

Ferroptosis by nanomaterials: targeting cancer stem cells and overcoming drug resistance

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ABSTRACT

Tumor ferroptosis, a regulated form of cell death driven by iron-dependent lipid peroxidation, has emerged as a promising therapeutic strategy for combating cancers, particularly in cases involving cancer stem cells (CSCs) and drug resistance. In recent years nanomaterial-based approaches have gained significant attention for the potential to selectively induce ferroptosis in cancer cells while sparing normal tissues. This review aims to provide a comprehensive overview of the current state-of-the-art in utilizing nanomaterials for targeting tumor ferroptosis with a specific focus on the application in eradicating CSCs and overcoming drug resistance mechanisms. The molecular mechanisms underlying ferroptosis induction by nanomaterials, the unique properties and functionalities of various nanomaterial platforms, and strategies for targeting CSCs and overcoming drug resistance using nanoferroptosis approaches will be discussed. In addition, the preclinical and clinical evidence supporting the efficacy of nanomaterial platforms will be evaluated. Furthermore, the challenges and future perspectives in the development and translation of nanoferroptosis-based therapies for precision cancer treatment will be highlighted.

Keywords: Ferroptosis, drug resistance, cancer stem cell, nanomaterials

1. INTRODUCTION

Cancer presents a significant global medical challenge due to adaptive drug resistance and metastasis. One of the major reasons for drug resistance is the anti-apoptosis mechanisms of cancer cells [1, 2]. For example, cancer cells tend to overexpress anti-apoptotic proteins and downregulate pro-apoptotic factors [3, 4]. Cancer cells often increase levels of proteins, like Bcl-2, which inhibit the apoptotic pathways and allow cancer cells to survive despite drug treatment. Downregulation of proteins, such as Bax and Bak, reduce cell death [5, 6]. Additionally, a subset of tumor cells exhibits stem cell-like properties, known as cancer stem cells (CSCs), which have the ability to self-renew and differentiate into various cell types that exist in cancer [7, 8]. These cells contribute to tumor growth, metastasis and relapse, and drug resistance [9, 10]. Therefore, designing strategies to target CSCs and overcome the cellular anti-apoptotic mechanisms is essential for cancer therapy.

Ferroptosis, a distinct form of regulated cell death characterized by iron-dependent lipid peroxidation, offers a novel approach for cancer therapy [11-14]. Unlike traditional apoptosis or necrosis, ferroptosis specifically targets cellular metabolic pathways, presenting unique advantages in addressing CSCs and drug-resistant tumors. These CSCs, known for a role in tumor initiation, metastasis, and recurrence, often evade conventional therapies, contributing to treatment failure and relapse [15].

Recent advances in nanotechnology have introduced innovative platforms capable of inducing ferroptosis selectively within tumor cells. Nanomaterials, with customizable properties and multifunctional capabilities, provide a targeted approach to modulating ferroptosis pathways. These platforms enhance therapeutic precision by minimizing damage to normal tissues and overcoming the challenges posed by CSCs and drug resistance.

While several studies have explored the potential of ferroptosis to overcome drug resistance and the role

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of nanomaterials in combating CSCs, few studies have systematically integrated these two aspects. The combination of ferroptosis with strategies targeting drug resistance and CSCs holds promise for advancing more comprehensive cancer therapies.

This review examined the current landscape of nanomaterial-based strategies for tumor ferroptosis and ferroptosis-mediated combination therapy to combat CSCs and drug resistance (Figure 1). The biological pathways related to CSCs, drug resistance, and ferroptosis were investigated first. Additionally, the molecular mechanisms by which nanomaterials initiate ferroptosis, the design and functionality of various nanoplatforms, and the role in targeting CSCs and combating drug resistance were explored. Finally, the challenges and future directions for the development of these promising therapeutic interventions were discussed, highlighting the potential to transform cancer treatment paradigms.

