



Application of glutathione depletion in cancer therapy: Enhanced ROS-based therapy, ferroptosis, and chemotherapy



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ABSTRACT

Glutathione (GSH) is an important member of cellular antioxidative system. In cancer cells, a high level of GSH is indispensable to scavenge excessive reactive oxygen species (ROS) and detoxify xenobiotics, which make it a potential target for cancer therapy. Plenty of studies have shown that loss of intracellular GSH makes cancer cells more susceptible to oxidative stress and chemotherapeutic agents. GSH depletion has been proved to improve the therapeutic efficacy of ROS-based therapy (photodynamic therapy, sonodynamic therapy, and chemodynamic therapy), ferroptosis, and chemotherapy. In this review, various strategies for GSH depletion used in cancer therapy are comprehensively summarized and discussed. First, the functions of GSH in cancer cells are analyzed to elucidate the necessity of GSH depletion in cancer therapy. Then, the synthesis and metabolism of GSH are briefly introduced to bring up some crucial targets for GSH modulation. Finally, different approaches to GSH depletion in the literature are classified and discussed in detail according to their mechanisms. Particularly, functional materials with GSH-consuming ability based on nanotechnology are elaborated due to their unique advantages and potentials. This review presents the ingenious application of GSH-depleting strategy in cancer therapy for improving the outcomes of various therapeutic regimens, which may provide useful guidance for designing intelligent drug delivery system.

1. Introduction

Achieving successful cancer therapy still faces great challenges. An ideal treatment is supposed to precisely target and kill cancer cells while being blind to normal cells. Taking advantage of the differences between cancer cells and normal cells is a promising way. Researchers have found many distinctive features in tumor microenvironment (TME) that differ from normal tissues, including weakly acidic pH, hypoxia, increased reactive oxygen species (ROS), upregulated antioxidative system, and overexpression of certain enzymes [1]. Among these features, ROS and antioxidative system are important for cells to maintain redox homeostasis and perform normal physiological activities. ROS is mainly produced from mitochondrial respiratory chain during aerobic metabolism [2,3]. Cancer cells generate considerable ROS to support their rapid progression. However, an excessively high level of ROS, often known as oxidative stress, will cause damage to deoxyribonucleic acid (DNA),

proteins, and lipids, eventually triggering cell death [4,5]. To resist the impairment caused by oxidative stress, the level of antioxidative system that can scavenge ROS is upregulated accordingly [6]. Intracellular antioxidative system consists of enzymes including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), and thioredoxin (Trx), and non-enzymatic antioxidants including glutathione (GSH), ascorbic acid, and tocopherol [7]. GSH is a predominant antioxidant in antioxidative system. It is a tripeptide consisting of glutamate, cysteine, and glycine. Most intracellular GSH exists in the reduced form, which can react with oxidizing substances like ROS and meanwhile be oxidized to the oxidized form, glutathione disulfide (GSSG) [8]. The concentration of intracellular GSH is around 2–10 mM, which is about 1000 folds higher than that in extracellular environment (2–10 μM) [9,10]. This GSH concentration gradient has been used in various redox-responsive drug delivery systems to activate drugs in cancer cells [11–13]. For example, Laskar et al. prepared redox-sensitive

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dendrimersomes with disulfide linkers for drug and gene delivery. A significant decrease in the particle size of dendrimersomes and sustained release of the cargos were observed in the presence of 10 mM GSH [14].

The intracellular redox state is in a dynamic equilibrium as a result of controlled ROS production and elimination. Loss of GSH will break the redox homeostasis and cause ROS accumulation, eventually triggering cell dysfunction and death [15,16]. As for cancer cells, the high level of oxidative stress makes them more sensitive to GSH deficiency, which is a fatal weakness and can be utilized in cancer therapy [17]. ROS-based therapy is a kind of therapeutic strategy to kill cancer cells by amplifying intracellular ROS levels. Exogenous compounds or materials are delivered to cancer tissues, which produce considerable ROS and trigger cell death under the irritation of light, ultrasound or chemical reaction. A number of commercial products of ROS-based therapy have come into market and received good results [18]. Although ROS-based therapy has been applied in clinical treatment, there are still some barriers that limit its therapeutic efficacy. One of the main obstacles is the ROS scavenging by cellular antioxidative system, especially GSH. Reducing the GSH levels in tumor cells has been reported to increase ROS levels and improve the therapeutic efficacy of ROS-based therapy [19–22]. In addition, GSH also plays an important role in the detoxification of xenobiotics including toxins, pollutants, and drugs [23–25]. Under

physiological conditions, this function protects cells from disturbance or death caused by exogenous factors. However, it becomes an obstacle for chemotherapy based on several commonly used drugs, especially platinum drugs. Studies have found that GSH-mediated detoxification was involved in the cisplatin resistance of several types of tumors [26–28]. Moreover, reducing the GSH levels in cancer cells has been proved to successfully enhance the therapeutic efficacy of cisplatin and even reverse the drug resistance [29,30].

Since reducing intracellular GSH level is beneficial for so many cancer therapeutic regimens, researchers have proposed various promising strategies to achieve GSH depletion, especially those based on functional nanomaterials. Different from traditional strategies that achieve GSH depletion by bioactive molecules, these nanomaterials-based strategies focus on developing functional nanocarriers with GSH-depleting ability, which reduce the complexity of multi-drug co-delivery. Recently, varieties of metal-based and metal-organic nanomaterials, such as manganese dioxide (MnO_2), metal-organic frameworks (MOFs), nanoscale coordination polymers, have cut a conspicuous figure on GSH depletion-involved cancer therapy [31–34]. However, to our knowledge, there is a lack of systematical summary and classification of these strategies based on different mechanisms. In this review, various strategies for GSH depletion in cancer therapy are

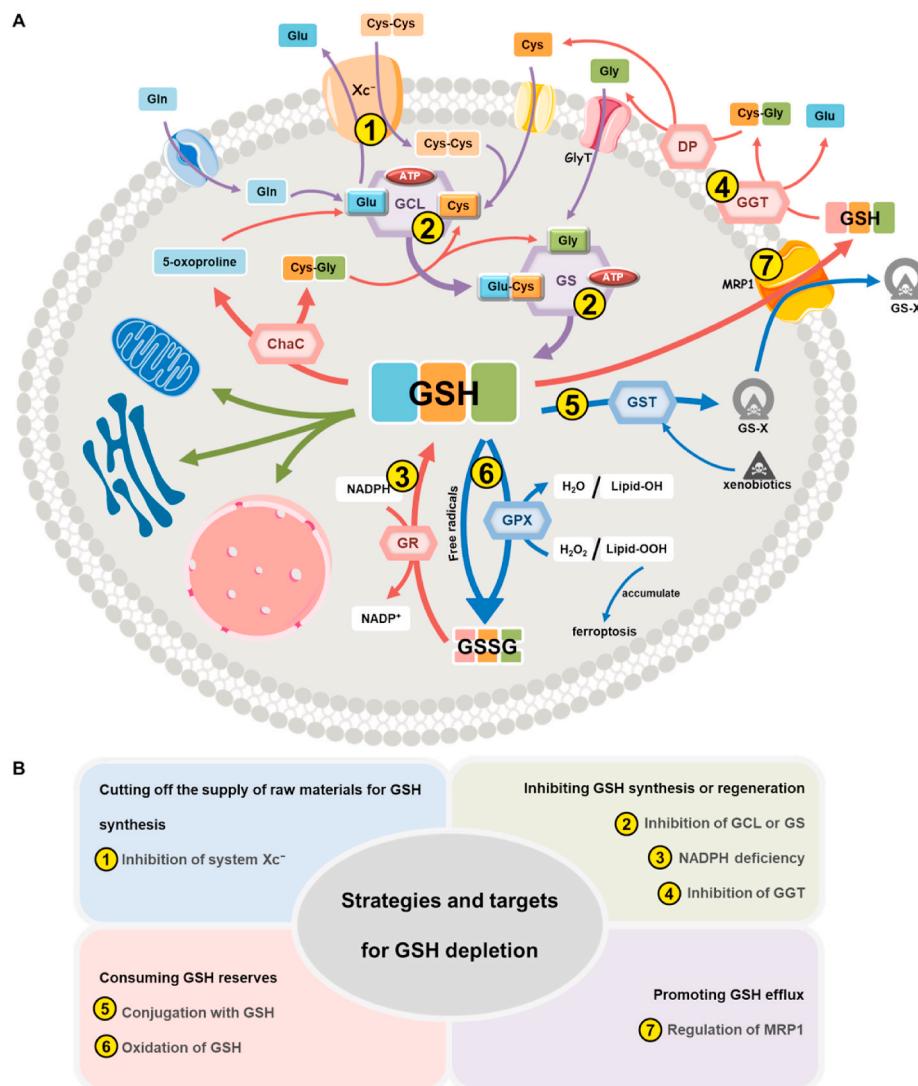


Fig. 1. (A) Schematic illustration of the fate of cellular GSH. The biosynthetic pathway (purple), metabolic and regenerative pathways (red), distribution (green), and main functions (blue) of GSH were illustrated by arrows with different colors. (B) Strategies for GSH depletion and their corresponding targets numbered in (A). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

collected and summarized. First, we elucidate the functions of GSH in cells and the relationships between GSH and cancer formation and progression. Subsequently, we briefly introduce the synthetic and metabolic processes of GSH, in which there exist certain targets for modulating GSH. Then, various approaches to GSH depletion in the literature are systematically classified and presented (Fig. 1). Among these approaches, the application of functional nanomaterials in GSH depletion is specially elaborated. We particularly focus on the mechanisms behind these strategies and how they improve the efficacy of different therapeutic regimens. Finally, we provide perspectives on the application of GSH depletion in cancer therapy and how to adopt proper strategy to improve the therapeutic outcomes.

2. Roles of GSH in cancer

2.1. Physiological functions of GSH

GSH participates in many metabolic activities and physiological processes in human body. One of the most basic roles of GSH is an antioxidant that can scavenge oxidant species and prevent oxidative stress, maintaining the redox homeostasis in cells. GSH reacts with oxidizing substances in direct or enzymatic way while GSH is oxidized into GSSG [35]. Free radicals and ROS can be quenched by GSH directly. In enzymatic way, GSH is used as a co-substrate of GPX to reduce hydrogen peroxide (H_2O_2) and lipid peroxide (Lipid-OOH) into water and lipid alcohol (Lipid-OH), respectively [36]. Another important function of GSH is detoxification. The intracellular GSH detoxifies the electrophilic xenobiotics by directly conjugating with them under the catalysis of glutathione S-transferases (GST) [28,37]. The conjugates of GSH and xenobiotics, often denoted as GS-X, are further extruded by cells via multidrug resistance-associated protein 1 (MRP1) efflux pump [38]. Other functions of GSH include [35,36,39,40]: (i) maintenance of cysteine pools; (ii) maintenance of cysteine under a reduced state within proteins; (iii) the maturation of iron-sulfur clusters in proteins; (iv) regulation of transcription factors related to redox signaling; (v) participation in the metabolism of oestrogens, leukotrienes, and prostaglandins, and the production of deoxyribonucleotides; (vi) storage and transportation of nitric oxide (NO); (vii) transference of copper and iron; (viii) modulation on the activity of proteins via reversible protein glutathionylation.

The disturbances in GSH homeostasis have severe influences on cell biological behaviors and human physiological status, which were observed in many pathological conditions including cancer, diabetes, neurodegenerative disorders, and cystic fibrosis [41–45]. In terms of cancer, researchers found that GSH probably played a dual role in cancer initiation and progression, which depended heavily on the stage of cancer [46,47]. At the early stage of cancer initiation, intracellular GSH protects cells from carcinogenesis by detoxifying the carcinogens and preventing ROS-induced DNA oxidation and subsequent DNA damage. Several studies have reported that GSH, coordinated with GST or GPX, could prevent the occurrence of skin, liver, and colon cancer in mice that had been exposed to carcinogens or lost tumor suppressors [48–51]. At the progressive stage of cancer, considerable ROS is produced by cancer cells to support their fast metabolism and malignant proliferation [52]. The intracellular GSH level is also upregulated to resist the excessive ROS that may cause DNA damage and the disturbance of protein homeostasis [53,54]. Thus, high level of GSH can protect cancer cells from programmed cell death activated by oxidative stress.

2.2. GSH depletion in cancer therapy

Although additional work is needed to clarify the complex relationships between GSH and cancers, most of the demands in clinical treatments focus on cancers that have already developed. Therefore, GSH depletion can be a potential strategy to magnify oxidative stress in cancer cells and improve the outcomes of cancer therapy. Generally,

GSH depletion is adopted in several different treatment regimens for cancer therapy (Fig. 2 & Table 1).

The first is to magnify the therapeutic efficacy of ROS-based therapy by reducing ROS scavenging. ROS-based therapy mainly includes photodynamic therapy (PDT), sonodynamic therapy (SDT), and chemodynamic therapy (CDT). PDT employs photosensitizers to generate cytotoxic singlet oxygen from ambient oxygen under optical excitation [143]. Photosensitizers are in advance accumulated in the tumor tissues, and then the photoactivation process promotes ROS generation and tumor cell death. SDT utilizes sonosensitizers to convert oxygen into ROS under ultrasound activation. Due to the high penetrability of ultrasound, SDT is superior in the treatment of deeper tumor compared with light-activated therapy [81]. Different from PDT and SDT, CDT is based on the *in situ* Fenton or Fenton-like reaction, in which H_2O_2 in TME reacts with exogenous catalysts and generates hydroxyl radical ($\cdot OH$) [97]. The thing in common for these ROS-based therapies is the generation of large amounts of ROS in tumor tissues, which initiates oxidative stress and induces cell death. Considering this mechanism, ROS-based therapy usually does not cause tumor resistance as compared with other traditional therapies like photothermal therapy (PTT) and chemotherapy. However, the efficacy of ROS-based therapy is limited by ROS scavenging mediated by high level of intracellular GSH [22,81,97,144]. Therefore, combining GSH depletion with ROS-based therapy can be a promising strategy to improve the therapeutic outcomes. For example, in one study, the combinational therapy of CDT and GSH depletion was tested on a 4T1 tumor-bearing mouse model. Treatments with Fenton catalyst and GSH inhibitor showed superior curative effects compared with treatment with only Fenton catalyst, in terms of tumor weight, histological damages, and apoptosis levels in tumor tissues. This oxidative stress-amplifying strategy was also combined with chemotherapy and radiotherapy, which exhibited enhanced therapeutic efficacies [96].

