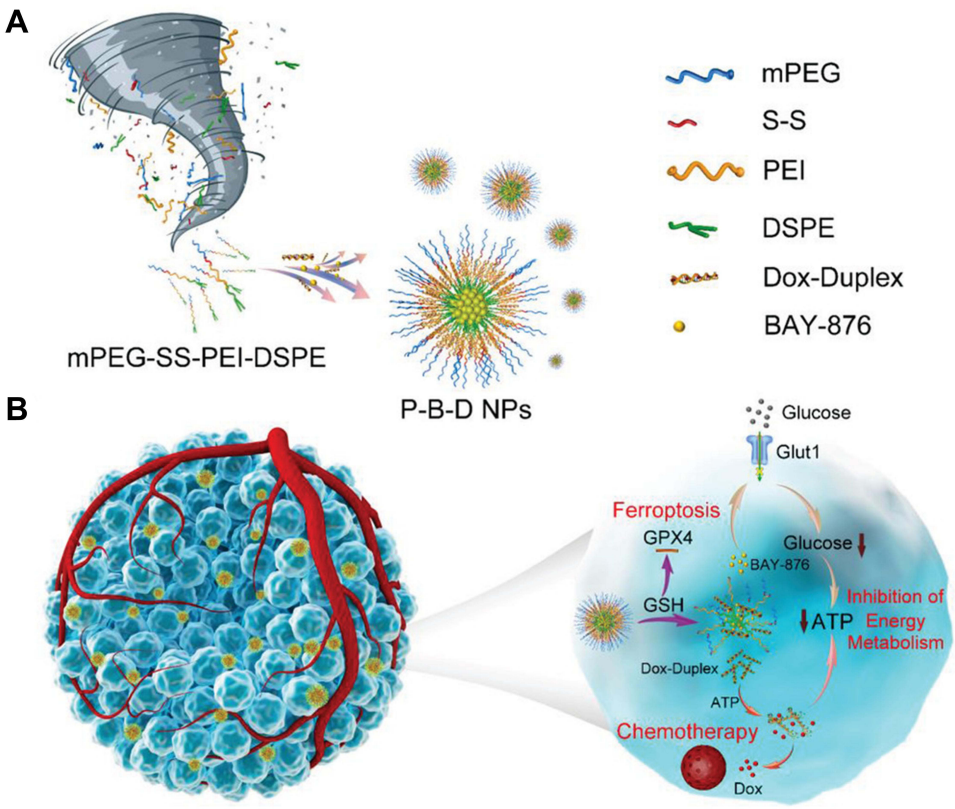

Figure 5 (**A**) Schematic illustration of the structure of P-B-D NPs. (**B**) Schematic illustration of the anti-tumor mechanism for synergistic ST/chemotherapy. Reproduced with permission from: Jiang W, Luo X, Wei L, et al. The Sustainability of Energy Conversion Inhibition for Tumor Ferroptosis Therapy and Chemotherapy. *Small*. 2021;17(38):2102695. doi:10.1002/smll.202102695.[30] Copyright 2021, Wiley-VCH.

A upconversion nanosystem (UCNP)-based nanocatalyst activated by TME was designed by Wang et al (Figure 6).[86] UCNPs with peroxidase-like catalytic activity were grafted by cysteine (Cys) complexed by Cu. They were further covalently linked with GOx to form UCNPs@Cu-Cys-GOx (abbreviated as UCCG). Intratumoral GSH was exhausted by a reaction involving disulfide bonds and Cu^{2+}. Subsequently, Cu^{+} deriving from Cu^{2+} elevated ROS concentrations by Fenton-like reactions. M2 phenotype TAMs were satisfactorily repolarized to the M1 phenotype, attributable to the formation of ROS by cyclic reactions of CDT and ST. In addition, certain factors conducive to the immune response, such as the ratio of dendritic cells (DC) maturation, the number of cytotoxic T cells (CTLs), and the secretion of interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), rose considerably. The population of regulatory T cells (Tregs), previously thought to be a cell population associated with a poor prognosis, was suppressed. In general, ROS transformed the immunosuppressive TME into a "hot" state. UCCGs also teamed up with α-PD-L1, a checkpoint inhibitor licensed by the US Food and Drug Administration (FDA). Not only was the growth of tumors impaired in situ, but distal tumors were also remarkably attenuated, indicating that the introduction of immunotherapy was a promising treatment modality.

Moreover, immunogenic cell death (ICD) might play an important role in M1 phenotype TAM repolarization. During the period, dying tumor cells release damage-associated molecular patterns (DAMPs) and tumor-associated antigens (TAAs), such as calreticulin and high mobility group box 1, for antigen presentation and CTL infiltration.[87–89] It was discovered that ROS generated when GOx oxidizes glucose induces ICD. Sun et al found a method that utilized tadpole-ovoid manganese-doped hollow mesoporous silica to administer gold nanoparticles (AuNPs), DOX, and aspirin (ASA) to strengthen ICD (Figure 7).[90] When the structure collapsed in an acidic and GSH-sufficient environment, AuNPs were exposed to glucose for GOx-like catalysis, and Mn^{2+} was liberated for a Fenton-like reaction. ROS was then produced by the dual effects. DOX was put into nanoparticles and coupled with ROS to trigger ICD. Furthermore, ASA inhibited the cyclooxygenase-2 expression and prostaglandin E2 secretion, which are barriers between tumor cells and T cells due to the anti-inflammatory ability. As a result of the enormous release of TAAs, DCs matured, increased antitumor cytokines