2. MECHANISMS

Ferroptosis offers a promising strategy for treating drug-resistant tumors by inducing cell death through oxidative stress and related pathways [11, 16]. Additionally, ferroptosis demonstrates enhanced therapeutic efficacy when combined with other treatment modalities for drug-resistant tumors. Following an overview of the various types of nanomaterials and treatment approaches, it is essential to explore the underlying therapeutic mechanisms. In this section, an in-depth discussion of ferroptosis, CSCs, and the molecular pathways linked to drug resistance are provided (Figure 2). A thorough understanding of these mechanisms is crucial for advancing cancer therapies and overcoming the challenges posed by drug resistance.

2.1 Mechanisms of drug resistance

Chemotherapy remains a cornerstone of cancer treatment. However, the efficacy of chemotherapy is often

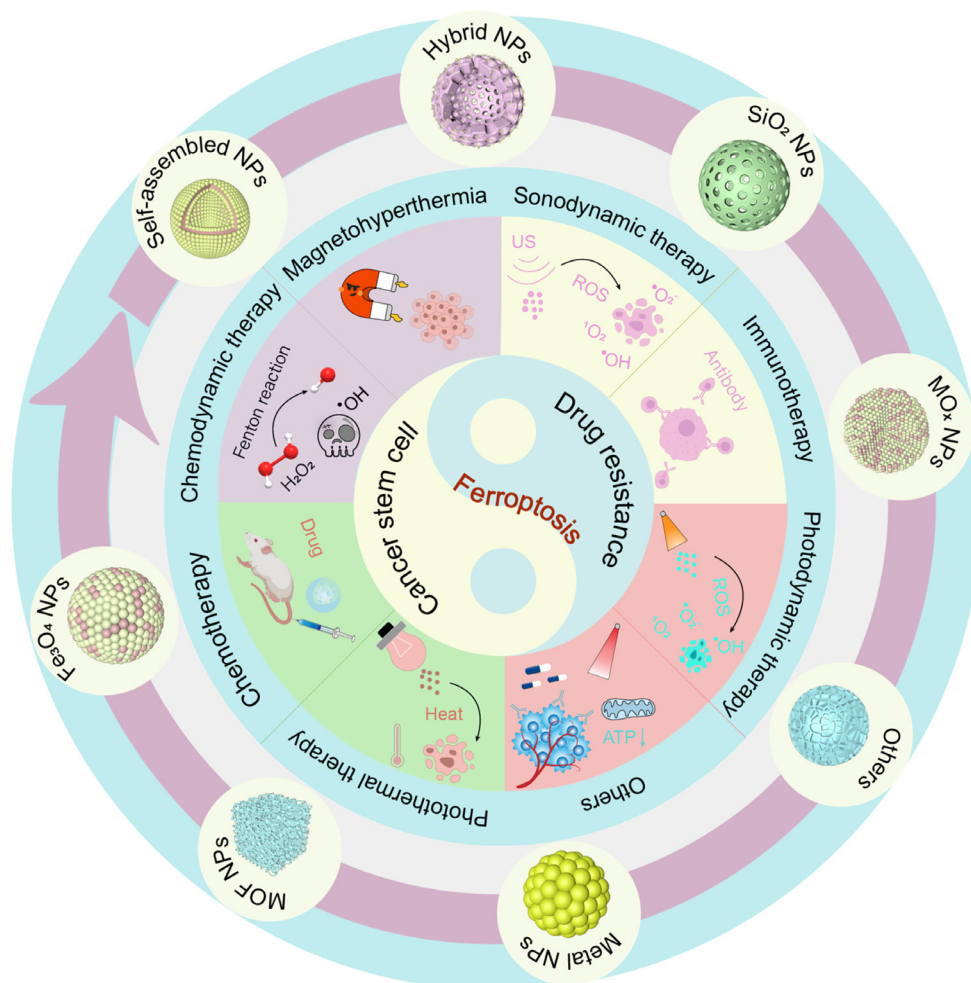


Figure 1 | Schematic illustration of nanomaterial-mediated ferroptosis for targeting drug-resistant tumors and CSCs.