The second is to enhance the efficacy of chemotherapeutics by reducing GSH detoxification. As a kind of xenobiotics, many chemotherapeutic drugs are the targets of GSH detoxification, including cisplatin, doxorubicin (DOX), and chlorambucil [123,145,146]. These drugs can be conjugated with intracellular GSH under the catalysis of GST and then extruded by cancer cells. The detoxification process significantly weakens the therapeutic efficacy of chemotherapy and may even develop drug resistance in tumors [147,148]. GSH depletion can efficiently impede this detoxification process and has shown prominent efficacy in drug-resistant tumors. For example, Li et al. investigated the influences of the inhibitor of GSH synthesis on the cell-killing effects of cisplatin and gemcitabine against biliary tract cancer cells. The results showed that cell apoptosis induced by cisplatin was significantly increased by adding a low concentration of GSH synthesis inhibitor. The anti-proliferative effect of gemcitabine to cancer cells was also enhanced [149].

The third is to induce cell death via a non-apoptotic manner called ferroptosis. Ferroptosis is an iron-dependent cell death pathway defined by Stockwell et al. in 2012, which has been used in cancer therapy [150,151]. Jiang et al. have found that the mutations in some cancers made them more susceptible to ferroptosis, which provided a promising cancer therapy with higher specificity and targeting ability than other traditional therapies [152]. The characteristic of this process is the accumulation of Lipid-OOH caused by the disturbances of intracellular Lipid-OOH scavenging systems. The cystine/glutamate antiporter (system X_c^-) and glutathione peroxidase 4 (GPX4) are two crucial regulators of this scavenging systems [153]. Since GSH is the reducing co-substrate of GPX4, ferroptosis can be triggered by disturbing system X_c^- , inactivating GPX4 or depleting GSH. Many studies have confirmed successful cancer cell killing via ferroptotic pathway initiated by GSH depletion [134–136,140]. In a research conducted by Wang et al., a nanoagent based on arginine-rich manganese silicate nanobubbles that possessed high efficiency of GSH depletion was developed. Significant tumor suppression effects were observed in tumor xenograft-bearing nude

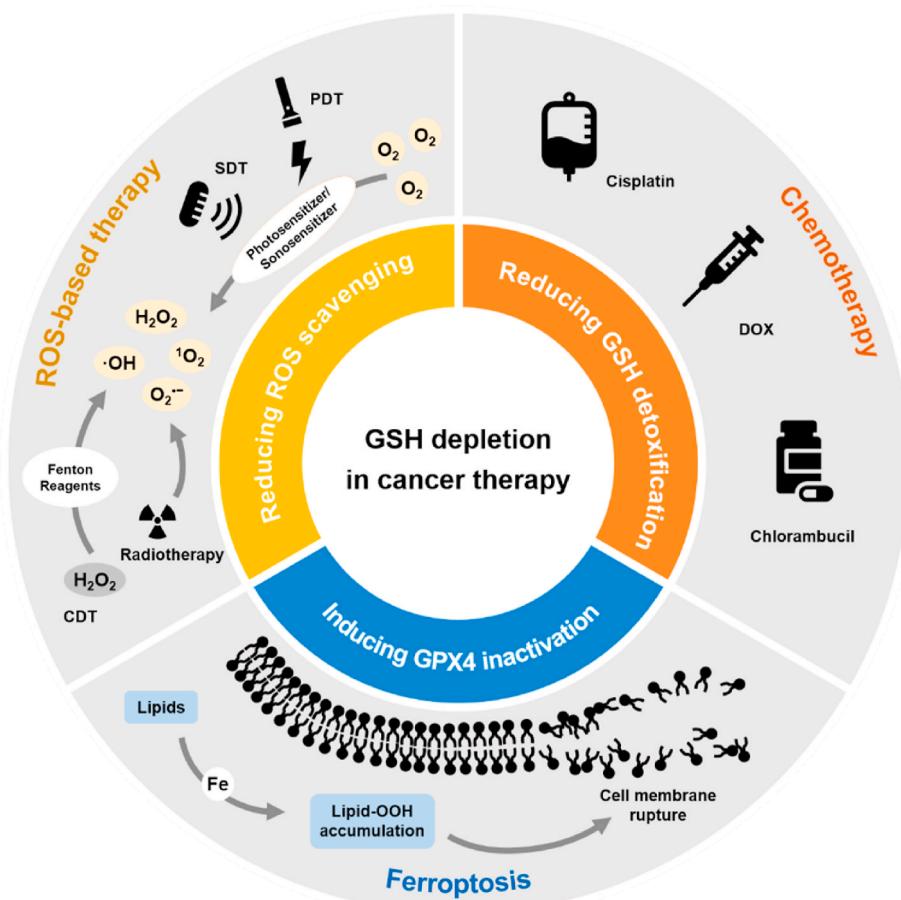


Fig. 2. Applications of GSH depletion in different treatment regimens for cancer therapy.

mice. Mechanism studies indicated that tumor cells died in a ferroptotic manner resulting from GPX4 inactivation induced by GSH depletion [135].

3. Synthesis and metabolism of GSH

Understanding the synthetic and metabolic process of GSH is necessary before we search for key sites to intervene and deplete intracellular GSH (Fig. 1A). GSH is a tripeptide synthesized from glutamate (Glu), cysteine (Cys), and glycine (Gly) via two adenosine triphosphate (ATP)-dependent enzymatic reactions, which occurred in cytoplasm. The three kinds of amino acids used for GSH synthesis are from different pathways. Glu in cytoplasm is primarily produced by the hydrolysis of glutamine (Gln), which is transported into cells by several transmembrane amino acid transporters [17]. Most of Cys is obtained by the reduction of cystine, a dimer of Cys. Cystine is transported into cells by the system X_c^- , which is a crucial target of controlling intracellular Cys supply [154]. During the transportation, one Glu molecule is transported out of cells in exchange for each cystine molecule. Cys also can be directly transported into cells via an amino acid transporter [155]. The transportation of Gly is mediated by glycine transporter (GlyT). The two-step synthetic process of GSH involves two important enzymes, glutamate-cysteine ligase (GCL) and glutathione synthetase (GS). Firstly, GCL catalyzes the formation of γ -glutamylcysteine from Glu and Cys. Subsequently, the dipeptide is conjugated with Gly under the catalysis of GS to form GSH. Each step consumes one molecule of ATP [156].

Given the facts above, it is speculated that GSH synthesis is controlled by three factors—raw materials, enzymes, and energy. Abundant supply of amino acids is the premise of GSH synthesis.

Generally, Cys shortage accounts for most of the dysfunction of GSH synthesis. The transporter of cystine, system X_c^- , is considered to be an important target to limit Cys supply and interfere with GSH synthesis [154]. In addition, the deficiency of Glu or Gly can also limit GSH synthesis in some cases [40,157]. GCL is a vital enzyme that limits the rate of GSH synthesis, which is another important target for GSH depletion. The function of GCL is affected by the expression level of GCL, the ratio of its two subunits, and the enzymatic activity, which are related to the redox levels in cells [41,158,159]. Specifically, the expression of GCL is regulated by nuclear factor erythroid 2-related factor 2 (Nrf2) that is sensitive to oxidative stress [36], and the heterodimer of GCL is regulated by the feedback inhibition of its product GSH [41]. ATP provides energy for the transportation of amino acids and the synthesis of GSH, which also can be a limiting factor of intracellular GSH level [160,161].

Most of the generated GSH distributes in the cytoplasm and plays multiple roles in different physiological processes. A small part of GSH enters the subcellular organelles including mitochondria, nucleus, and endoplasmic reticulum [39]. Although the mechanism of GSH transportation into organelles has not been well elucidated, it was reported that the dicarboxylate carrier and the oxoglutarate carrier probably contributed to the transportation of GSH across the mitochondrial inner membrane [162], and the ryanodine receptor type 1 might participate in the accumulation of GSH in endoplasmic reticulum [163]. Part of GSH is transported out of the cells to maintain the dynamic balance of cellular redox level. MRP1 is the prime efflux pump of GSH [38]. The extruded GSH can be further degraded into Glu and cysteinylglycine, which is catalyzed by γ -glutamyltransferase (GGT), a membrane-bound enzyme on the external surface of certain cells [164]. Cysteinylglycine is further decomposed to Cys and Gly under the catalysis of dipeptidase (DP) [35].

Table 1
Summary of treatment regimens involving GSH depletion.

Purpose of GSH depletion	Main treatment strategies	Ref.
Reducing ROS scavenging	PDT	[19,33, 55–65]
	CDT	[20,32,34, 66–73]
	SDT	[21,74]
	Radiotherapy	[75]
	PDT + CDT	[76–79]
	CDT + SDT	[80–82]
	PDT + PTT	[83]
	CDT + PTT	[84–87]
	PDT + Chemotherapy	[88–92]
	PDT + Antiangiogenesis	[93]
	PDT + NO generation	[94,95]
	CDT + Chemotherapy	[31,96–98]
	CDT + Radiotherapy	[96,99]
	CDT + Immunotherapy	[99]
	CDT + Starvation therapy	[100]
	CDT + MHT	[101]
	PDT + CDT + PTT	[102–104]
	PDT + CDT + Chemotherapy	[105,106]
	PDT + PTT + Immunotherapy	[107]
	PDT + Chemotherapy + Immunotherapy	[108]
	PDT + CDT + PTT + Immunotherapy	[109]
	CDT + SDT + Gene therapy	[110]
	CDT + Chemotherapy + PTT	[111,112]
	PTT + Immunotherapy	[113]
	ROS generation by TeO ₆ ⁶⁻	[114]
	¹ O ₂ generation by the Russell mechanism	[115]
	-OH generation by non-Fenton-type reaction + PTT	[116]
	Chemotherapy + Starvation therapy + H ₂ O ₂ generation	[117]
	H ₂ O ₂ generation by GOD + GSH depletion	[118]
	NAMPT-Regulating therapy + ROS generation by Bi-HA/FK866	[119]
Reducing GSH detoxification	ROS generation by AuNPs and He-CAP	[120]
	ROS generation + GSH depletion by AOBQ	[121,122]
	Chemotherapy by cisplatin	[29,123,124]
	Chemotherapy by Pt (IV) prodrugs	[30, 125–128]
	Chemotherapy by carboplatin	[129]
	Chemotherapy by chlorambucil	[130]
	Chemotherapy by doxorubicin	[131]
	Targeted therapy by lenvatinib + PDT	[132]
	Chemotherapy by ursolic acid	[133]
	Ferroptosis	[134]
Inducing GPx4 inactivation	Ferroptosis + Chemotherapy	[135]
	Ferroptosis + PDT	[136]
	Ferroptosis + CDT	[137]
	Ferroptosis + PTT	[138,139]
	Ferroptosis + CDT + Autophagy	[140]
	Free-Radical-Based Therapy	[141]
	Sensitization of tumor cells to therapy	[142]

Notes: glutathione, GSH; reactive oxygen species, ROS; photodynamic therapy, PDT; chemodynamic therapy, CDT; sonodynamic therapy, SDT; photothermal therapy, PTT; nitric oxide, NO; magnetic hyperthermia therapy, MHT; tellurium hexoxide, TeO₆⁶⁻; singlet oxygen, ¹O₂; hydroxyl radical, -OH; glucose oxidase, GOD; nicotinamide phosphoribosyltransferase, NAMPT; FK866 loaded bismuth-humic acids heterojunction, Bi-HA/FK866; gold nanoparticles, AuNPs; helium-based cold atmospheric plasma, He-CAP; 4-acetamido-o-benzoquinone, AOBQ; glutathione peroxidase 4, GPx4.

These amino acids are transported into cells again for *de novo* synthesis of GSH. This process, known as γ -glutamyl cycle, is indispensable to maintain the concentrations of intracellular GSH and Cys [165]. Recent findings showed that the decomposition of GSH also occurred inside of

cells [166]. In this process, cation transport regulator-like protein (ChaC) family enzymatically degrades GSH into 5-oxoproline and cysteinylglycine, which are further degraded and participate in a new round of synthesis [167]. After reaction with oxidizing substances, GSH is converted to its oxidized form GSSG. The accumulation of GSSG is potentially toxic to cells [167]. Excess GSSG can be extruded by cells or be reduced to GSH under the catalysis of glutathione reductase (GR) [168]. Nicotinamide adenine dinucleotide phosphate (NADPH) is an essential substrate in the GSSG reduction process. This conversion is another important source of GSH, so the modulation of GR or NADPH can also affect the intracellular GSH level.

4. Strategies for GSH depletion

Varieties of strategies have been proposed to reduce the intracellular GSH levels based on different demands for cancer therapy. According to the synthetic and metabolic process of GSH, these strategies can be divided into four categories based on different mechanisms: i) cutting off the supply of raw materials for GSH synthesis; ii) inhibiting GSH synthesis or regeneration; iii) consuming GSH reserves; iv) promoting GSH efflux (Fig. 1B & Table 2).

4.1. Cutting off the supply of raw materials for GSH synthesis

Normal supply of amino acids is the premise of GSH synthesis. If the extracellular amino acids used for GSH synthesis cannot be transported into cells, the routine biological synthesis of GSH will be inhibited and the intracellular GSH levels will decrease. Cys starvation is a common strategy often utilized to reduce GSH levels, which depends on the regulation of the system X_c⁻. Extracellular cystine is transported into cells via system X_c⁻ and further reduced into Cys for protein and GSH synthesis. Disturbance of system X_c⁻ can cause Cys starvation, resulting in intracellular GSH depletion. Studies showed that targeting the system X_c⁻ to induce ferroptosis in cancer cells might be a promising approach to cancer therapy [154,171].

Several inhibitors of system X_c⁻, including erastin, imidazole ketone erastin (IKE), sulfasalazine, and sorafenib, have shown apparent efficacies on GSH depletion and cancer therapy. Erastin is the first ferroptosis inducer that selectively inhibits system X_c⁻ and depletes GSH [169]. Yu et al. used folate-targeting exosomes to deliver erastin to triple negative breast cancer cells. The system could selectively target MDA-MB-231 cells and deplete intracellular GSH, efficiently leading to GPX4 suppression and ferroptotic cell death [170]. IKE is an erastin analogue with high metabolic stability and moderate water solubility, which has shown potent inhibition effect on system X_c⁻ [218]. A study conducted by Zhang et al. demonstrated that IKE could induce GSH depletion, lipid peroxidation, and ferroptosis, exerting antitumor effect on a mouse xenograft model. In addition, IKE exhibited lower toxicity after being loaded into nanoparticles compared with free drugs [171]. Sulfasalazine is an anti-inflammatory drug as well as an inhibitor of system X_c⁻ [219]. One study showed that sulfasalazine could decrease intracellular GSH levels and increase platinum levels, enhancing DNA damage caused by cisplatin in colorectal cancer cells [172]. In another study, the combination of sulfasalazine and vitamin C was demonstrated to trigger significant GSH depletion and ROS accumulation in prostate cancer cells [173]. A Phase I clinical study of sulfasalazine in combination with cisplatin and pemetrexed for advanced non-small cell lung cancer (NSCLC) suggested that triplet regimen tended to prolong the progression-free survival (PFS) compared with the regimens containing cisplatin or pemetrexed alone [174]. Sorafenib is a clinically approved kinase inhibitor for cancer therapy, which can also inhibit system X_c⁻ and trigger ferroptosis [220]. Low dose of sorafenib in combination with cisplatin could effectively trigger ferroptosis in NSCLC cells by depleting intracellular GSH and inhibit tumor growth *in vivo* [175]. Tang et al. loaded sorafenib into manganese-doped mesoporous silica nanoparticles to induce ferroptosis in hepatocellular carcinoma cells (Fig. 3) [134].