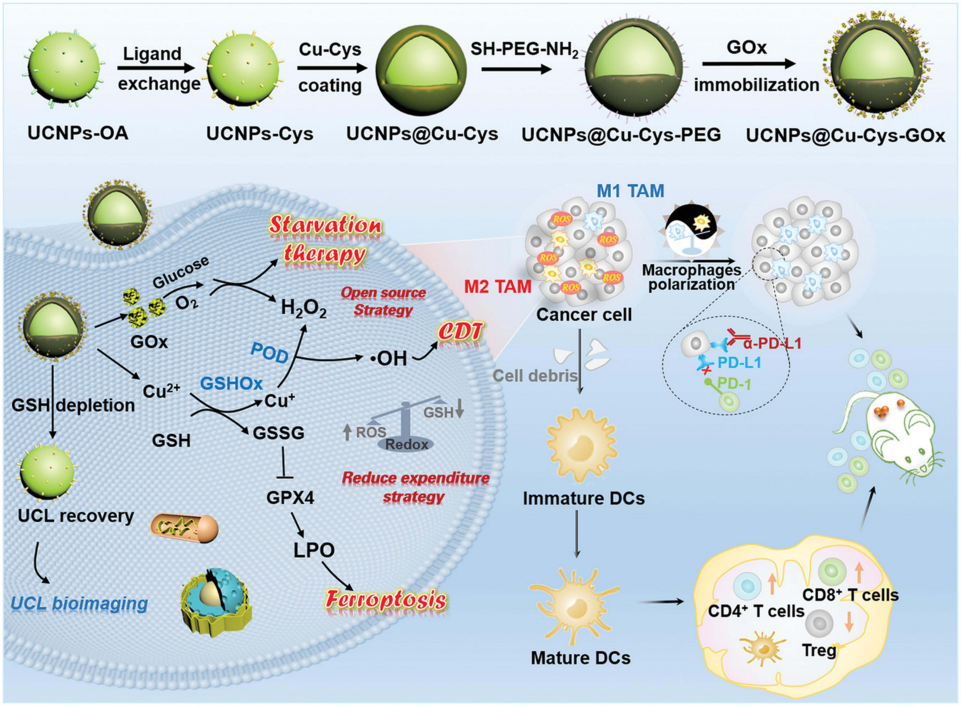

Figure 6 Synthetic route of UCCG and TME-activated enzymatic cascade catalytic reaction for synergistic cancer ST/CDT/immunotherapy process. Reproduced with permission from: Wang M, Chang M, Li C, et al. Tumor-Microenvironment-Activated Reactive Oxygen Species Amplifier for Enzymatic Cascade Cancer Starvation/Chemodynamic /Immunotherapy. *Adv Mater.* 2021;34(4):e2106010. doi:10.1002/adma.202106010.[86] Copyright 2021, Wiley-VCH.