First, the PLC γ /PKC signaling pathway has a pivotal role in regulating the expression of P-glycoprotein (P-gp), a key factor in drug resistance [22]. Activation of this pathway leads to increased P-gp protein levels, enabling tumor cells to actively efflux chemotherapeutic

Second, the PI3K/AKT pathway is a major driver of FGF/FGFR-mediated tumor progression and chemoresistance [20, 26]. The phosphatidylinositol 3-kinase (PI3K) family and the downstream effector, protein kinase B (AKT), regulate fundamental processes, such as proliferation, apoptosis, and differentiation [27–29]. AKT activation is linked to resistance against a range of anti-cancer agents, including cisplatin, paclitaxel, etoposide, receptor tyrosine kinase inhibitors, and radiation [30–33]. This resistance is primarily mediated through activation of inhibitory kappa B kinase beta (IKK β), inhibition of glycogen synthase kinase 3 beta (GSK3 β), nuclear translocation of nuclear factor kappa-light-chain-enhancer of

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activated B (NF- κ B), and upregulation of pro-survival genes, like Bcl2-A1 and Bcl-xL [34-36].

Third, activation of the extracellular signal-regulated kinase (ERK) pathway is pivotal for the development of drug resistance [37]. This pathway, regulated by factors controlling cell cycle progression, such as cyclin D1 (CCND1), and apoptosis regulators, like myeloid cell leukemia-1 (Mcl-1), contribute to tumor resistance to therapy [20, 38].

2.2 Mechanisms underlying CSCs

Drug resistance is not the sole factor contributing to poor cancer prognosis. A distinct subset of cells, known as CSCs, has been identified in tumor hypoxic regions [39, 40]. These cells, which share properties with normal stem cells, possess self-renewal capabilities that drive the persistent, uncontrolled growth of malignant tumors [41, 42]. CSCs are instrumental in cancer progression, metastasis, recurrence, and resistance to treatment, rendering CSCs a major obstacle to effective cancer therapies [43-45].

Key regulatory pathways governing CSCs include Wnt, NF- κ B, Notch, and Hippo [9, 46-48]. The Wnt signaling pathway, mediated by the cysteine-rich glycoprotein, Wnt, is essential for regulating cell proliferation, differentiation, and migration [46, 49]. Inhibition of β -catenin, a central component of the Wnt/ β -catenin pathway, suppresses CSC activity [50] by disrupting the epithelial-mesenchymal transition (EMT), a process regulated by transcription factors, such as the snail family transcriptional repressor 1 (SNAIL) and the twist family BHLH transcription factor (TWIST) [51, 52]. Blockade of this pathway promotes CSC differentiation and limits regenerative potential.

Furthermore, stable β -catenin translocates to the nucleus, where β -catenin forms a complex with T-cell factor (TCF) and lymphoid enhancer-binding factor (LEF), acting as a transcriptional co-activator [53, 54]. This interaction enhances cell proliferation, facilitates loss of E-cadherin expression, increases invasiveness, and leads to colony formation, all of which contribute to drug resistance and CSC persistence [55].

The Hippo signaling pathway, a conserved set of kinase cascade, functions as a growth inhibitor and also has a vital role in cancer development, metastasis, tissue regeneration, and immune regulation [56]. Dysregulation of the Hippo pathway promotes CSC stemness and accelerates tumor progression [57]. Thus, targeting pathways, such as Wnt, Notch, and, is critical for the development of effective anti-cancer therapies.

2.3 Mechanisms underlying ferroptosis

Ferroptosis has emerged as a promising therapeutic strategy for addressing the challenges posed by CSCs and drug resistance. First identified by Stockwell in 2012, ferroptosis is a form of regulated cell death driven by iron-dependent lipid peroxidation and accumulation of reactive oxygen species (ROS) [13]. Key pathways

implicated in ferroptosis include iron metabolism, lipid metabolism, the system Xc⁻ antiporter, and the mevalonate pathway [58-60].

Iron has a central role in ferroptosis by catalyzing the formation of ROS via Fenton chemistry, thereby inducing lipid peroxidation [61]. Elevated levels of free iron or dysregulated iron homeostasis can amplify ferroptotic cell death. A hallmark of ferroptosis is the peroxidation of polyunsaturated fatty acids (PUFAs) within cell membranes, which is primarily driven by ROS and lipid hydroperoxides (LOOH) and compromises membrane integrity and functionality [62, 63].