Table 2
Summary of strategies for GSH depletion.

Strategy	Mode of action	Substance	Ref.
Cutting off the supply of raw materials for GSH synthesis	Inhibition of system X _c ⁻	Erasin	[169,170]
		IKE	[171]
		Sulfasalazine	[172–174]
		Sorafenib	[134,137,175]
		Capsazepine	[176]
		Pseudolaric acid B	[177]
		Artemisinin and its derivatives	[178]
		Metadherin	[179]
	Depletion of plasma cystine	Cyst(e)inase	[180,181]
	Inhibition of GCL	BSO	[71,74,104,129,182]
Inhibiting GSH synthesis or regeneration	Inhibition of GS	Sulfinosine	[183]
	Inhibition of GCL and GS	UNC0638	[142]
		AgNPs	[184–187]
	NADPH deficiency by inhibiting PPP	Polydatin	[188]
		Curcumin	[91,189]
		6-aminonicotinamide	[190,191]
		Dehydroepiandrosterone	[190,192]
	NADPH deficiency by consuming NADPH	β-lapachone	[20]
		Nitroimidazole	[72,90]
	NADPH deficiency by downregulating NAD ⁺	(E)-Daporinad	[119]
Consuming GSH reserves	Inhibition of GGT	Acivicin	[193,194]
	Conjugation with GSH	PEITC	[60]
		Sulforaphane	[29]
		Cinnamaldehyde	[59]
		Quinone methide	[83,118,126,130,195]
		Oridonin	[196–198]
		Gambogic acid	[61,92]
		Piperlongumine	[75]
		Maleimide	[113]
		AOBQ	[121,122]
Oxidation of GSH	Luteolin		[199]
	Docosahexaenoic acid		[161]
	Vinyl groups		[58]
	Iodide		[128]
	3-bromopyruvate		[200–202]
	AuNPs		[120,127,138,203–205]
	Sanguinarine		[123]
	Manganese: Mn(IV), Mn(III)		[19,31,56,57,64,79,86–88,93,97,98,107,111,112,116,134,135,137,140]
	Iron: Fe(III), Fe(VI)		[56,63,68,78,81,101–103,105,106,110,139]
	Copper: Cu(II)		[22,33,34,55,65–67,69,73,76,77,82,84,100,102,109,115,139,206,207]
Platinum: Pt (IV)	Platinum: Pt (IV)		[106,108,125]
	Tin: Sn(IV)		[103]
	Tellurium nanowires		[114]
	Molybdenum disulfide		[141]
	Cobalt (II)-based ZIF-67		[32]
	Bimetallic oxide MnWO _x nanoparticles		[21]

Table 2 (continued)

Strategy	Mode of action	Substance	Ref.
		Bimetallic Oxide FeWO _x Nanosheets	[99]
		Gallium indium liquid metal eutectic alloy	[87]
		PtCu ₃ nanocages	[80]
		Cerium oxide	[85,131]
		CoO@AuPt nanozyme	[70]
		Disulfide bonds	[30,62,89,117,133,136,139,142]
		Calcium peroxide nanoparticles	[124]
		ZnPc	[132]
Promoting GSH efflux	Regulation of MRP1	NO/Nitrate ester Verapamil and its derivatives Flavonoids Stauroporine PAK-104P	[94,95][208,209][210–215][216][217]

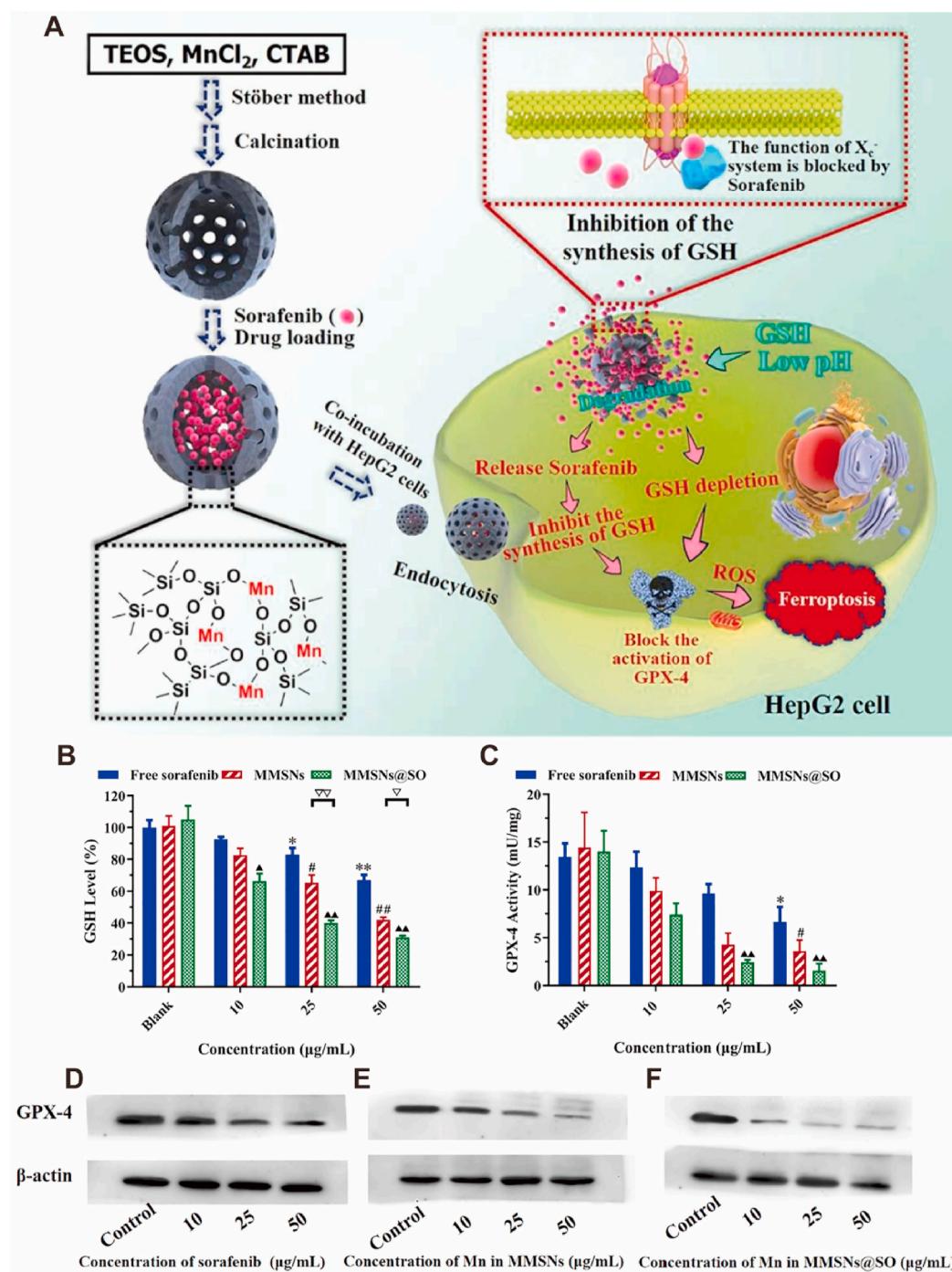
Notes: glutathione, GSH; imidazole ketone erasin, IKE; glutamate-cysteine ligase, GCL; L-buthionine sulfoximine, BSO; glutathione synthetase, GS; silver nanoparticles, AgNPs; nicotinamide adenine dinucleotide phosphate, NADPH; pentose phosphate pathway, PPP; NAD⁺; γ-glutamyltransferase, GGT; β-Phenylethyl isothiocyanate, PEITC; 4-acetamido-o-benzoquinone, AOBQ; gold nanoparticles, AuNPs; zinc phthalocyanine, ZnPc; nitric oxide, NO; multidrug resistance-associated protein 1, MRP1.

Significant GSH depletion and GPX4 inactivation were achieved through the inhibition of GSH synthesis by sorafenib and the consumption of GSH by reducing the manganese-oxidation bonds in nanoparticles. A number of other compounds, like capsazepine [176], pseudolaric acid B [177], artemisinin and its derivatives [178], and metadherin [179] have also been confirmed to exhibit inhibition effects on system X_c⁻ and trigger ferroptosis by depleting cellular GSH. Besides targeting system X_c⁻, depleting plasma cystine by administration of cyst(e)inase, an engineered enzyme that degrades both cystine and Cys in circulation, has been demonstrated to cause tumor suppression via ferroptosis [180, 181].

4.2. Inhibiting GSH synthesis or regeneration

The synthesis and regeneration of GSH are controlled by several critical enzymes and molecules, which are indispensable for maintaining intracellular GSH level. Regulation of these enzymes or molecules provides an effective approach to GSH depletion.

GCL is a vital enzyme that limits the rate of GSH synthesis. L-buthionine sulfoximine (BSO), an inhibitor of GCL, was often utilized to reduce GSH levels via blocking GSH synthesis. BSO was usually used in combination with reactive species-producing agents to reduce ROS scavenging or with chemotherapeutics to protect them from detoxification. Yoo et al. used chlorin e6 (Ce6)-loaded polymer nanoparticles and BSO for enhanced PDT [182]. The combination of BSO and Ce6-loaded NPs resulted in significant suppression of tumor growth compared with the treatment without BSO (Fig. 4A–C). Cruz et al. investigated the effects of GSH synthesis inhibition on the restoration of ovarian cancer cells sensitivity to carboplatin by using folate-targeted and BSO-loaded polyuria dendrimer nanoparticles (Fig. 4D) [129]. The results showed that this formulation improved the cytotoxicity of carboplatin to ovarian cancer cells while having minor effects on non-cancer cells. Besides BSO, sulfinosine, a purine nucleoside analog, was reported to inhibit the expression of GCL and decrease intracellular GSH levels [183]. In addition, GSH depletion could also be achieved by inhibiting GS. Wang et al. found that the expression of GS was positively correlated with histone methyltransferase G9a in pancreatic ductal adenocarcinoma (PDAC). They used a L-cysteine-based poly (disulfide amide) polymer to encapsulate a G9a inhibitor (UNC0638), which



decreased the GSH levels in PDAC by simultaneously blocking GSH biosynthesis and consuming GSH reserve (Fig. 4E–H) [142]. Silver nanoparticles (AgNPs) also showed a size-dependent GSH depletion ability in several cell types [184–186]. Although the inhibition on GSH-synthesizing enzymes (GCL and GS) was observed in human liver cells after AgNPs treatment [187], the mechanism of AgNPs on GSH depletion is still unclarified.

GSH can be regenerated from GSSG under the catalysis of GR in a NADPH-dependent manner, which is also an important source of intracellular GSH. NADPH is essential for this reduction process and its deficiency will result in GSH depletion as well as enhanced oxidative stress in cells [221]. Generally, there are two approaches to depleting NADPH. One way is to inhibit the pentose phosphate pathway (PPP) that

Fig. 3. (A) Schematic illustration of preparation and ferroptosis-inducing mechanism of sorafenib-loaded manganese-doped mesoporous silica nanoparticles (MMSNs@SO). (B) GSH levels and (C) GPX4 activity in HepG2 cells treated with free SO, MMSNs, and MMSNs@SO at different concentrations. Western blot results of GPX4 expression levels in HepG2 cells after treatment with (D) free SO, (E) MMSNs, and (F) MMSNs@SO at different concentrations. * $P < 0.05$, ** $P < 0.01$, ^ $P < 0.05$, ^ $P < 0.01$ and # $P < 0.05$, ## $P < 0.01$ vs blank group, $\nabla P < 0.05$, $\nabla\nabla P < 0.01$ vs cells treated with MMSNs. Adapted with permission from Ref. [134]. Copyright 2019 Elsevier Ltd.

produces NADPH. Glucose-6-phosphate dehydrogenase (G6PD) is a vital enzyme of PPP, which can be a target for NADPH depletion. The inhibition of G6PD by a natural molecule polydatin was proved to enhance oxidative stress and suppress malignant proliferation and metastasis *in vivo* [188]. Curcumin could decrease GSH and induce oxidative stress in melanoma A375 cells, which was attributed to its interference on PPP by decreasing G6PD expression [189]. The combination of G6PD inhibitor and cisplatin was demonstrated to improve the cytotoxic effects of cisplatin and help to overcome drug resistance in cancer cells [190]. Another way is to consume the produced NADPH. β -lapachone is a novel anticancer drug that can consume NADPH and generate ROS via a quinone oxidoreductase-1 (NQO1)-dependent futile cycle [222]. Chen et al. loaded β -lapachone into iron oxide nanocarriers to construct a