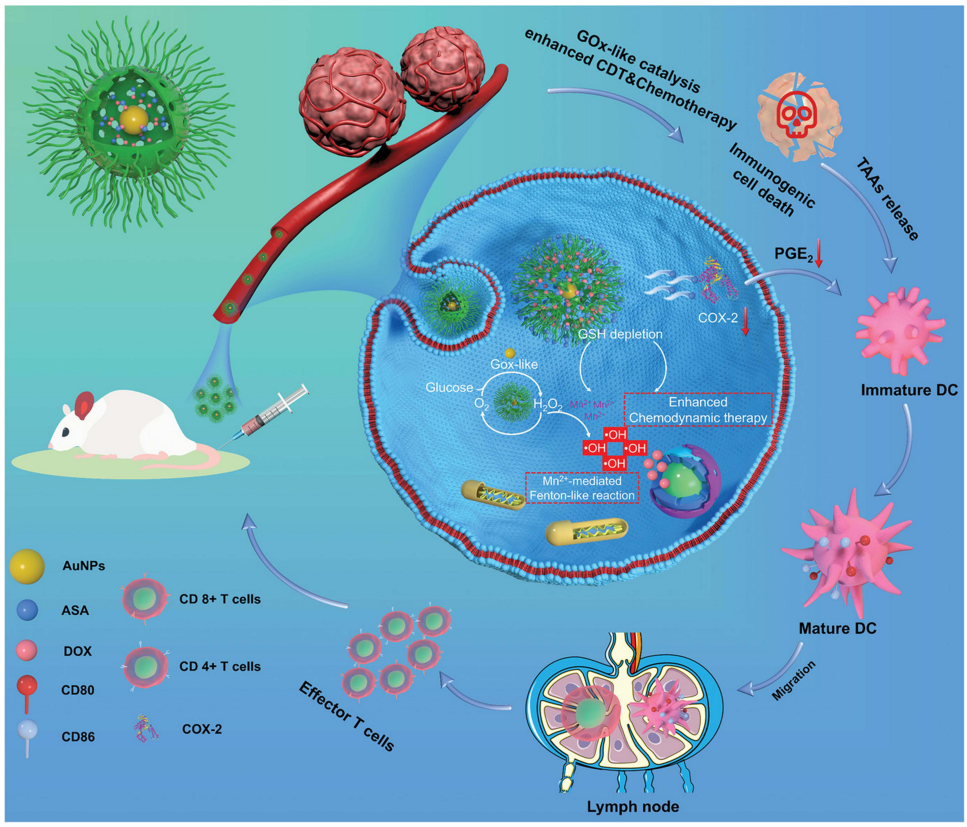

Figure 7 Schematic diagram of PEGylated Au@HMnMSNs ICD nanoinducers for eliciting potent antitumor immunotherapeutic efficacy. Reproduced with permission from: Sun K, Hu J, Meng X, et al. Reinforcing the Induction of Immunogenic Cell Death Via Artificial Engineered Cascade Bioreactor-Enhanced Chemo-Immunotherapy for Optimizing Cancer Immunotherapy. *Small.* 2021;17(37):e2101897. doi:10.1002/smll.202101897.[90] Copyright 2021, Wiley-VCH.

were released, and more CTLs infiltrated. Above all, the combination of GOx-strengthened ROS production and chemotherapy is an ideal method to promote ICD for oncology immunotherapy.

PDT Based on Glucose Metabolism Intervention

Photodynamic therapy is a novel treatment approach that has excellent selectivity, noninvasiveness, and minimal adverse effects.[25] Under irradiation, photosensitizers generate ROS such as singlet oxygen ($^1O_2$), hydroxyl radical ($^{\bullet}OH$), superoxide radical ($O_2^{\bullet-}$), or H_2O_2 to eliminate tumors.[91] However, hypoxia, which is one of the challenges of O_2-dependent PDT,[92] is a characteristic of the tumor microenvironment due to increased oxygen consumption, limited oxygen diffusion, and inadequate blood supply.[93] Limited H_2O_2 concentration in TME is another obstruction. The participation of GOx offers more abundant H_2O_2 through the oxidation of glucose, which could be converted to $^{\bullet}OH$ by irradiation or O_2 with the assistance of other molecules. PDT would be consequently enhanced by the oxidation of glucose.

Plenty of devices that utilize MnO_2[94–97] or catalase[98–101] to raise local oxygen concentration have been reported. Recently, a cascade bioreactor Ce6/GOx@ZIF-8/PDA@MnO2 (abbreviated as CGZPM) permitted synergizing PDT, CDT, and ST, which was aided by self-oxygen production and GSH consumption.[102] CGZPM was synthesized by a one-pot method as the scheme, co-loading GOx and chlorene6 (Ce6) with zeolitic imidazolate framework-8 (ZIF-8). The nanoparticle was also wrapped with PDA and MnO_2. After the disintegration of ZIF-8 in acidy TME, the cargos underwent the following reactions:

$$GSH \overset{PDA/MnO_2}{\rightarrow} GSSG + Mn^{2+} \quad (1)$$

$$MnO_2 + H_2O_2 + 2H^+ \rightarrow Mn^{2+} + 2H_2O + O_2 \quad (2)$$

$$Glucose + O_2 + H_2O \overset{GOx}{\rightarrow} Gluconic\ acid + H_2O_2 \quad (3)$$

$$Mn^{2+} + H_2O_2 \overset{HCO_3^-}{\rightarrow} {}^{\cdot}OH \quad (4)$$

The decomposition of glucose by GOx produced H_2O_2. It was further catalyzed by MnO_2 to O_2, which served as a substrate for PDT and continued glucose oxidation. Moreover, the PDA shell and MnO_2 interacted with GSH, a cellular antioxidant defense system obstructing ROS-based therapy, and produced Mn^{2+} as a Fenton-like agent for CDT. The nanosystem made full use of each component. The volume of 4T1 tumors in mice was significantly suppressed when only GOx was transported, which reflected the therapeutic effect of ST. After adding Ce6 and light irradiation, the tumors were almost eradicated thanks to the combined therapy.

Although PDT is a potential anticancer treatment, limited penetration ability impedes its practical applicability.[103] Instead of photoexcitation, scientists have looked at employing chemical energy produced by bis[2,4,5-trichloro-6-(pentoxycarbonyl)phenyl]oxalate to overcome this issue.[104,105] For deeper penetration, a biomimetic UCNP was reported by Wang et al.[106] The UCNPs took advantage of near-infrared (NIR) light that penetrates deeper to emit blue light, which has the capacity to directly photolyze H_2O_2 into $^{\bullet}OH$ but has a low penetrating ability. After embedding GOx and UCNPs in polyacrylic acid-η-octylamine micelles, the cancer cell membrane was coated on that for homotypic targeting. Following cellular absorption, oxidation mediated by GOx released abundant H_2O_2 and cut off the essential energy sources of tumor cells. Upon 980 nm laser stimulation, UCNPs emitted 470 nm light, which photolyzed excessive H_2O_2 into hydroxyl radicals directly, damaging tumor cells. The in vivo intervention was found to effectively target subcutaneous 4T1 tumors and lung metastatic lesions. The subcutaneous 4T1 tumors were effectively controlled even without 980 nm light irradiation, whose volumes were about 30% compared to the controls. Their volumes were lowered much more once PDT was added. Regrettably, the authors failed to evaluate the therapeutic effect of lung metastatic lesions as an indicator of deep irradiation capability.