The system Xc⁻ antiporter, composed of the light chain subunit solute carrier family 7 member 11 (SLC7A11) and the heavy chain subunit solute carrier family 3 member 2 (SLC3A2), regulate ferroptosis by importing cystine [64, 65], which is reduced to cysteine and utilized for glutathione (GSH) synthesis. GSH supports the activity of glutathione peroxidase 4 (GPX4), an enzyme responsible for neutralizing lipid peroxides. Inhibition of system Xc⁻ disrupts GSH synthesis [66], reduces GPX4 activity, weakens the antioxidant defenses of the cell, and leads to the accumulation of lipid ROS, ultimately resulting in ferroptosis [58, 67, 68].

The mevalonate pathway, which generates isopentenyl pyrophosphate (IPP), squalene, coenzyme Q10 (CoQ10), and cholesterol, also regulates ferroptosis [58, 69-71]. GPX4 expression and activity are influenced by selenium, which is incorporated into the active site of the enzyme as selenocysteine [72]. The maturation of selenocysteine tRNA involves isopentenyl transferase, which transfers an isopentenyl group from IPP, a product of the mevalonate pathway. Downregulation of IPP impairs selenocysteine tRNA synthesis, thereby disrupting GPX4 function and promoting ferroptosis [73, 74]. Additionally, IPP serves as a precursor for the synthesis of squalene and CoQ10 [75, 76].

Ferroptosis suppressor protein 1 (FSP1) uses CoQ10 to prevent lipid peroxidation, a role shared by dihydroorotate dehydrogenase (DHODH) [77, 78]. There is a high content of cholesterol, especially in CSCs. Therefore, selecting appropriate cholesterol inhibitors to block cholesterol synthesis and uptake can inhibit tumor formation and growth [74]. Statins, by inhibiting the mevalonate pathway, promote ferroptosis by modulating these processes. Thus, the mevalonate pathway regulates ferroptosis by influencing IPP levels, selenocysteine tRNA maturation, CoQ10 synthesis, and cholesterol metabolism [58]. Statin-induced inhibition of this pathway could enhance iron-dependent cell death, offering a potential strategy for overcoming drug resistance in tumors [58, 79].

3. NANOMATERIALS FOR TREATMENT DRUG RESISTANCE

As previously discussed, ferroptosis has a critical role in targeting CSCs and overcoming drug resistance,

positioning ferroptosis as a promising therapeutic strategy. Nanoparticles, with their unique properties, not only enhance drug targeting and increase drug concentration at the tumor sites but also minimize toxicity to healthy tissues. The distinctive structural design of nanomaterials can induce ferroptosis, making nanomaterials a potential new approach to overcoming drug resistance. Furthermore, nanomaterials can act as effective delivery vehicles for small-molecule drugs, enhancing targeted delivery to tumors. By integrating ferroptosis with other cell death modalities, nanomaterials offer a powerful strategy to address both drug resistance and CSC-related challenges. An overview of the latest advances in targeted drug delivery to tumors is summarized in [Table 1](#), along with research on combining ferroptosis with other therapeutic approaches to improve treatment efficacy.