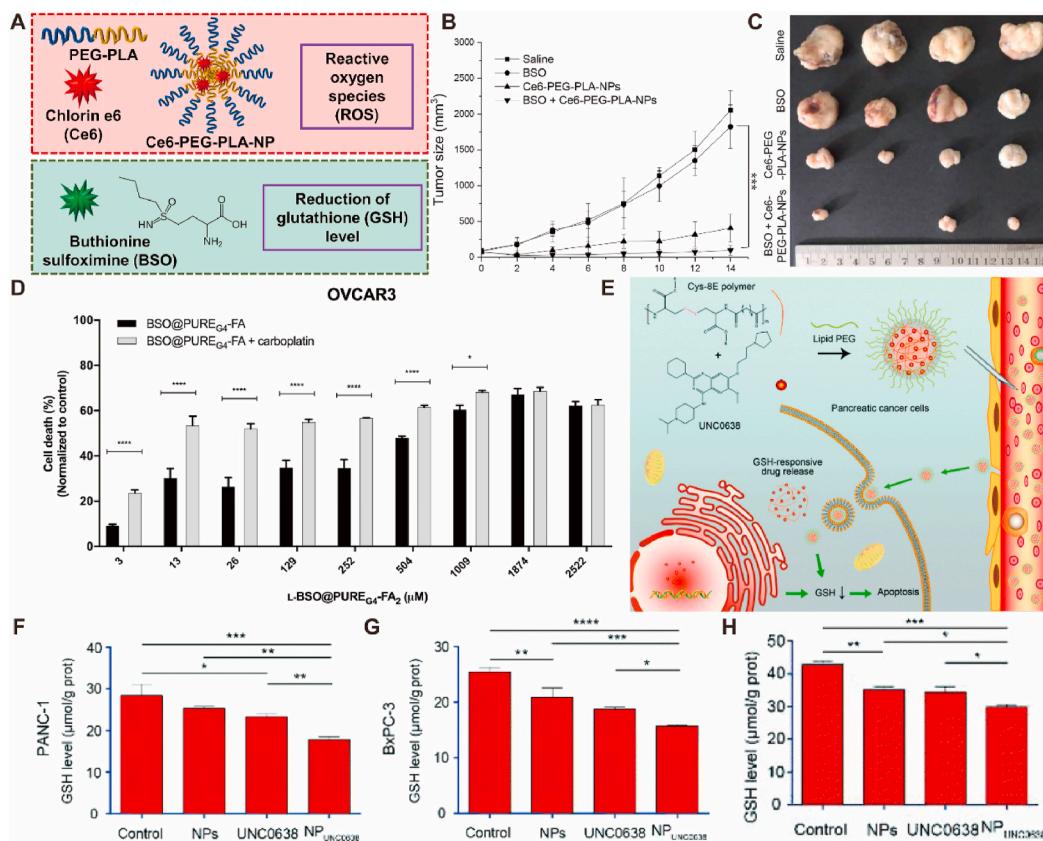


Fig. 4. (A) Schematic illustration of combination tumor therapy with BSO and Ce6-loaded NPs. (B) Tumor growth curve and (C) tumor images after different treatments ($n = 4$). *** $P < 0.001$. Adapted with permission from Ref. [182]. Copyright 2020 Elsevier Ltd. (D) Folate-targeted and BSO-loaded polyuria dendrimer nanoparticles ($L\text{-BSO}@PUR{E}_{G4}\text{-FA}_2$) sensitized ovarian cancer cells to carboplatin toxicity. Adapted with permission from Ref. [129]. Copyright 2020 Cruz et al. CC by license. (E) Schematic illustration of UNC0638-loaded Cys-8E polymer-based nanoparticles for the treatment of PDAC. GSH levels in (F) PANC-1 cells, (G) BxPC-3 cells, and (H) PDAC tumor tissues after different treatments. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$. Adapted with permission from Ref. [142]. Copyright 2020 The Royal Society of Chemistry.

nanosystem that had both Fenton-like reagents and GSH depletion properties (Fig. 5) [20]. The system significantly increased ROS production and decreased intracellular GSH levels, enhancing the therapeutic efficacy of CDT. The reduction process of nitroimidazole (NI) to aminoimidazole under hypoxia condition can consume NADPH, which also can be used to inhibit GSH regeneration. Deng et al. built hypoxia-responsive micelles based on NI-bearing polymer for DOX and Ce6 delivery (Fig. 6) [90]. Under the hypoxia condition in TME, the NI moiety was reduced accompanying by NADPH consumption, which resulted in GSH depletion, micelle disassembly, and cargo release. Besides, Song et al. reported the method of downregulation of NAD⁺ by FK866 to decrease the expression of NADPH [119]. However, the mechanism was not well verified or clarified. GR also can be a target to regulate the GSH/GSSG ratio for cancer therapy. 2-acetylamino-3-[4-(2-acetylamino-2-carboxyethylsulfanylcarbonylamino) phenyl carbamoylethyl] propionic acid (2-AAPA) is an irreversible GR inhibitor. The oxidative stress caused by 2-AAPA-induced GR inhibition effectively suppressed melanoma metastasis and enhanced killing ability of anticancer agents to human glioblastoma cells [223,224]. However, the elevated oxidative stress was attributed to the increase of GSSG, while no significant change of GSH level was observed as a result of GR inhibition [225].

The amino acids degraded from extruded GSH are another source of raw materials for GSH synthesis. This degradation process is catalyzed by GGT. Increased expression of GGT was observed in a few types of tumors [226]. Acivicin is an irreversible inhibitor of GGT that was demonstrated to be able to reduce GSH levels in some types of cells [193, 194]. Several other GGT inhibitors like L-DON

(6-diazo-5-oxo-L-norleucine) and azaserine (O-diazoacetyl-L-serine) were also reported, although the toxicities of these compounds were still a problem [227]. However, in view of the complex roles of GGT in modulating redox homeostasis and physiological activity in cells, more investigations are necessary before taking advantage of it in cancer therapy [228].

4.3. Consuming GSH reserves

A lot of studies focused on consuming the GSH that is already generated, achieving significant decrease of intracellular GSH levels within a short time. This kind of strategy takes advantage of the inherent properties and functions of GSH by delivering certain substances to react with GSH. One approach is to conjugate GSH with specific molecules based on GSH detoxification, forming GS-X conjugates that will be extruded out of the cells later. Another approach is to oxidize GSH with oxidizing substances or groups based on the reducibility of GSH, producing GSSG that will be extruded by cells or reduced back to GSH later.

4.3.1. Conjugation with GSH

Under the catalysis of GST, GSH detoxifies certain xenobiotics by directly conjugating with them and forming GS-X conjugates that will be further extruded by MRP1. This GSH-consuming detoxification process can be used to reduce intracellular GSH levels. Isothiocyanates (ITC) and α , β -unsaturated aldehydes or ketones are commonly used compounds for GSH depletion in this way.

ITC are naturally occurring compounds enriched in cruciferous vegetables which have been shown to exhibit definite activities in cancer

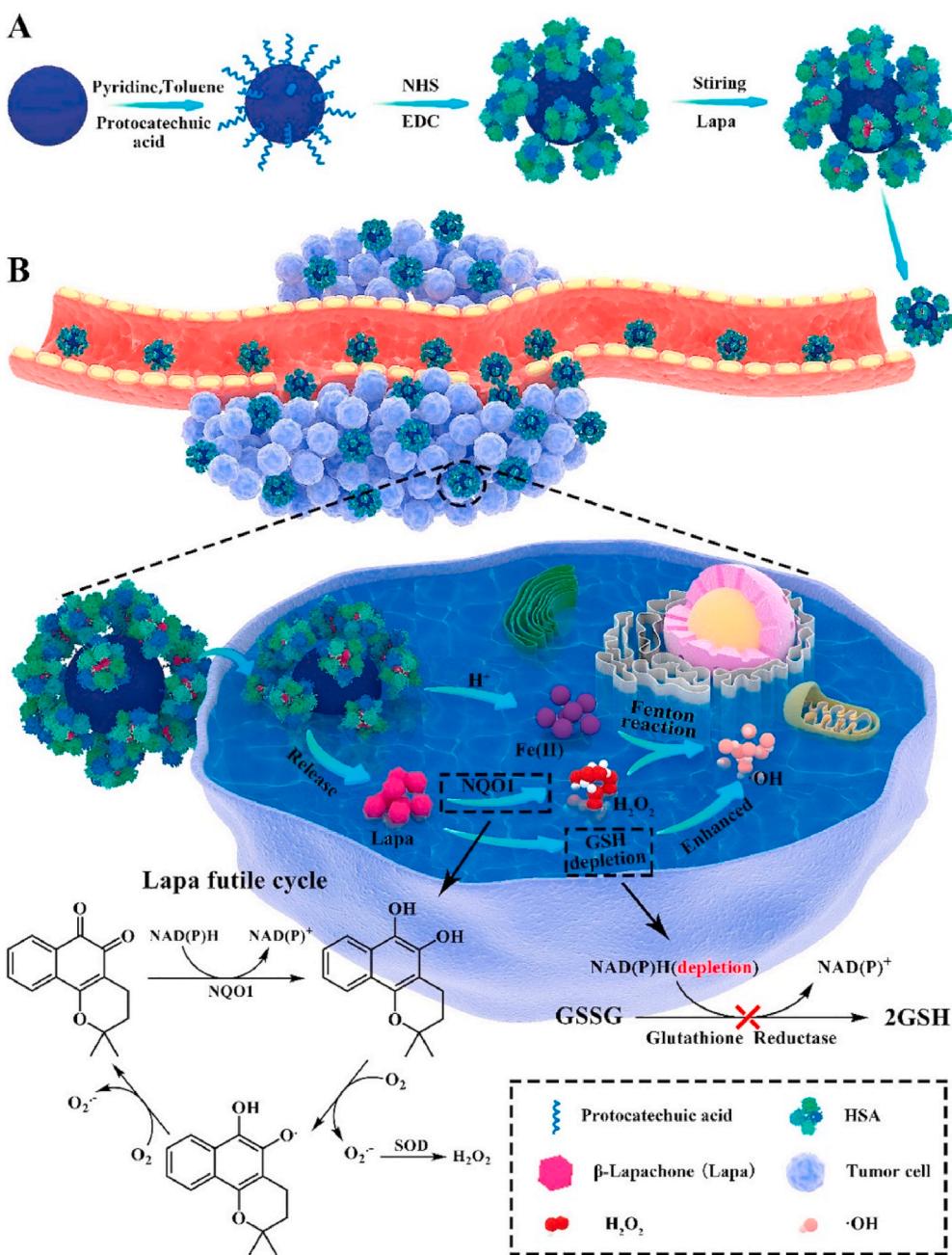


Fig. 5. (A) Schematic illustration of the preparation of β -lapachone-loaded iron oxide nanoparticles ($\text{Fe}_3\text{O}_4\text{-HSA@Lapa NPs}$). (B) The mechanism of $\text{Fe}_3\text{O}_4\text{-HSA@Lapa NPs}$ for collaborative enhancement of CDT efficacy based on GSH depletion and Fenton reaction. Adapted with permission from Ref. [20]. Copyright 2019 American Chemical Society.

chemoprevention and tumor suppression [229,230]. The conjugation of ITC and GSH is driven by the reaction between the highly electrophilic central carbons of ITC and the sulphydryl groups (-SH) of cysteine residues in GSH [17]. ITC like β -Phenylethyl isothiocyanate (PEITC) and sulforaphane (SFN) have been reported to effectively deplete GSH in cancer therapy. Hu et al. used PEITC to deplete GSH for enhancing PDT based on indocyanine green (ICG)-loaded nanoparticles. *In vitro* and *in vivo* results showed that PEITC depleted GSH in a dose-dependent manner and its combination with PDT exhibited a synergistic anti-tumor effect [60]. However, PEITC was administrated by intraperitoneal injection, which would probably cause undesirable systemic toxicity. Drug delivery by nanotechnology based on tumor-targeting ability provides a better choice with less systemic toxicity and side effects. Xu et al. constructed a polymeric nanoparticles-based co-delivery system

containing a cisplatin derivative and SFN for breast cancer treatment (Fig. 7A) [29]. This nanoformulation could be effectively internalized by breast cancer cells, inducing significant GSH depletion and cell apoptosis, as compared with simply combinational treatment of cisplatin and SFN.

α , β -unsaturated aldehydes or ketones are a kind of substance that can specifically react with thiols by Michael Addition, showing potentials in conjugating and depleting GSH [59,231]. Cinnamaldehyde (Cin) is a natural compound with a α , β -unsaturated aldehyde group in the structure. Liu et al. used Ce6 and Cin as photosensitizer and GSH scavenger, respectively, to build a H_2O_2 -activated oxidative stress amplifier [59]. The GSH levels in tumor tissues after different treatments were measured by Ellman's assay. A marked decrease of GSH was observed in groups treated with the addition of Cin, which promoted ROS

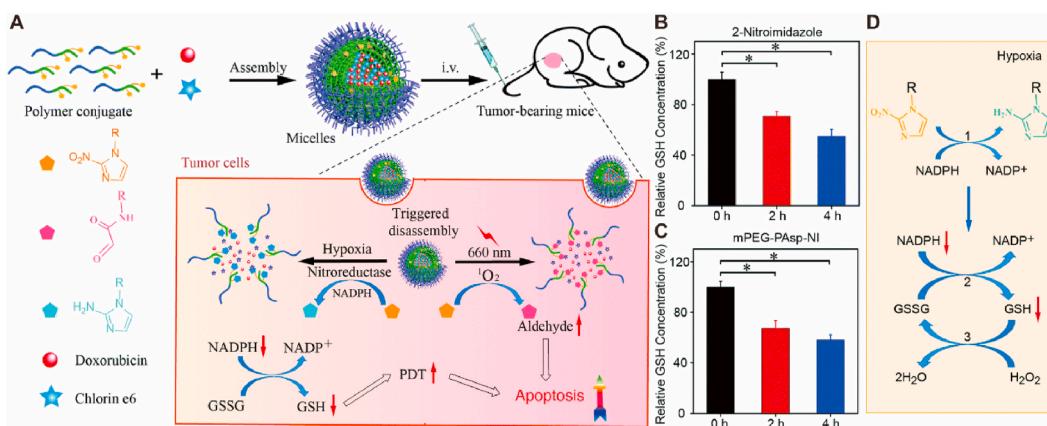


Fig. 6. (A) Schematic illustration of the hypoxia- and singlet oxygen-responsive micelles based on NI-bearing polymer for chemotherapy and PDT. Relative GSH concentrations in the 4T1 cells treated with (B) 2-nitroimidazole and (C) NI-bearing polymer (mPEG-PAsp-NI) under hypoxia. (D) The proposed mechanism of NI-induced GSH depletion (1: nitroreductase; 2: GR; 3: GPX). * $P < 0.05$. Adapted with permission from Ref. [90]. Copyright 2019 The Royal Society of Chemistry.

accumulation and enhanced PDT efficacy. Quinone methide (QM) has a structure of α , β -unsaturated ketone that can react with GSH via nucleophilic addition reaction, resulting in cytotoxic and cytostatic effects [232]. The application of QM in GSH depletion for cancer therapy has been reported in several studies [118,126,130,195]. Usually, the precursors of QM were integrated in the phenylboronic ester (PBE) moieties of the designed polymers or prodrugs, which have H_2O_2 -responsive properties. High levels of H_2O_2 in TME would initiate polymer disintegration and QM release. Li et al. constructed a glucose oxidase (GOD)-loaded nanoreactor based on PBE-containing polymers (Fig. 7B) [118]. GOD could catalyze the oxidation of glucose, producing large amounts of H_2O_2 to increase the ROS levels. Subsequently, considerable H_2O_2 induced the destruction of nanoreactor and released QM that can deplete GSH to suppress the antioxidative system. This nanoreactor efficiently increased oxidative stress in tumor cells and ablated tumors *in vivo*. Similar strategy was adopted by Yin et al. on hybrid micelles assembled from PBE-containing polymers and palmitoyl ascorbate, a prooxidant to upregulate the H_2O_2 levels in tumor sites [195]. They also utilized this system to weaken the GSH detoxification of cisplatin by changing palmitoyl ascorbate with a Pt (IV) prodrug. Superior therapeutic efficacy against cisplatin-resistant tumor was observed compared with free cisplatin [126]. Oridonin, a diterpenoid extracted from *Rabdosia rubescens*, was proved to induce apoptosis or necroptosis in several kinds of cancer cells by depleting GSH and enhancing ROS, which could be used to enhance the therapeutic efficacy of chemotherapeutic agents [196–198]. In addition, gambogic acid [61,92], piperlongumine [75], maleimide [113], 4-acetamido-o-benzoquinone (AOBQ) [121,122], and luteolin [199] were also reported to exhibit GSH conjugation and depletion properties.