CDT Based on Glucose Metabolism Intervention

CDT is described as the production of oxidative $^{\bullet}OH$ in tumors by disproportionation of H_2O_2 through a Fenton or Fenton-like reaction catalyzed by Fe^{2+} or other chemical compositions.[26] As one of the most harmful ROS, $^{\bullet}OH$ can effectively kill cancer cells by disrupting biomolecules.[107] However, inadequate acidity and insufficient H_2O_2 render therapy ineffective.[108]

Combining Fenton reagents with GOx to fight cancer makes sense. GOx-based ST improves CDT by supplying gluconic acid and H_2O_2, whereas H_2O_2-deficient Fenton reactions produce O_2 to provide raw ingredients for glucose oxidation.[29] Thus, CDT could be enhanced through the mutual promotion of the two treatment modalities. Introducing Fenton reagents and GOx into one nanomedicine is a conventional practice.[110–113] Zhang et al developed a liposomal nanosystem named lipoCaO_2/$Fe(OH)_3$-GOx to synergize the complementarity of CDT and ST by co-loading $Fe(OH)_3$-doped CaO_2 nanocomposites and GOx.[29] In an acidy environment, the antitumor reaction of lipoCaO_2/$Fe(OH)_3$-GOx could be promoted greatly by H_2O_2 and O_2 produced from CaO_2. They serve as substrates for CDT and ST separately in this system. As designed, CaO_2/$Fe(OH)_3$ nanocomposites decomposed in acidic TME, H_2O_2 and Fe^{3+} were generated for the following Fenton reactions as well. Besides producing $^{\bullet}OH$, GOx-expedited Fenton reactions generated O_2 to enhance the catalytic efficiency of GOx in turn. LipoCaO_2/$Fe(OH)_3$-GOx could relieve the hypoxic TME and inhibit MDA-MB-231 cells both in vivo and in vitro, owing to its self-supplied oxygen function and cycle-like catalytic process. In addition to synergizing CDT agents and GOx into a unified system, efforts have been undertaken to broaden the therapeutic direction. A nanomedicine was created that exploits broking endoperoxide bridges in artemisinin to boost ROS levels.[85] Combining CDT and ST with PTT,[113–116] SDT,[117] chemotherapy,[62,63,118,119] immunotherapy,[84] and metal ion therapy[120] are also gaining traction.

SDT Based on Glucose Metabolism Intervention

SDT utilizes ultrasound to generate ROS for tumor ablation. It possesses the advantage of penetrating deeper than light for visceral tumor treatment and opens up new therapeutic avenues.[27,121] As a popular therapeutic, the combination of SDT and ST has been researched.[122–125] Similar to PDT, the efficacy of SDT was also boosted by the involvement of starvation therapy. PCN-224@Pt@GOx@EM nanocarriers (short for PPGE NCs) made most of the nanosized porphyrin-based MOF called PCN-224.[126] PPGE co-loaded platinum nanoparticles (Pt NPs) and GOx molecules and camouflaged by erythrocyte membranes. Under the catalysis of Pt, a natural catalase-like enzyme with steady catalytic characteristics, oxygen generated from H_2O_2 aided the SDT and ST process. Therefore, even under a hypoxia environment, the viability of BxPC-3 cells decreased to less than 30% due to the function of O_2-promoted glucose oxidation. The efficacy can be further enhanced under ultrasound irradiation. Overall, the reaction process can be mutually moderated by one another's byproducts, bringing about a cycle-like process.

PTT Based on Glucose Metabolism Intervention

With NIR light irradiation, PTT mediated by photothermal agents can raise the temperature of the tumor area over 42 °C, causing cancer cells to undergo apoptosis by cell membrane disintegration, cytoskeleton damage, and DNA synthesis inhibition.[127,128] With the advantages of noninvasive qualities and remarkable therapeutic accuracy, PTT has attracted increasing attention.[129] However, upregulation of intracellular heat shock proteins (HSPs) expression might correct misfolded proteins, maintain intracellular homeostasis, and protect cells against hyperthermia-induced cell damage.[130] As a consequence, restricting HSP production appears to be the most likely remedy to this problem, and several molecules have been adopted.[131,132] The biosynthesis of HSPs is highly reliant on the level of intratumor ATP.[130] From this perspective, the suppression of glucose metabolism, which prevented the generation of ATP, is critical in the nanodrugs combining ST and PTT. It offered a novel approach to lowering HSPs without the usage of HSP inhibitors.

GOx has been incorporated into multiple nanomedicines for PTT/ST synergistic treatment as a star molecule.[133–137] Furthermore, multimodal treatments combining PTT/ST with PDT,[98,138–140] CDT,[113–116,141] chemotherapy,[142–144] gas therapy[145] and immunotherapy[146,147] have been developed. Since nanomaterials utilizing GOx were discussed in detail in previous reviews,[46,148] we will focus on other compounds altering glucose metabolism introduced in PTT/ST bimodal therapy.