3.1 Ferroptosis for overcoming drug resistance and targeting CSCs

Breast cancer stem cells (BCSCs) use anti-apoptotic mechanisms that reduce susceptibility to traditional apoptosis-based therapies. However, the reliance on iron makes BCSCs particularly vulnerable to ferroptosis. To exploit this vulnerability, Wu et al. developed hyaluronic acid (HA)-modified, siPROMIN2-loaded, spindle-like FeOOH-based nanoparticles (FeOOH/siPROM2@HA). Using hydroxyl iron oxide (FeOOH) as a carrier, these nanoparticles exhibit low iron ion leakage and heightened sensitivity in acidic environments. HA modification enhances selective targeting of BCSCs, promoting Fe³⁺ generation in the acidic tumor microenvironment. This process triggers a redox reaction with endogenous GSH, releasing Fe²⁺, elevating intracellular iron levels, and depleting GSH. In response to ferroptosis stimuli, CSCs overexpress the five-transmembrane protein, PROMIN2, which facilitates the formation of iron-containing multivesicular bodies (MVBs) and exosomes to expel iron, thereby reducing cellular iron levels. This export mechanism presents a significant obstacle to ferroptosis-based therapies. By loading siPROMIN2 into FeOOH-based nanoparticles, the formation of MVBs and iron export is inhibited, leading to increased Fe²⁺ levels and GSH depletion. This results in elevated lipid hydroperoxide (LPO) levels and downregulation of GPX4, effectively inducing ferroptosis in BCSCs. FeOOH and siPROM2 work synergistically to inhibit drug efflux and induce ferroptosis in this nanoplatform, thus combating drug resistance in cancer cells. This study highlights the potential of selectively triggering ferroptosis in BCSCs to improve cancer treatment outcomes, offering a promising approach for targeted CSC elimination ([Figure 3a](#)) [82]. *In vitro* and *in vivo* experiments demonstrated that pH-sensitive nanomaterials significantly inhibit tumor growth, primarily by downregulating GPX4. However, the study primarily focused on BCSCs and applicability to other cancer types requires further investigation. Future studies

should validate these findings across a broader spectrum of tumor models to enhance generalizability.

GPX4 inhibitors, which trigger ferroptosis, have emerged as promising therapeutic agents for tumor suppression. However, the limited tumor-targeting efficiency and non-specific activation have hindered broader application in cancer therapy. To address these limitations, Hou et al. developed a peptide-iron porphyrin conjugate designed to activate specifically within the tumor microenvironment, improving tumor penetration and cellular uptake. This self-assembling nanomaterial demonstrates deep tumor penetration and increased accumulation, effectively inhibiting GPX4 and promoting ferroptosis to enhance anti-cancer efficacy. The conjugate (Gi-F-CAA) is synthesized by coupling the GPX4 inhibitory peptide (GACNWLPLYPCPV) with an assembly peptide linker (LKLLK), modified with a pH-sensitive cis-aconitic anhydride (CAA) and iron porphyrin (FeTCPP). The CAA component facilitates deeper tumor penetration, enhancing therapeutic outcomes. The Gi-F system amplifies oxidative stress through a Fenton reaction mediated by iron porphyrin, significantly inhibiting GPX4 activity. Findings suggest that this conjugate can enhance treatment efficacy for overcoming drug resistance and improving therapeutic efficacy ([Figure 3b](#)) [93]. This study demonstrated that nanomaterials can intelligently self-assemble within the body, exhibiting multivalent synergistic interactions to generate potent ferroptosis-based anti-tumor effects across various tumor models. However, further exploration of the combination with other therapeutic modalities could further enhance clinical relevance.

The activation of cancer-associated fibroblasts (CAFs) within the tumor microenvironment creates a dense stromal barrier that impedes drug penetration and contributes to drug resistance. To inactivate CAFs and enhance drug delivery, Huang et al. introduced a novel iron-containing nanoparticle formulation (PTFE) designed to trigger tumor ferroptosis and promote macrophage polarization. PTFE consists of erastin-loaded poly(lactic-co-glycolic) acid (PLGA) nanoparticles coated with tannic acid (TA) and Fe³⁺ ([Figure 3c](#)) [96]. The erastin-mediated ferroptosis, along with Fe³⁺-associated Fenton reaction, disrupts cellular redox balance and inhibits pancreatic cancer progression. Additionally, PTFE repolarizes macrophages from the M2-to-M1 phenotype, inactivating CAFs and reducing dense tumor stroma, thereby facilitating improved drug penetration ([Figure 3d](#)). This strategy offers a promising approach to overcome intrinsic drug resistance in pancreatic cancer.