Other electrophilic molecules or groups that can be conjugated with GSH were also reported. Alkene can react with sulphydryl to form thioether via the thiol-ene click reaction, which is usually initiated by light in the present of initiator [233]. Hu et al. used docosahexaenoic acid to couple with GSH under light irradiation in the present of initiator 2, 2-dimethoxy-2-phenylacetophenone (DMPA). The docosahexaenoic acid, DMPA, as well as photosensitizer zinc phthalocyanine (ZnPc) were loaded in a ROS responsive nanocarrier for GSH depletion-boosted PDT [161]. Cao et al. used an amphiphilic branched copolymer with pendant vinyl groups to react with GSH via thio-ene click reaction. Photosensitizer Ce6 was loaded into the micelles self-assembled from the copolymers and its release was triggered by the reaction. Remarkable GSH depletion and enhanced PDT were demonstrated by *in vitro* and *in vivo* studies [58]. Zhang et al. proposed an approach to depleting GSH via iodo-thiol click chemistry. They prepared a Pt (IV)-containing polymer with pendant iodides to load the photothermal agent IR780. The anti-cancer efficiency of cisplatin was enhanced by iodide-mediated GSH

depletion and near-infrared (NIR)-activated mild hyperthermia (Fig. 8) [128]. 3-bromopyruvate (3-BP) is an electrophilic alkylator which has shown antitumor activities in some tumor types [200,201]. 3-BP's mechanism of action is rather complex. It can be directly conjugated with GSH and also can reduce NADPH levels via inhibiting G6PD, both of which can deplete intracellular GSH [202]. Gold nanoparticles (AuNPs) are regarded as a promising nanoplateform for diagnose and drug delivery, which also exhibit GSH-depleting ability. The strong Au-S bonding interaction between AuNPs and GSH was deemed to contribute to the AuNPs-induced cytotoxicity [203,204]. Mateo et al. found that the GSH depletion ability of AuNPs was size-dependent and smaller AuNPs caused a stronger depletion of GSH compared with larger ones [205]. In addition, sanguinarine, a plant-derived alkaloid was also reported to consume intracellular GSH by direct conjugation [123,234].

4.3.2. Oxidation of GSH

GSH is usually oxidized into GSSG by reacting with oxidizing substances to maintain the redox homeostasis in cells. Taking advantage of this antioxidant role of GSH, we can deliver large amount of oxidizing substances into cells to consume GSH continuously. Metals in oxidation state and disulfides are the most widely used oxidizing substances for this strategy. They are usually integrated into the nanosystems for cancer diagnosis and treatment by distributing in the frameworks, coatings or being used as linkers of the nanostructures.

4.3.2.1. Metals in oxidation state. Several redox-active metal ions in high valence states including manganese (IV), iron (III), and copper (II) can oxidize and consume GSH, while the metal ions themselves are reduced to lower valence states. Metal-organic nanomaterials, especially MOFs, are popular host of metal ions. MOFs are a kind of porous coordination networks composed of metal ions and organic linkers, which has been widely studied for various applications. The unique properties of MOFs including high porosity, large surface area, and tunable structure make them ideal carriers for drug delivery [235,236]. Iron (III) and copper (II) are common central atoms of various MOFs, which give these materials GSH-depletion abilities.

4.3.2.1.1. Manganese-based materials. Tetravalent manganese [Mn (IV)] widely exists in natural minerals in the form of MnO₂. MnO₂ coating on the core nanoparticle is a simple and convenient way to construct a nanosystem with GSH-depletion ability. Moreover, the MnO₂ shell will decompose and further release the encapsulated drugs when Mn(IV) is reduced into Mn(II) by GSH, achieving a redox-responsive drug release effect. Min et al. constructed a photosensitive porphyrin-based MOFs loaded with apatinib for combinational antiangiogenesis and PDT (Fig. 9A) [93]. The nanoparticles were coated with MnO₂ and tumor cell membrane layers for GSH consumption and camouflage,

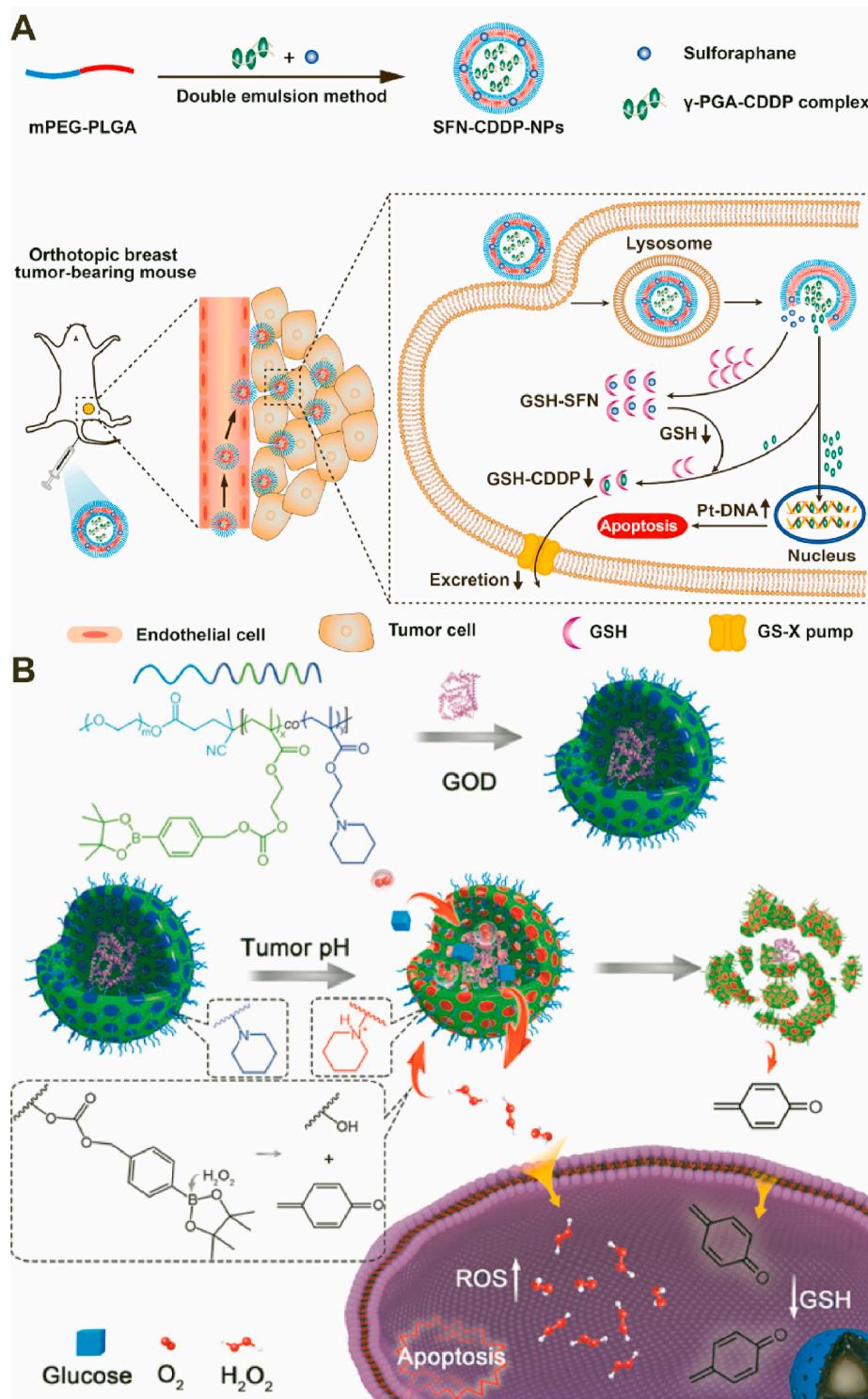


Fig. 7. (A) Schematic illustration of the preparation of polymeric nanoparticles co-loaded with cisplatin derivative and SFN (SFN-CDDP-NPs) and the proposed mechanism of SFN-CDDP-NPs for enhanced chemotherapy. Adapted with permission from Ref. [29]. Copyright 2019 American Chemical Society. (B) Schematic illustration of GOD-loaded nanoreactor based on PBE-containing polymers and its mechanism for synergistic cancer therapy. Adapted with permission from Ref. [118]. Copyright 2017 Wiley-VCH.

respectively. Significant releases of Mn²⁺ and apatinib from the nanoparticles were observed after the addition of GSH. The intracellular GSH levels in 4T1 cells decreased much after treatment with MnO₂-coated nanoparticles. In addition, the produced Mn²⁺ by GSH activation could be used as a T1-weighted magnetic resonance imaging (MRI) contrast agent for *in vivo* tumor imaging. The status of GSH depletion could also be monitored by this GSH-activated MRI to give light irradiation at proper time for more effective PDT [88]. Mn²⁺ is also a Fenton-like reagent that can generate ·OH from H₂O₂ in the presence of HCO₃⁻, which is abundant in physiological medium. Lin et al. prepared

MnO₂-coated mesoporous silica nanoparticles (MS@MnO₂ NPs) with both Fenton-like ion delivery and GSH depletion properties (Fig. 9B) [97]. After being reduced from MnO₂ by GSH, Mn²⁺ performed Fenton-like activity for GSH depletion-enhanced CDT. Besides Mn(IV) in MnO₂, Mn(III) was also used to consume GSH in nanoagents (Fig. 9C) [57]. Therefore, considering the great potential application in GSH depletion, MRI, and CDT, Mn is a fine choice in the construction of multifunctional nanoagents for cancer theranostics.

4.3.2.1.2. Iron-based materials. Iron is another utility player with versatile applications in GSH depletion, MRI, and CDT. Iron in high

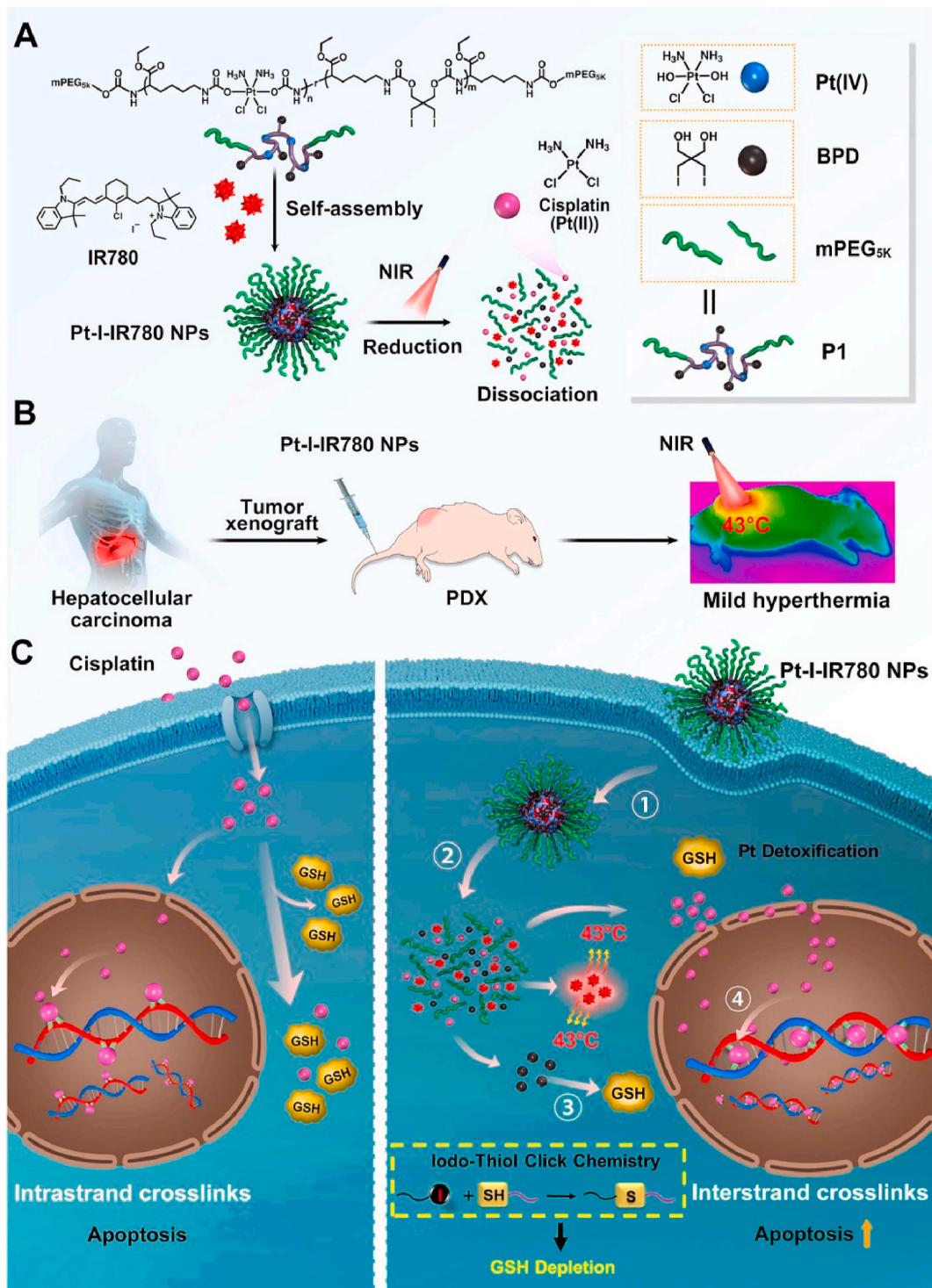


Fig. 8. Schematic illustration of the process of GSH depletion via iodo-thiol click chemistry and the enhanced chemotherapy by self-assembled nanoparticles containing Pt (IV) prodrug and IR780 (Pt-I-IR780 NPs). (A) The composition and the dissociation mechanism of Pt-I-IR780 NPs. (B) The establishment of the hepatocellular cancer (HCC) patient-derived xenograft (PDX) model and local irradiation of the tumor. (C) The mechanism of mild hyperthermia-enhanced GSH depletion and increased formation of interstrand Pt-DNA cross-links by Pt-I-IR780 NPs under NIR light irradiation. Adapted with permission from Ref. [128]. Copyright 2020 American Chemical Society.