Dai et al provided novel therapeutic concepts by encapsulating 2DG and a newly synthesized semiconducting polymer termed DPQ inside FA-modified liposomes.[31] The synthetic nanodrug was named Lip(DPQ+2DG). FA awarded the system merit for its capacity of targeting malignant cells overexpressing folate receptors. As the cornerstone of PTT, DPQ had outstanding NIR-II fluorescence imaging performance and PTT effectiveness. Meanwhile, as a glucose analog acting as an antiglycolytic agent in clinical trials (Phase I/II),[149,150] 2DG not only starved tumor cells by cutting off glycolysis but also inhibited the production and function of HSPs, allowing for a superimposed impact of PTT. More crucially, 2DG outperformed GOx as 2DG does not denature or deactivate under high-temperature conditions. Beneficial from the specific targeting ability on glycolysis, Lip(DPQ+2DG) demonstrated extraordinary sensitivity to tumor cells compared to normal cells preferring to synthesize ATP through oxidative phosphorylation (OXPHOS) rather than glycolysis. On the other hand, such an effect allowed normal cells to defend themselves and lessened the negative effects. As a result of the outstanding photothermal conversion efficiency of DPQ and glucose starvation ability of 2DG, cell viability in vitro decreased to 8.41% and tumor weight in vivo declined by 90.4%. Similarly, Chen et al reported a PTT/ST bimodal nanomedicine by decreasing glucose uptake with diclofenac, a small drug targeting GLUT1.[151]

Apart from HK targeted by 2DG, PKM2 has also been considered a potential cancer-fighting target. Certain noncoding ribonucleic acids (RNAs), such as siRNAs and micro ribonucleic acids (microRNAs), have revealed the tremendous potential for cancer therapy by reducing the expression of target proteins.[152–154] Interestingly, Dang et al developed an intelligent system named D-I/P@HSA NCs co-loading the photothermal agent indocyanine green (ICG) and siRNA against PKM2 (siPKM2) for PTT/ST synergistic therapy.[155] Spherical helical polypeptides (DPPs) carrying ICG and siRNAs were prepared using amine-terminating polyamidoamine and N-carboxy anhydride. Guanidines and human serum albumin (HSA) were utilized as well for serum stability. Well-designed nanoparticles facilitated cell membrane penetration and endolysosomal escape for siRNA distribution. ATP levels fell because of the high effectiveness of PKM2 silencing at the messenger ribonucleic acid (mRNA) and protein levels. Therefore, HSPs, the bridge between ST and PTT, were repressed. MCF-7 cell apoptotic levels in vitro were 94.34%, and tumors in vivo were fully suppressed or even slightly ablated when exposed to comparable interactions as those described above.

Gas Therapy Based on Glucose Metabolism Intervention

Gas therapy appears to be an emerging and promising "green" therapeutic option due to its high efficacy, biosafety, and biocompatibility.[156] It utilizes specific gases, such as nitric oxide (NO),[157] carbon monoxide (CO),[158,159] hydrogen sulfide (H_2S),[160] and sulfur dioxide (SO_2),[161] to complement other treatments. However, it is a challenge to transport gases to defined areas for poor solubility, diffusivity, and inaccurate release. Therefore, nanocarriers encapsulating gas releasing molecules (GRMs) for tumor targeting and stimuli-responsive release are desired.[156] Gas release induced by starvation therapy products provides superb inspiration.

NO is able to react with ROS to produce extremely toxic peroxynitrites ($ONOO^-$),[162] inhibit P-gp expression,[163] and maintain vascular homeostasis for oxygen supply.[164] Certain nanosystems have been manufactured with the combination of GOx and $_L$-arginine ($_L$-Arg) serving as the GRM.[165–167] A typical tumor targeting and TME-activatable nanomedicine known as GCAH was constructed by Fu et al (Figure 8).[168] With spherical calcium phosphate (CaP) biomineralized on the foundation of GOx, GCAH carried $_L$-Arg for ST-facilitated gas therapy. Due to the unique interactions between HA on the nanoparticles and glycoprotein CD44, GCAH could concentrate in tumor tissues overexpressing CD44. GOx and $_L$-Arg were released as primary therapeutic agents and underwent the following two-step cascade reactions:

$$\text{Glucose} + O_2 + H_2O \xrightarrow{\text{GOx}} \text{Gluconic acid} + H_2O_2 \quad (1)$$

$$\text{L} - \text{Arginine} + H_2O_2 \xrightarrow{H^+} \text{L} - \text{Citrulline} + H_2O \quad (2)$$

As a result, glucose was depleted, and NO was discharged for gas therapy. In vitro experiments showed that when the drug concentration reached 1.5μg/mL, the effect of starvation treatment alone could reduce the cell viability by about 50%. Additionally, NO was systematically produced for optimal response productivity. It converted the proangiogenic