Tumor-associated macrophages (TAMs) have a crucial role in supporting CSC survival by delivering iron to CSCs. Feng et al. developed an intelligent nanoplatform leveraging this pathway aimed at inducing TAM-mediated ferroptosis in CSCs. This platform consists of iron-doped mesoporous silica nanoparticles loaded with citrates and dextran (DFHC), which accumulate in orthotopic lung tumors following aerosol inhalation ([Figure 3e](#)) [85].

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Table 1 | Classification of therapeutic modalities for drug resistance and CSC.

Host materials	Modification ^a	Therapies	Tumor model	Mechanism	Reference
DL-HMCON	CPT; ATRA; HA		4T1	differentiation, apoptosis, the Fenton-like reaction, deplete GSH	[80]
Iron (III)-based MOF	DOX; red blood cell (RBC) membrane	Chemotherapy	MCF-7, MCF-7/ADR	Downregulate P-gp protein, deplete GSH, and elevate ROS levels	[81]
FeOOH	siPROM2; HA	Gene therapy	MCF-7-derived CSCs	Increase Fe ²⁺ level, deplete GSH, accumulate LPO, downregulate GPX4	[82]
RF@LA-Fe-MOF	RSL3; iFSP1; LA		C5WN1	Downregulate Twist, alters EMT related proteins, inhibit GPX4 and FSP1	[83]
SPION	Atranorin			Weaken the Xc ⁻ /GPX4 axis and the 5-hydroxymethylcytidine modification of mRNAs	[84]
Fe-HMSNs	Ct; Dex		LLC	Elevate the iron level surrounding CSC niches and destroy redox equilibrium	[85]
CeO ₂	Nano-PMI		LLC	Reactivate the p53 signaling pathway, downregulate GPX4	[86]
FeCDs	PAE-PEG		B16F0	Consume GSH, suppress GPX4, oxidative stress	[87]
Vc-Fe(II)	OTUB2-siRNA (si-OTUB2), ASO-MALAT1; PEG2K-DSPE, (DOPA); CaP cholesterol		H1975; HCC827	Produce hydroxyl radicals (*OH), consume GPX4, deplete GSH	[88]
DFeONPs DFe ₂ O ₃ NPs	Diethyldithiocarbamate (DDC)		MDA-MB 231	Inhibit ALDH1A, GSH dysfunction, apoptosis	[89]
Arsenic trioxide (ATO)			A549	Increase ROS and iron ion content, inhibit GPX4	[90]
Ferrous oxide nanoparticles (F(II) NPs)	diethyldithiocarbamate (DE)		HepG2	Elevate ROS and lipid peroxidation and suppress anti-ferroptotic parameters	[91]
ZIF-8	DHA; SNP; ICG; FA		HN6	Increase ROS, deplete GSH and GPX4	[92]
(Gi-F-CAA)			MCF- 7/MDR	Inhibit GPX4 activity, increase ROS	[93]
Lipid nanocapsules	Salinomycin (Sal); SN38		HCT116		[94]
Ethylene glycol, mPEG-PLA-NO	PTX		Bel-7402	Inhibit ATPase activity and P-gp	[95]
Erastin@ PLGA NPs	MOF shell (Fe ³⁺ and tannic acid.)		KPC1199	Regulate TAFs and tumor dense matrix by inducing M2 to M1 polarization of macrophages, Fe ³⁺ -induced Fenton reaction	[96]
Arsenene nanosheets (ANS)	Anti-Her2 Affibody; BSA; cisplatin	Chemotherapy	U2OS; 143B	Inactivate GPX4, apoptosis, and ferroptosis	[97]
DOX@Fc-SS-ATRA	DSPE-PEG-HA	Chemotherapy	4T1	Generate *OH, by differentiation and chemotherapy	[98]
Fe ₃ O ₄ -PGA-DHA Fe ₃ O ₄ -PASP-DOX	DOX; DHA	Chemotherapy	4T1	Accumulation of ROS and LPO, inhibit phosphatidylinositol 3-kinase (PI3K)/AKT/ mammalian target of rapamycin (mTOR)/ GPX4 pathway	[99]
MIL-101	SLC7A11 siRNA; DOX	Chemotherapy	MCF7/ADR	Inhibit P-glycoprotein activity, regulate Bcl-2/Bax expression, suppress GPX4 and GSH	[100]