valence state, usually Fe(III), consumes GSH via redox reaction while Fe (III) itself is converted to Fe(II). Wan et al. prepared Fe(III)-TCPP [4,4,4,4-(porphine-5,10,15,20-tetrayl) tetrakis (benzoic acid)] MOFs with dihydroartemisinin (DHA) loading and CaCO₃ coating for the synergistic CDT, PDT, and oncosis therapy (Fig. 10A) [105]. When the nanoparticles reached tumor sites, the outer CaCO₃ coating would

dissolve in weakly acidic TME and release Ca²⁺. The intracellular GSH was decreased by MOFs due to the reduction of Fe³⁺ into Fe²⁺, followed by photosensitizer TCPP activation and DHA release. DHA was an anticancer drug that could be activated by Fe²⁺ and generated free radicals for CDT. Moreover, DHA also had an effect on the Ca²⁺ pump ATPase and caused cytosolic Ca²⁺ increase, which induced oncosis-like

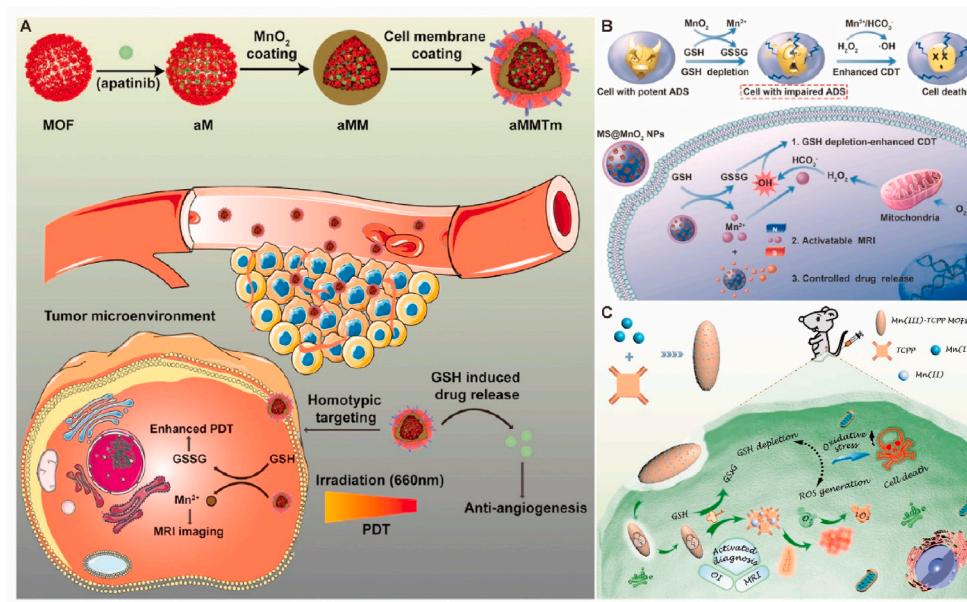


Fig. 9. (A) Schematic illustration of the preparation of MnO₂- and tumor cell membrane-coated photosensitive porphyrin MOFs (aMMTm) and the proposed mechanism of aMMTm for combinational PDT and antiangiogenesis. Adapted with permission from Ref. [93]. Copyright 2019 Wiley-VCH. (B) Schematic illustration of the mechanism of MnO₂ as a chemodynamic agent for enhanced CDT and the application of MS@MnO₂ NPs for MRI-monitored chemo-chemodynamic combination therapy. Adapted with permission from Ref. [97]. Copyright 2018 Wiley-VCH. (C) Schematic illustration of the Mn(III)-sealed MOFs for enhanced PDT by controlled ROS generation and GSH depletion. Adapted with permission from Ref. [57]. Copyright 2019 American Chemical Society.

cell death with exogenous Ca²⁺. Iron also can form other metal-organic nanomaterials based on coordination interaction. Huang et al. constructed a ferric pyrophosphate-based nanoagent (FeP-ZnPc) for synergistic NIR-triggered photo/chemodynamic therapy with GSH depletion ability [78]. Zhu et al. developed a Fe(III)-porphyrin coordinated nanostructure anchored with RGD ligands and manganese superoxide dismutase (SOD2) siRNA for combinational sonodynamic and gene therapy guided by fluorescence/MRI. The results demonstrated that ROS production, GSH depletion, and down-regulation of SOD2 synergistically enhanced the efficacy of SDT (Fig. 10B) [110]. Besides Fe(III), Fe (VI) was also used to deplete GSH. Fu et al. integrated ferrate (VI) and sonosensitizer protoporphyrin IX into hollow mesoporous organosilica nanoparticles for SDT. The ferrate (VI) could not only react with GSH to achieve GSH depletion, but also effectively react with water or H₂O₂ to produce oxygen [81]. These properties implied the application potential of Fe(VI) in hypoxic solid tumor treatment.

4.3.2.1.3. Copper-based materials. Copper (II) is another popular choice to deplete GSH by its redox reaction with GSH. Copper ions are usually integrated into nanoplatforms in the form of MOFs. Cu(II)-based or Cu(II)-doped MOFs with GSH-depleting property have been used to load chemotherapeutic drugs, photosensitizers, and photothermal agents for combination therapy. Wang et al. synthesized Cu(II) carboxylate-based MOFs loaded with photosensitizers for PDT against cancer (Fig. 11A) [55]. The Cu(II) of MOFs effectively scavenged intracellular GSH, followed by the decomposition of MOFs and photosensitizer release. The enhanced antitumor efficacy was confirmed in a hyperplastic liver tumor model based on transgenic zebrafish. In addition to being loaded into the cavity of MOFs, certain photosensitizers like TCPP could serve as the organic ligands of Cu(II)-based MOFs, which greatly improved the loading efficiency and versatility of the nanocarriers [115]. Cu(II) is reduced into Cu(I) after reaction with GSH, which is also a Fenton-like reagent that can generate toxic ·OH by decomposing H₂O₂. An et al. used Cu²⁺-doped zeolitic imidazolate frameworks (ZIF-8) to wrap polydopamine (PDA) nanoparticles, a kind of photothermal agent, for combined CDT and PTT (Fig. 11B) [84]. The GSH content in MCF-7 cells treated with the nanoparticles significantly decreased in a Cu concentration-dependent manner. The results also indicated that PDA-induced photothermal effect could accelerate GSH consumption and improve ROS production. Moreover, the doped Cu²⁺ was reported to enhance the oxygen storage capacity of ZIF-8 matrix, which probably helped to relieve the hypoxia dilemma of

oxygen-dependent PDT [77]. Besides MOFs, Copper can form other metal-organic compounds. Ma et al. synthesized copper-cysteine mercaptide nanoparticles (Cu-Cys NPs) through the coordination interaction between copper ions and sulphydryl groups for GSH-activated CDT. Cu-Cys NPs reacted with intracellular GSH to induce GSH depletion, while Cu²⁺ was reduced to Cu⁺. The generated Cu⁺ would react with H₂O₂ and generate toxic ·OH via Fenton-like reaction [34]. Copper can also coordinate with nonmetal inorganic materials. Ju et al. integrated Cu²⁺ with graphitic carbon nitride, forming Cu²⁺-g-C₃N₄ nanosheet as a photosensitizer. The GSH depletion ability of Cu²⁺-g-C₃N₄ protected the ROS generated under light irradiation and improved the efficacy of PDT [22]. Endogenous copper can also be utilized to deplete intracellular GSH through specific transportation. Bao et al. designed a Cu(II) pro-ionophore using boronate-protected naphthazarin (PNap) as a pro-oxidant (Fig. 12A and B) [206]. The H₂O₂ in cancer cells would activate the PNap and then release naphthazarin (Nap) with the help of GSH. Nap could rapidly alkylate GSH and form Nap-GSH adduct, which was extruded out of the cells. This Nap-GSH adduct worked as a pro-ionophore to transport Cu(II) into cells, followed by reduction by GSH, generating Cu(I) and Nap-GSH adduct. The Nap-GSH adduct was then extruded out for next cycle. This process achieved continuous GSH depletion, resulting in the redox imbalance of cancer cells. The authors also developed other copper pro-ionophore based on similar mechanism [207]. This strategy probably can be applied in combination with exogenous Cu(II) delivery, further enhancing the GSH depletion efficacy.

4.3.2.1.4. Platinum-based materials. GSH depletion also can be induced by the reduction of Platinum (IV). Platinum (II)-based anti-cancer drugs including cisplatin, carboplatin, and oxaliplatin have been commonly used in clinical therapy. However, these drugs still have some drawbacks including poor stability, low bioavailability, and drug resistance. To solve these problems, versatile Pt (IV) prodrugs have been designed by modifying the axial positions of platinum, which was proved to be more stable and effective [237]. After uptake by cells, Pt (IV) can be reduced to the active form Pt (II) by GSH, accompanying with the depletion of GSH. Ling et al. developed a self-assembled nanoparticle platform for Pt (IV) prodrug delivery (Fig. 12C) [125]. The Pt (IV) prodrug effectively consumed the intracellular GSH in cisplatin-resistant A2780 cells and released active Pt (II) metabolites. As a result, GSH detoxification of cisplatin was significantly relieved, which contributed to superior therapeutic efficacy towards cisplatin-resistant

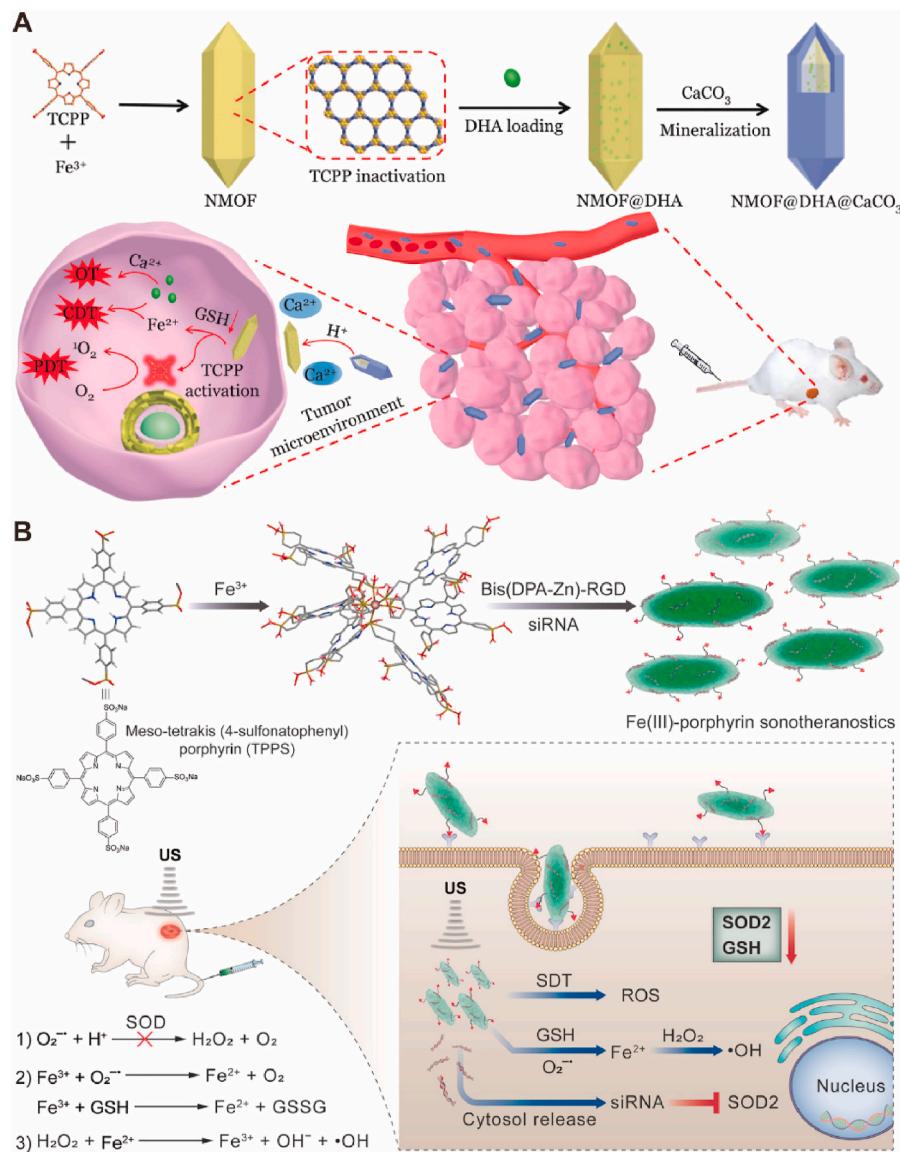


Fig. 10. (A) Schematic illustration of the preparation of the Fe(III)-TCPP MOFs with DHA loading and CaCO₃ coating (NMOF@DHA@CaCO₃) and the proposed mechanism of NMOF@DHA@CaCO₃ for cancer therapy. Adapted with permission from Ref. [105]. Copyright 2019 Wiley-VCH. (B) Schematic illustration of the preparation of Fe(III)-porphyrin sonotheranostics and the mechanism of sonotheranostics for enhanced SDT based on ROS production, GSH depletion, and down-regulation of SOD2. Adapted with permission from Ref. [110]. Copyright 2019 Wiley-VCH.

tumor.

4.3.2.1.5. Polymetal-based materials and other metal-based materials.

In terms of the successful application of single metal-based nanoagents, polymetallic composites containing two or more kinds of redox-active metal ions can be an attractive choice to integrate more functions for different therapeutic needs. Liu et al. prepared biodegradable mesoporous copper/manganese silicate nanospheres with biomimetic cancer cell membrane coating (mCMSNs) (Fig. 13) [76]. The copper silicate in mCMSNs could act as photosensitizer and produce singlet oxygen for PDT under light irradiation. After redox reaction with GSH, mCMSNs released Cu⁺ and Mn²⁺, which could act as Fenton-like reagents to generate ·OH for CDT by catalyzing endogenous H₂O₂. In addition, the released Mn²⁺ could also be used for MRI-guided therapy. This polymetallic silicate nanosystem achieved multifunctional and multi-strategy cancer therapy, enhancing the anticancer efficacy without complex design. Other polymetallic composite materials, such as the combination of Cu and Fe [102], Mn and Fe [56], and Pt and Fe [106] were also reported to construct multifunctional anticancer nanosystems with GSH-depletion ability.