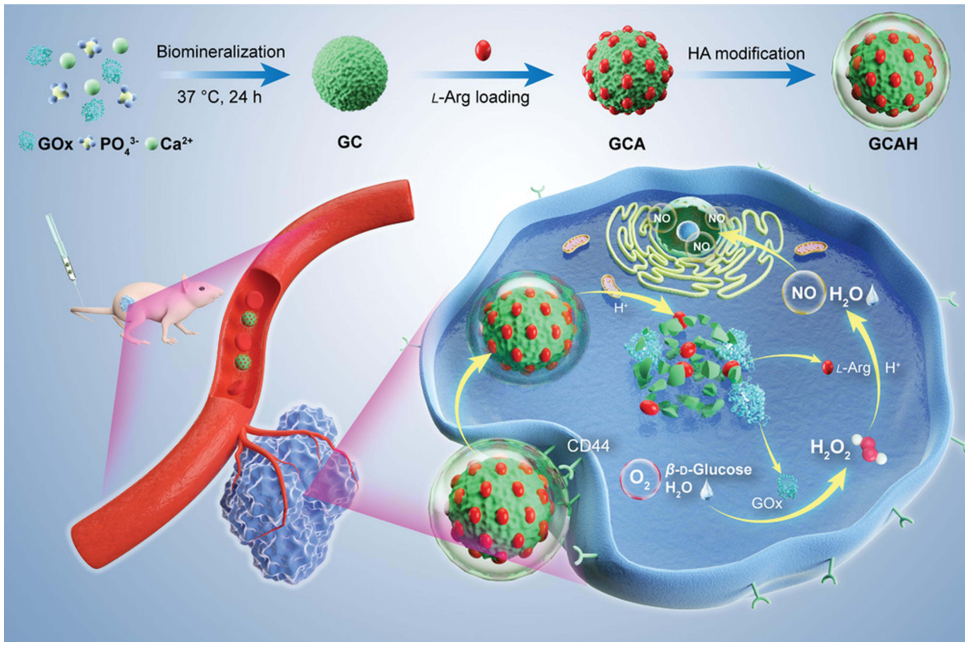

Figure 8 Schematic illustration of the preparation process of GCAH and its application for synergistic cancer ST/gas therapy. Reproduced with permission from: Fu LH, Li C, Yin W, et al. A Versatile Calcium Phosphate Nanogenerator for Tumor Microenvironment-activated Cancer Synergistic Therapy. *Adv Healthc Mater.* 2021;10(23):e2101563. doi:10.1002/adhm.202101563.[198] Copyright 2021, Wiley-VCH.

phenotype into vascular stabilization signals in addition to directly eradicating tumor cells. Thus, organically combining starvation therapy with GOx and NO-gas therapy has been illustrated to be a promising therapeutic strategy.

In addition to NO, CO has been proven to coordinate momentous biological effects as a homeostatic and cytoprotective molecule.[168] Since stimuli-responsive CO-releasing molecules can be initiated by a high level of H_2O_2, it is promising to unite CO-based gas treatment with GOx-based ST. Manganese carbonyl ($Mn_2(CO)_{10}$, simplified as MnCO), a CO prodrug, was coupled with GOx in the platform of hollow mesoporous organosilica nanoparticles (HMONs).[169] It was further decorated with arginine-glycine-aspartic acid (RGD) on the exterior for selectively recognizing tumor cells overexpressing $\alpha_v\beta_3$ integrin, allowing tumor-targeted delivery. The disulfide bonds in the spherical framework and the benzoic-imine covalent bonds between HMONs and GOx enabled the release of MnCO in the TME. These subtle designs guaranteed the spatiotemporal delivery of MnCO regardless of negative effects. Furthermore, the inherent effects of the nanocatalyst could reinforce therapeutic functions each other by chemical reactions listed below:

$$\mathrm{Glucose}+\mathrm{O_2}+\mathrm{H_2O}\overset{\mathrm{GOx}}{\rightarrow}\mathrm{Gluconic\ acid}+\mathrm{H_2O_2} \quad (1)$$

$$\mathrm{MnCO}+\mathrm{H_2O_2}\rightarrow\mathrm{MnO_X}+\mathrm{CO} \quad (2)$$

$$\mathrm{MnO_X}\overset{\mathrm{H^+}}{\rightarrow}\mathrm{Mn^{2+}}+\mathrm{H_2O}+\mathrm{O_2} \quad (3)$$

GOx was able to oxidize glucose to gluconic acid and H_2O_2, accelerating the production of CO from MnCO concurrently. Conversely, MnO_x originating from MnCO supplied raw materials for further redox reactions. The ATP level was thence further reduced by the addition of MnCO. With the interaction between ST and ROS derived from damaged mitochondria impaired by CO, the apoptotic signaling pathway was notably upregulated. More interestingly, CO might block the respiratory chain as a complement to starvation therapy.[170] Above all, these explorations exhibited a viable technique for optimizing the nanotherapeutic efficacy by targeting the microenvironment dedicatedly with a high concentration of H^+, GSH, and glucose.