Table 1 | Continued

Host materials	Modification ^a	Therapies	Tumor model	Mechanism	Reference
Dendritic mesoporous silica nanoparticles (DMSNs)	Fe ₃ O ₄ ; Mn ²⁺ ; CB-839	Chemotherapy	CT26	POD-like activity and GSH depletion properties, further improving •OH-mediated catalytic therapy and enhancing the chemosensitivity of oxaliplatin.	[101]
Small extracellular vesicles (sEV)	miR-654-5p	Chemotherapy	HCC-R	Enhance sora-induced ferroptosis by binding to HSPB1 and reducing its protein levels	[102]
AuNP	Dox; PHF	Chemotherapy	(PacR/MCF-7CSC)	The autophagy necroptosis axis	[103]
FeO NPs	Diethyldithiocarbamate	Chemotherapy	GSCs	Induce lipid peroxidation, reduce anti-ferroptotic factors	[104]
GA-Fe	CMRALi	Chemotherapy	OS	Differentiation, magnify ROS-triggered ferroptosis and apoptosis	[105]
Zinc oxide nanoparticles (ZONs)	Dox; erastin	Chemotherapy	MDA-MB-231/Dox		[106]
DOX-SAHA		Chemotherapy	MCF-7/ADR	Inhibit histone deacetylase (HDAC) activity	[107]
DOX@F-68/TA/Fe ³⁺		Chemotherapy	MCF-7	Produce additional H ₂ O ₂ , create a high •OH level	[108]
MTO-Cu (II) nanolocks	DSPE-PEG-cRGD	Chemotherapy		Deplete GSH, inactivate GPX4, accumulate LPO, the destruction of oxidative stress	[109]
GOx loading Fe ₃ O ₄ , PEG	Fe ³⁺ , doxorubicin (pDOX)	Chemotherapy; Starvation therapy	MCF-7, MCF-7/ADR	Consume glucose, generate H ₂ O ₂	[110]
PGF ⁺ CaCO ₃	PEG	Chemotherapy		Fenton catalytic capacity and lipid peroxidation	[111]
Fe-MOF	DOX	Chemotherapy	A549	Enhance the generation of ROS	[112]
ZnO nanoparticles (NPs)	bio-barcode (BBC)	Chemotherapy	A549/DDP	Depletion of GSH, amplify oxidative stress, increase LPO, silence early growth response protein 1 (Egr-1) mRNA, suppresses the P-gp-mediated drug efflux	[113]
PEG-AuNPs	Salinomycin (Sal)	Chemotherapy	MCF-7	Induce ROS, mitochondrial dysfunction, and lipid oxidation.	[114]
Fe ₃ O ₄ NPs	DMMA; TA; sorafenib; GOD anti-LILRB4 mesoporous silica nanoparticles (MSN)	Chemotherapy	A549	Fenton reaction, LPO accumulation, down-regulate GPX4	[115]
RSL3@CPT-SS-Fc	DSPE-PEG2000-RGD	Chemotherapy	4T1	Fenton reaction, elevated LPOs, GPX4 inhibition	[116]
Nut@FSSG	DSPE-PEG-PTP	Chemotherapy	Panc02-Luci	Generate LPOs, activate the p53 signal pathway to enhance the apoptosis	[117]
GA-Fe(II)	DOX; DPPC; DSPE-mPEG2000	SDT	MCF-7/ADRA	Produce toxic •OH, consume GSH, promote LPO, US-augmented Fenton reaction enables the down-regulation of PGC-1 α and Bcl-2 expression	[118]
Iron porphyrin-based MOF (FePCN)	siRNA; OS cell membranes	SDT	143B	Accelerate ROS generation, GSH depletion	[119]
NH ₂ -MIL-101(Fe)	Gemcitabine; DVDMS; TpPa-1; NRP2 mAb	SDT	PANC-1/GEM	ROS, lysosomal autophagy. upregulation of Nuclear Receptor Coactivator 4 (NCOA4)	[120]