In addition to Mn, Fe, Cu, and Pt, other metal-based materials, such as tellurium nanowires [114], molybdenum disulfide [141], cobalt (II)-based ZIF-67 [32], MnWO₄ nanoparticles [21], FeWO₄ Nanosheets

[99], gallium indium liquid metal eutectic alloy [87], PtCu₃ nanocages [80], Cerium oxide (CeO₂) [85,131], and CoO@AuPt nanzyme [70] have also been reported to exhibit GSH-depleting ability, although some of the mechanisms were not explained clearly.

4.3.2.2. Disulfide bonds. Disulfide bonds (S-S) in groups or molecules can be cleaved by GSH via redox reaction, generating sulfhydryl groups and GSSG. This strategy is commonly used to release drugs in GSH-abundant tumor cells, known as redox-responsive drug delivery [238]. Considering the mechanism, it is not difficult to infer that sufficient disulfide bonds may induce GSH depletion in cells. Framework doping is an effective way to integrate substantial S-S in the structure of nanoparticles. Generally, S-S is previously integrated into the building blocks of biomedical materials, such as ligands and polymers. Then, these S-S-containing blocks can be used to form the nanostructure in specific ways. Meng et al. synthesized a kind of MOFs for Ce6 delivery based on the coordination interaction between the S-S-bearing imidazole ligand and zinc (Fig. 14A) [136]. Compared with the control MOFs, the obtained S-S-containing MOFs showed significant GSH-depletion ability and superior *in vivo* antitumor efficacy of PDT. Ling et al. constructed poly (disulfide amide) polymers-containing nanoparticles with a high disulfide density to achieve GSH scavenging [30]. These nanoparticles

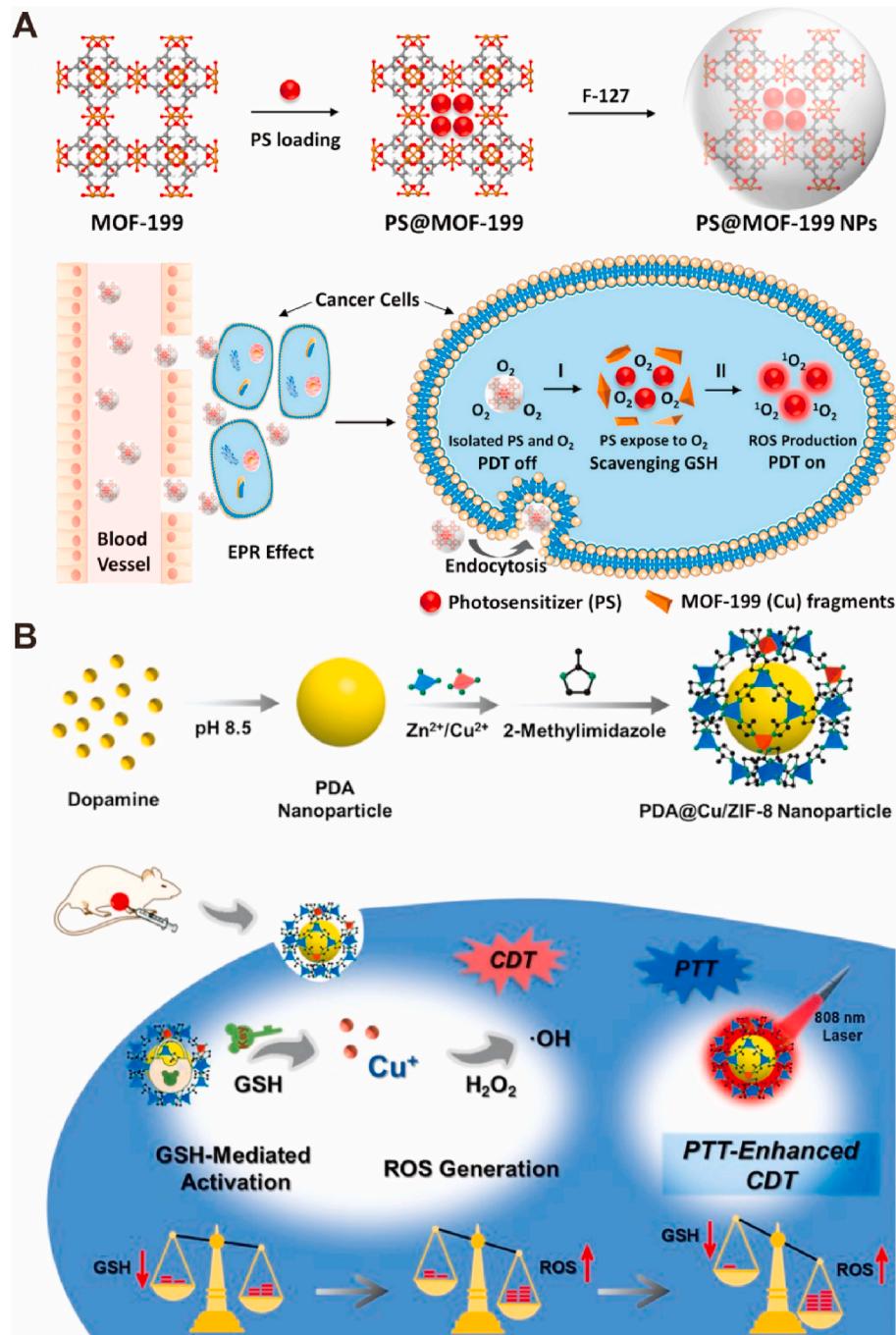


Fig. 11. (A) Schematic illustration of the preparation of photosensitizer-loaded and F127-coated MOFs (PS@MOF-199 NPs) and the quench and trigger of photosensitization originated from PS@MOF-199 NPs in the tumor microenvironment. Adapted with permission from Ref. [55]. Copyright 2019 American Chemical Society. (B) Schematic illustration of the synthesis of PDA@Cu/ZIF-8 nanoparticles and the GSH-triggered and photothermal-reinforced sequential catalytic therapy based on PDA@Cu/ZIF-8 Nanoparticles. Adapted with permission from Ref. [84]. Copyright 2020 Elsevier Ltd.

were used for Pt (IV) prodrug delivery, which effectively reversed cisplatin resistance in ovarian cancer.

Disulfide bonds can also be doped in the inorganic structure. Yang et al. prepared tetrasulfide-bridged dendritic mesoporous organosilica nanoparticles (DMONs) for drug and GOD enzyme delivery (Fig. 14B) [117]. The organosilica was synthesized through the hydrolysis and condensation of hybrid silica precursors consisting of tetraethylorthosilicate (TEOS) and bis [3-(triethoxysilyl)propyl] tetrasulfide. DMONs would undergo framework degradation after intracellular GSH activation and consumption, releasing GOD and a hypoxia-activated prodrug, AQ4N. GOD catalyzed the oxidation of glucose to produce H₂O₂ and consume O₂. The hypoxia environment further activated the conversion of nontoxic AQ4N to toxic AQ4. This nanoplatform integrated multiple cascading and synergistic functions including GSH depletion, starvation,

oxidative cytotoxicity, and chemotherapy, achieving improved anti-tumor therapeutic efficacy. It is worth noting that the S-S linker on the surface of nanoparticles, which is supposed to be much less than the S-S in the frameworks, was also reported to decrease the GSH levels in cells [89]. However, how much disulfide bonds in the nanoparticles is enough to induce effective GSH depletion is still unclear, considering the differences of GSH levels among different kinds of cancer cells.

4.3.2.3. Other oxidant species. In addition to oxidizing metals or disulfides, excessive ROS can be utilized to consume GSH as well. In this case, elevating ROS level is not the purpose of depleting GSH, but the approach to depleting GSH. This strategy was used when researchers intended to resist the GSH detoxification of drugs. Calcium peroxide (CaO₂) can react with dilute acid and produce H₂O₂. Delivery of CaO₂

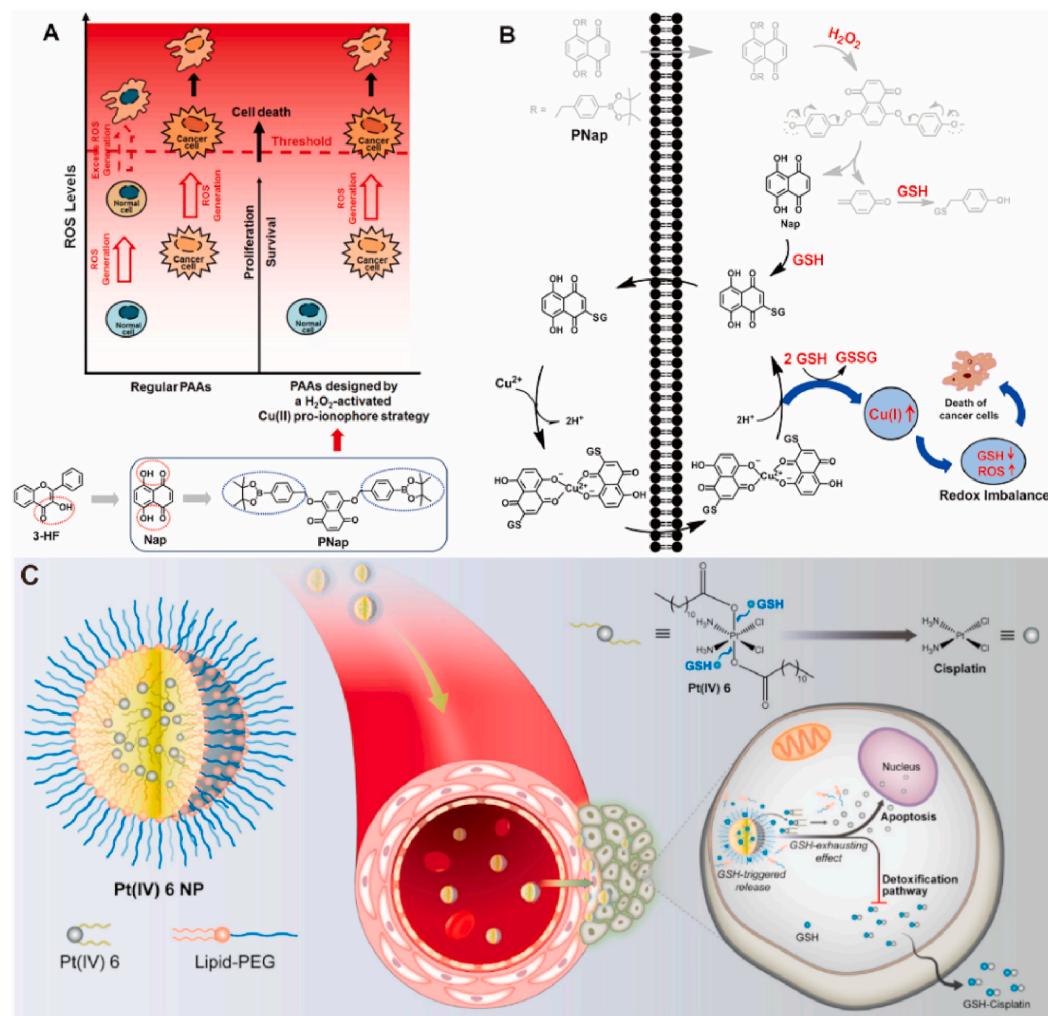


Fig. 12. (A) A comparison of regular pro-oxidative anticancer agents (PAAs) with PNap designed by a H_2O_2 -activated Cu(II) pro-ionophore strategy. (B) Schematic illustration of the proposed mechanisms of PNap as a Cu(II) pro-ionophore to induce GSH depletion and kill cancer cells. Adapted with permission from Ref. [206]. Copyright 2019 Elsevier Ltd. (C) Schematic illustration of the self-assembled Pt (IV) prodrug nanoparticles for specific delivery of Pt drugs and effective suppression of cisplatin-resistant tumors. Adapted with permission from Ref. [125]. Copyright 2018 American Chemical Society.

nanoparticles to weakly acidic TME could effectively enhance oxidative stress and deplete GSH to overcome cisplatin resistance [124]. Photosensitizer ZnPc can generate ROS under light irradiation and induce GSH depletion, which was also reported to downregulate the expression levels of multidrug resistance protein P-glycoprotein and reverse lenvatinib resistance [132]. However, the causal relationship between ROS enhancement and GSH depletion is complex, especially in the combination therapy based on multi-strategies [161,239]. Profound investigation and understanding of cell death pathway are necessary to find out the primary mechanism behind this strategy. NO or Nitrate ester also can oxidize GSH. In one study conducted by Liu et al., nitrated mannan could react with GSH, generating GSSG and NO gas, which induced GSH depletion and relieved hypoxia, respectively. This design promoted ROS amplification based on PDT for cancer therapy [95].

4.4. Promoting GSH efflux

Extruding substantial GSH out of the cells may also induce intracellular GSH depletion, during which process MRP1 plays an important role. MRP1 is a member of the ATP-binding cassette (ABC) transporter family, which is related to chemoresistance of cancer cells to several anticancer drugs including vinca alkaloids, camptothecins, and anthracyclines [240,241]. These drugs can be conjugated with GSH, forming GS-X substrates that will be further eliminated by cancer cells via MRP1-mediated transportation. Apart from GS-X conjugates, MRP1 can also transport GSH alone without a co-substrate [242]. A study showed that high expression of MRP1 in tumor cells was related to their

hypersensitivity to GSH modulation [211]. Therefore, proper modulation of MRP1 to promote GSH efflux can be used to induce GSH depletion in tumor cells. A number of compounds that cannot be transported by MRP1 in themselves have been reported to facilitate GSH efflux. Verapamil is a calcium channel blocker that is often used in the treatment of cardiovascular diseases [243]. This drug was reported to exhibit MRP1-modulating activity and accelerate GSH efflux, resulting in apoptosis of MRP1-overexpressing cells [208]. The derivatives of verapamil had similar or better activities [208,209]. Certain flavonoids were reported to increase the apparent affinity of MRP1 to GSH, although they were not co-transported [210]. Apigenin and chrysin are common flavonoids with potent MRP1-stimulating activity, which have been used to induce GSH depletion in several studies [211–213]. Proper structure modification can further improve the efficacy of flavonoids [214,215]. Besides verapamil and flavonoids, staurosporine [216] and PAK-104P [217] were also reported to stimulate GSH efflux.