Other Treatments Based on Glucose Metabolism Intervention

Several metallic materials, such as silver nanoparticles (AgNPs), zinc oxide nanoparticles, and gold nanoparticles, have been proven to induce mitochondrial damage, oxidative stress, and apoptosis through their inherent cytotoxicity.[171,172] Because of the accompaniment of the generation of gluconic acid and H_2O_2, GOx has been incorporated in nanosystems as an enhancer with AgNPs that generate Ag^+ at high concentrations of H_2O_2 and low pH.[173,174] Sun et al developed ZIF-8@GOx-AgNPs@MBN based on ZIF-8 MOF, co-delivering GOx and AgNPs.[175] Owing to its acidic breakdown property, ZIF-8 crumbled to release cargos while generating Zn^{2+}, realizing spatial tumor treatment. Zn^{2+}, along with Ag^+ generated from AgNPs, served as metal-ion therapy agents. In the absence of glucose, Ag^+ and Zn^{2+} were able to kill cancer cells at a lower concentration, indicating that ST could induce increased sensitivity of tumor cells to metal-ion therapy. Notably, Zn^{2+} has been reported to inhibit glycolysis by inactivating GAPDH and decreasing NAD^+.[176] Zn^{2+}-activating DNAzymes cleaving GLUT1 mRNA were loaded in zinc-rich ZIF-8 for synergistic treatment as well.

Yue et al developed a nanomedicine for synergistic GOx-based glucose starvation and gene therapy by integrating a hypoxia-activated plasmid (RTP801::p53) holding the post of a wild type p53 gene.[177] In the nanodrug, GOx consumed oxygen to form a hypoxia environment and functioned as an inducer of gene therapy. To realize H_2O_2 and hypoxia dual activation, GOx was loaded in ferrocene (Fc)-capped Au nanoparticles and was released via the oxidation of Fc to ferrocenium (Fc^+) in an H_2O_2-sufficient environment. Additionally, GOx-mediated glucose oxidation would speed up the release of GOx by H_2O_2 and further activate the gene integrated with the hypoxia-activatable promoter RTP801 by oxygen consumption. With the delicate architecture, the nanomedicine above upregulated p53 mRNA and protein. Due to H_2O_2-triggered drug release, GOx exhibited cytotoxicity to tumor cells, while did little on normal cells. Tumor cells underwent apoptosis and necrosis under ST and gene therapy.

Another nanoplatform generating ROS by Pt NPs under an alternating electric field termed electrodynamic therapy (EDT) was established by Lu et al.[178] By combining with GOx, the efficiency of EDT could be further improved. Porous platinum nanospheres functioned as GOx carriers, catalysts for converting H_2O_2 to O_2, and EDT agents. Significant therapeutic benefits could be detected with the combination of EDT and GOx-based ST augmented by the O_2 generated through Pt catalysis. Overall, this research explored the wide range of applications of EDT as an emerging method to produce ROS without in situ O_2 or H_2O_2.

Conclusion and Outlook

The finite pathways of tumor cells remodeling their metabolism make it possible to adopt a unified and simplified tumor treatment scheme. Besides, there are conclusive clues to prove that metabolic disorders play a significant role in resistance to conventional therapies, including chemotherapy and immunotherapy.[179] Whether the resistance to carboplatin, 5-fluorouracil, or paclitaxel are all found to be related to glucose metabolism.[180–182] As for immunotherapy, PKM2 enhances the expression of PD-L1 as well as the recruitment of myeloid-derived suppressor cells, which leads to the failure of immunotherapy.[183,184] The metabolic intervention probably enhances the efficacy of traditional treatments or reinvigorates treatments that have been deemed ineffective. Therefore, starvation therapy has swiftly evolved into a potential complementary therapeutic approach for other therapies. Treatments targeting tumor-favored metabolites, such as the ketogenic diet, have grown in popularity in recent years.[185] Plenty of drugs are being explored in clinical trials, not only alone but also in combination with certain therapies. For example, 2-DG has been combined with docetaxel in a Phase I clinical trial with promising results.[186] What is more interesting, targeting the stronger glycolytic metabolism level and treatment-induced increased oxidative metabolism of cancer stem cells make it possible to alleviate cancer stem cell resistance.[179]

Regrettably, systemic starvation therapy itself remains defective and needs further exploration. The interconnected metabolic pathways also hinder the efficacy of starvation therapy.[179] Furthermore, long-term systemic starvation therapy would lead to side effects like weight loss and cardiovascular diseases, which impedes its clinical application.[187] Thence, spatiotemporal drug delivery with more precise therapeutic effects and combination with other therapeutic methods conceivably be the way forward.

Nanomaterial-assisted starvation therapy targeting glucose metabolism partly resolves the drawbacks of standard systemic drug delivery by improving targeting efficacy and precise drug release, avoiding harmful side effects, and

maximizing the benefits of ST. It is even more valuable that targeting tumor-specific glucose metabolic pathways is more accurate and has less impact on other organs. Therefore, glucose metabolism has been targeted by biological enzymes, small compound molecules, or inorganic substances with enzyme-like effects. PDT, SDT, PTT, chemotherapy, and immunotherapy were combined with ST for interactive therapeutic effects and enhanced therapeutic outcomes. In this review, we reviewed the significant progress made, which covers monotherapy and multimodal therapeutic methods combined with ST. The design of nanomedicines and exquisite connections between these therapy options were focused on.

Nevertheless, nanomaterial-assisted starvation treatment is still in its infancy. There are still some potential challenges before entering clinical application. First, systematic investigations on the long-term biosafety of nanomedicines should be conducted. Although every study listed biosafety data, most of these studies only observed biosafety for a very short period,[112] and the differences between rats and humans probably count a lot.[188] Therefore, long-term toxicity, pharmacokinetics, and pharmacodynamics should be validated. Second, although several nanomedicines have demonstrated impressive therapeutic effects, the majority of them were based on complex structures synthesized through complicated multistep reactions, resulting in heterogeneity. And it is difficult to reproduce them for batch production. Fewer components, on the other hand, would diminish refinement and therapeutic efficacy. Introducing substances with diverse functions may be a solution.[148] In general, the balance between the complexity and efficacy of nanodrugs is an urgent problem to be solved. Finally, the interaction between ST and other therapy approaches involves hypoxia, increasing acidity, and oxidative stress, all of which have been linked to a negative prognosis.[189,190] Therefore, whether the factors attributed to tumorigenesis and development or the therapeutic effects of drugs are dominant needs to be evaluated.

There is still much to investigate when it comes to starvation therapy. Apart from glucose metabolism referred to in this review, cancer cells also enhance the metabolism of amino acids,[191] fatty acids,[192] and other necessary nutrients. However, molecules interrupting the metabolism of these nutrients are like virgin land in the field of nanomedicine possibly due to a lack of understanding of the mechanisms. Although certain nanoparticles have been reported to target nutrients other than glucose,[193–195] more research is needed to fill the gap. Additionally, a combination of multiple drugs is the trend in starvation therapy. Thence, dual metabolic blockage and metabolic inhibition combined with other treatment methods are being investigated. It's also promising to compensate for the lack of fasting by using nanomedicines with starvation therapy properties. The combination of nanodrugs targeting specific nutrients and milder dietary interventions possibly enhance therapeutic efficacy while reducing systemic toxicity. Moreover, metabolic reprogramming influences the function of immune cells in addition to tumor cells. Tumor endothelial cells also exhibit a high glucose metabolism phenotype to promote blood vessel growth.[196] Tumor cells even obtain nutrients through crosstalk with cells in TME to ease metabolic stress.[197] Regulation of cellular metabolism within the TME and modulation of the relationship between tumor cells and infiltrating immune cells are additional inspiring directions of exploration. Developing nanoparticles specifically targeting cells in TME might be a feasible method. With the increasingly clear role of nutrients in tumors, it can be predicted that more nanodrugs conducting ST will be developed and boost cancer treatment in the future.

Abbreviations

ST, starvation therapy; ATP, adenosine triphosphate; GOx, glucose oxidase; PTT, photothermal therapy; PDT, photodynamic therapy; CDT, chemodynamic therapy; SDT, sonodynamic therapy; H_2O_2, hydrogen peroxide; O_2, oxygen; TME, tumor microenvironment; GLUT1, glucose transporter 1; PKM2, pyruvate kinase isozyme M2; HK, hexokinase; PFKFB3, 6-phosphofructo 2-kinase-fructose-2,6-biphosphatase 3; 2DG, 2-deoxy-d-glucose; siRNA, small interfering ribonucleic acid; PDA, polydopamine; MNs, microneedles; HA, hyaluronic acid; 3-MA, 3-methyladenine; BP, black phosphorus; PEG, polyethylene glycol; LDHA, lactate dehydrogenase A; MDR, multidrug resistance; DOX, doxorubicin; ROS, reactive oxygen species; P-gp, P-glycoprotein; TPZ, tirapazamine; AQ4N, banoxantrone dihydrochloride; DNA, deoxyribonucleic acid; GSH, glutathione; ICI, checkpoint inhibitor; TAM, tumor-associated macrophage; UCNP, upconversion nanosystem; Cys, cysteine; DC, dendritic cell; CTL, cytotoxic T cell; IL, interleukin; TNF-α, tumor necrosis factor-α; Treg, regulatory T cell; FDA, the US Food and Drug Administration; ICD, immunogenic cell death; DAMP, damage-associated molecular pattern; TAA, tumor-associated antigen; AuNP, gold nanoparticle; ASA, aspirin;

$^1O_2$, singlet oxygen; $^{\bullet}OH$, hydroxyl radical; $O_2^{\bullet-}$, superoxide radical; Ce6, chlorene6; ZIF-8, zeolitic imidazolate framework-8; NIR, near-infrared; Pt NP, platinum nanoparticle; HSP, heat shock protein; OXPHOS, oxidative phosphorylation; RNA, ribonucleic acid; microRNA, micro ribonucleic acid; ICG, indocyanine green; siPKM2, siRNA against PKM2; DPP, spherical helical polypeptide; HSA, human serum albumin; mRNA, messenger ribonucleic acid; NO, nitric oxide; CO, carbon monoxide; H_2S, hydrogen sulfide; SO_2, sulfur dioxide; GRM, gas releasing molecule; $ONOO^-$, peroxynitrites; $_L$-Arg, $_L$-arginine; CaP, calcium phosphate; HMON, hollow mesoporous organosilica nanoparticle; RGD, arginine-glycine-aspartic acid; AgNP, silver nanoparticle; Fc, ferrocene; EDT, electrodynamic therapy.

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Disclosure

The authors report no conflicts of interest in this work.

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