5. Conclusions and perspectives

GSH is one of the most important components in the antioxidative defense system of cells, which can protect cells from oxidative damage and detrimental xenobiotics to maintain redox homeostasis. In clinical practice, a series of diseases that related to oxidative stress can be cured or relieved by supplementing the precursor of GSH, N-Acetylcysteine (NAC). As an antioxidant, NAC has been approved by the Food and Drug Administration (FDA) for the treatment of acetaminophen overdose and as a mucolytic agent in respiratory diseases, as it can increase the

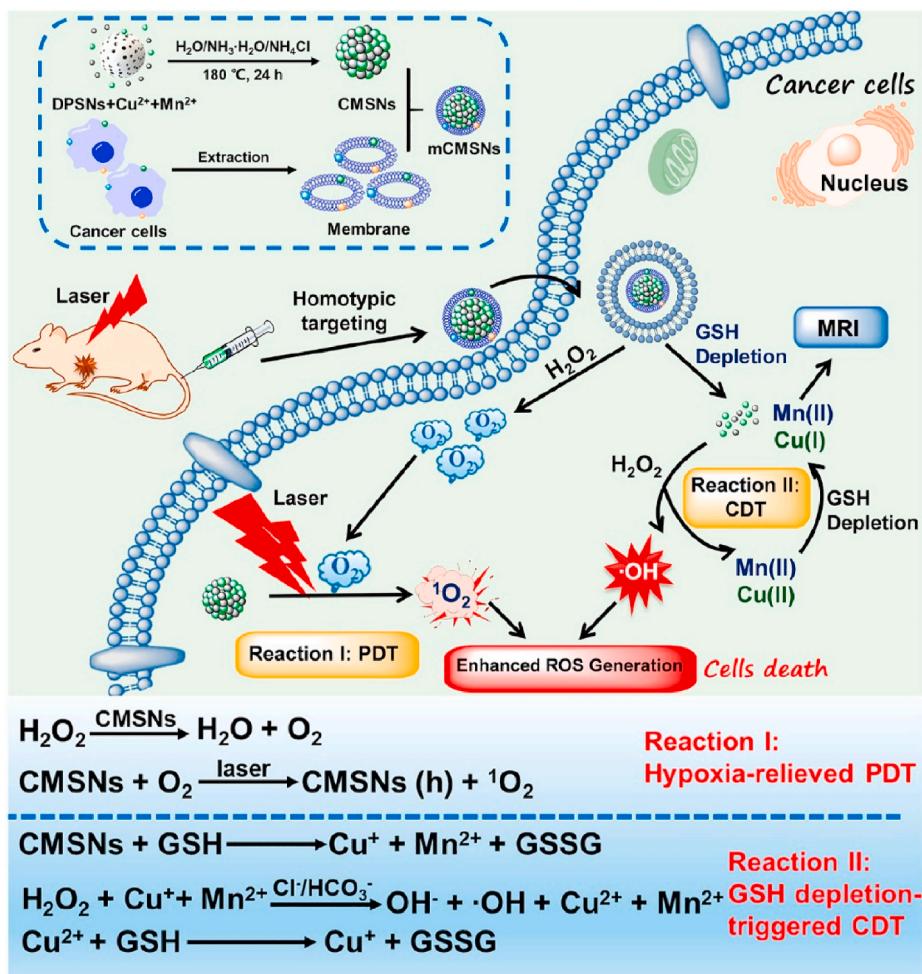


Fig. 13. The fabrication procedure for mCMSNs and schematic illustration of the mechanism of mCMSNs for PDT under laser and GSH-triggered CDT and MRI. Adapted with permission from Ref. [76]. Copyright 2019 American Chemical Society.

intracellular concentration of GSH [244]. Moreover, NAC is commonly used as a nutritional supplement in many countries due to its antioxidant and anti-inflammatory activity [245]. In tumor tissues, considerable ROS is produced with rapid metabolism and proliferation, which can be counteracted by elevated levels of GSH. Tumor cells are vulnerable to oxidative stress under the situation of GSH deficiency. Taking advantage of this, a strategy called GSH depletion was proposed in cancer therapy. Plenty of studies have confirmed the benefits of GSH depletion in various therapeutic regimens, more or less. In this review, we introduce the application of GSH depletion in cancer therapy, particularly focusing on the depletion strategies by showcasing representative examples according to different mechanisms. Some perspectives on the development of this field are proposed as follows.

GSH depletion shows promising value in several different cancer treatment regimens. In ROS-based therapy, GSH depletion can help to enhance the ROS levels by reducing ROS scavenging. Traditional ROS-based therapies increase the oxidative stress by producing more ROS, the efficacies of which are often compromised by cellular antioxidative system, especially GSH. Increasing ROS and simultaneously decreasing GSH can be an effective way to amplify intracellular oxidative stress and induce cell death. In this case, GSH is considered to be depleted primarily by other approaches instead of the produced ROS, although part of ROS will inevitably react with GSH. In chemotherapy, GSH depletion can reduce the cellular detoxification of chemotherapeutic drugs. After uptake by cells, electrophilic drugs like platinum and alkylating agents will be conjugated with GSH under the catalysis of GST, forming GS-X and being extruded by cells. As a result, the drug concentration in

cells decreased and the therapeutic effect is compromised. Reducing GSH levels can weaken cellular detoxification of drugs. In this situation, GSH can be counteracted by producing ROS, which is regarded as an approach instead of a purpose. However, ROS generation was not precisely controlled in most of the reports. If the amount of generated ROS is over the need of GSH depletion, excessive ROS may also promote cell death. Therefore, the mechanisms of cell death probably not only relate to the chemotherapeutic drugs, but also involve increased ROS, which might be neglected in some researches. In ferroptosis, GSH depletion also plays an important role. Ferroptosis is a programmed cell death process characterized by iron dependence, GPX4 inactivation, and accumulation of Lipid-OOH. As one of the co-substrates, GSH is crucial for GPX4-mediated conversion of detrimental Lipid-OOH into nontoxic Lipid-OH. GSH deficiency may disturb the activity of GPX4 and promote the accumulation of lipid ROS, and consequently triggering ferroptosis. However, there still exists a different viewpoint that disrupting GSH may not effectively induce ferroptosis in cancer cells [246]. More in-depth study is necessary to clarify the role of GSH in ferroptosis before we adopt proper strategy. Besides cancer therapy, GSH depletion also exhibits great potential in antibacterial therapy. The high level of GSH in bacterial biofilm limits the efficacy of ROS-based therapies [247]. As a result, GSH depletion can also enhance the efficacy of PDT and CDT towards bacterial infections [248,249]. Moreover, Shen et al. found that aqueous ferrous polysulfide could induce ferroptosis-like death in bacteria, in which GSH depletion was also the indispensable pathway [250]. Therefore, the GSH depletion-involved treatment regimens used in cancer therapy can also provide valuable reference for the treatment of

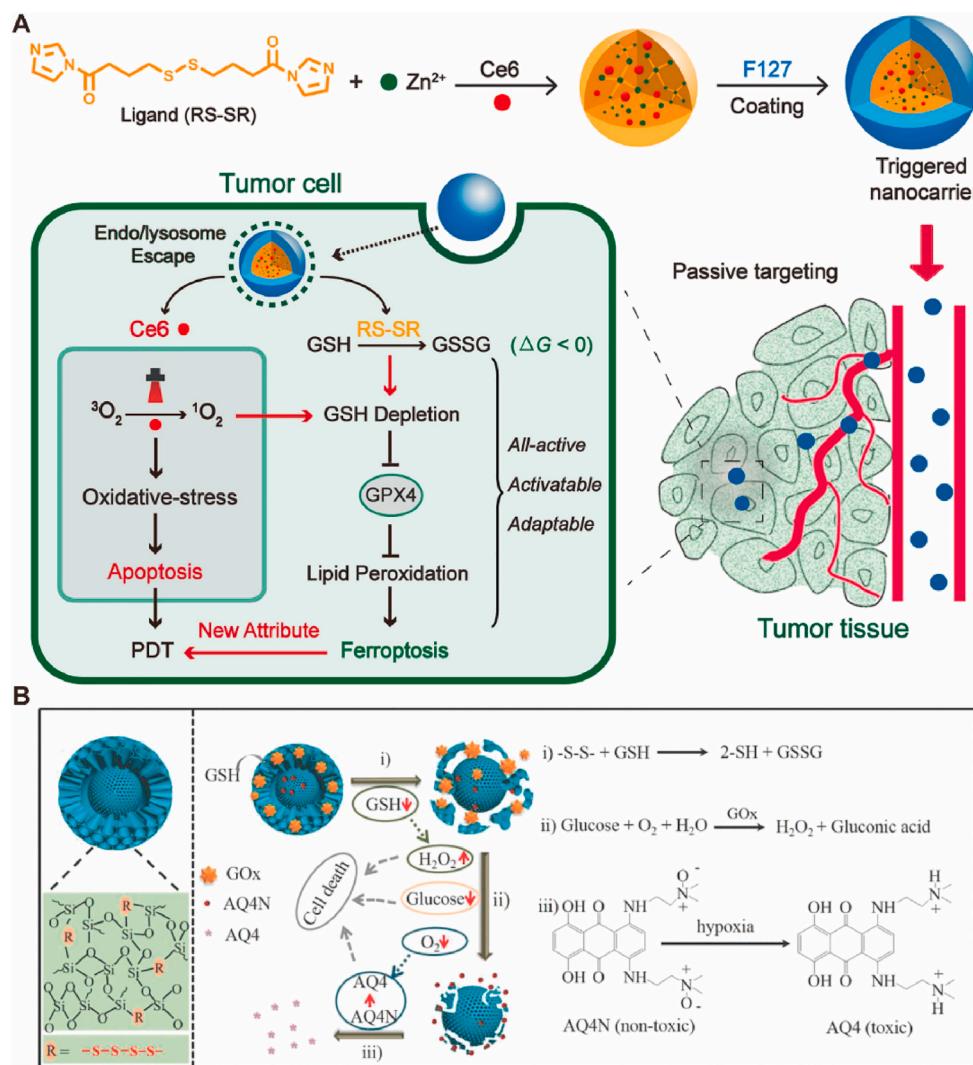


Fig. 14. (A) Schematic illustration of the preparation and mechanism of all-active MOF-based nanocarriers for antitumor PDT based on apoptosis and ferroptosis. Adapted with permission from Ref. [136]. Copyright 2019 American Chemical Society. (B) Schematic illustration of the structure of tetrasulfide-bridged DMONs and the mechanism of GOD- and AQ4N-loaded DMONs for synergistic cancer therapy based on GSH depletion, starvation, oxidative cytotoxicity, and chemotherapy. Adapted with permission from Ref. [117]. Copyright 2018 Wiley-VCH.

bacterial infections.

In order to achieve GSH depletion, researchers have tried various strategies aiming at different targets in the synthetic and metabolic processes of GSH. According to the mechanisms, these strategies were classified into four categories: i) cutting off the supply of raw materials for GSH synthesis; ii) inhibiting GSH synthesis or regeneration; iii) consuming GSH reserves; iv) promoting GSH efflux. Among these, we particularly emphasized the method of consuming GSH reserves by continuously oxidizing GSH. Unlike other methods of using bioactive molecules or inhibitors, this strategy can achieve GSH depletion via GSH-depleting nanocarriers. This method takes full advantage of the carrier and avoids the possible complexity of multi-drug delivery, which is critical for the scale-up production and clinical translation of nanomedicine. Metals in oxidation state and disulfide bonds are popular candidates for constructing this kind of functional nanocarrier that can bring other advantages as well. First, the reduction of metal ions or disulfides in the nanocarriers is often accompanied by the decomposition of nanocarriers, which is beneficial for interior drug release. Second, the integration of iron, copper, and manganese in the nanoagents can realize valence circulation between GSH reduction and Fenton/Fenton-like reaction, resulting in continuous GSH depletion and ·OH production. Third, iron and manganese can be used as the contrast agents in MRI and achieve MRI-guided drug delivery and therapy. However, the introduction of considerable metal ions may bring potential toxic and side effects, which limit their further applications. In

terms of the disulfide bonds, there is still an unanswered question—how many disulfide bonds is enough to deplete intracellular GSH. In most studies that claimed disulfides could effectively deplete GSH, the disulfide bonds were usually integrated in the framework of nanoparticles. Framework integration means there are a large amount of disulfide bonds available for GSH depletion. If the disulfide bonds only exist in the linkers of surface groups, their amount is much less. In this situation, the disulfide bonds are usually used as a GSH-triggered responder of redox-responsive system. Although disulfide bonds in the surface linkers of nanoparticles were also reported to consume GSH to some extent, their influences on the intracellular GSH levels were not investigated in those studies with similar designs. Possible variation in GSH levels caused by disulfide bond-containing linkers may affect the cell death process as well as the killing effect of nanomedicine on cancer cells. Therefore, it is recommended to detect intracellular GSH levels in the studies involving redox-responsive system to comprehensively analyze the mechanism of cell death.

In addition, we can also see the important roles that nanomaterials play in these various strategies. Nanomaterials have been an all-in-one platform in medical application with the functions of diagnosis, monitoring, delivery, and treatment. With the development of personalized medicine, nanomaterials-based GSH depletion is expected to achieve more accurate adjustment based on different needs. For example, when monitoring the intracellular GSH concentration in real time becomes possible [251], we are able to clarify the relationships between drug

resistance and GSH level, evaluate the required doses for GSH depletion, and the therapeutic responses to GSH depletion in different patients. Therefore, a kind of nanomedicine with GSH-depleting and GSH-monitoring ability may be a promising breakthrough in this field. However, before that, the potential issues of nanomaterials-based therapeutic regimens should be focused and well solved, including the long-term biological toxicity, metabolism and clearance, poor targeting capacity, and non-specific wide biodistribution.

According to the above reports and cases discussed in the review, we can see apparent decrease of GSH levels achieved via different strategies as well as its value in cancer therapy. However, the intracellular GSH is hard to be completely exhausted. If intracellular GSH is consumed, the GSH synthesis or regeneration in cells will be upregulated accordingly, which probably induce drug resistance in the long-term administration [26]. GSH depletion based on multi-strategy by simultaneously inhibiting upstream GSH synthesis and consuming downstream GSH reserves may be a promising solution. Furthermore, knowing the mechanism behind each strategy is very important for choosing proper approach to GSH depletion and enhancing the efficacy of cancer therapy.

Declaration of Competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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