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Table 1 | Continued

Host materials	Modification ^a	Therapies	Tumor model	Mechanism	Reference
MoS ₂	CF ₃ SO ₂ Na, HA, cisplatin	SDT		Produce •OH, accumulation of ROS and LPO, destroy the efflux protein (ATP7B), disturb ATP production, inhibit the repair of cisplatin-damaged DNA	[121]
Lipo-PpIX@ Ferumoxytol		SDT		Simultaneously induce two types of cooperative RCD, apoptosis and ferroptosis, to enable complete tumor removal	[122]
FPSN	Sorafenib (SF); Piceatannol (PCT); Fe ³⁺	PTT	Huh7/SF	Inhibit the expression of HIF-1α, the upregulation of oxidative stress level, suppress the stemness properties	[123]
AuNCS	RSL3; cell membrane-coating	PTT	143B-R	Inhibit GPX4	[124]
L820/CPT-CPT NPs		PTT		Offset oxidative stress, deplete GSH, inactivated GPX4, accumulate lipid peroxides	[125]
Dopamine (DA), tumor targeted folic acid modified dopamine (DA-FA)	Fe; CPT	PTT		Apoptosis/ferroptosis/photothermal	[126]
Lip@Fe-Cu-MOFs		PTT	4T1	Deplete GSH, cuproptosis and ferroptosis.	[127]
Fe ₃ O ₄	BV2 cell membrane Thiolated siPD-L1	Immunotherapy	Luc-GL261/ TR	Decrease GSH and GPX4, block PD-1/PD-L1 signaling pathway	[128]
Polyphenolic COX-2 inhibitors, Fe ³⁺ , DOX, (pHA-OH)		Immunotherapy	4T1	Generate LPO, inhibit the COX-2 pathway, suppressing P-gp	[129]
Cinnamaldehyde (CA) polymer prodrug	All-transretinoic acid (ATRA)	Immunotherapy	Lewis	Deplete intracellular GSH, amplified intracellular oxidative stress	[130]
Erastin, FdUMP, and siPD-L1		Immunotherapy	CT26	Induce ROS and downregulate GSH/GPX4	[131]
MNV@DHA		Immunotherapy	H22	Deplete glutathione, induce the polarization of M1 and repolarize M2 macrophages	[132]
Dendrimer (Den)	DOX; (tannic acid) TA-Fe ³⁺	CDT	MCF-7/ADR	Produce ROS and LPO, apoptosis/ferroptosis	[133]
UmFe-OA@hPM		CDT Immunotherapy	4T1		[134]
2D vermiculite nanosheets		CDT	Calu1	Deplete GSH, increase ROS and LPO	[135]
SPION	CSO-SS-Cy7-Hex; sorafenib (Srfn)	PDT	4T1; MCF-7; MDA-MB-231	Consume GSH and burst lot of LPO; resist the invasion and metastasis of breast cancers during EMT	[136]
Liposomes (CF3-CVJ NPs)	arginine-glycine-aspartic acid (RGD)	PDT	MCF-7/ADR	Upregulate the pro-apoptotic protein Bax, accumulation of ROS and LPO products, downregulate the levels of P-gp, mitochondrial damage	[137]
DHA, ICG, and LF		PDT	U251, U87		[138]
Erastin, Ce6		PDT		Accumulate lipid-based ROS and increase O ₂ concentration	[139]
Fe ₃ O ₄	MON; MnO ₂ Glucose oxidase (GOD); HA; Sor			Inhibit GPX4 expression, produce H ₂ O ₂ , Fenton reaction	[140]

Table 1 | Continued

Host materials	Modification ^a	Therapies	Tumor model	Mechanism	Reference
t-ML @DGLA/siDECR1		Magnetic	C4-2B _{Enz}		[141]
MIL-100	Methotrexate, MTX	Chemotherapy; CDT	JEG-3	Fenton reaction, deplete GSH	[142]
TK-Fc	LAE	Chemotherapy; CDT	DU145/R; DU145	Deplete GSH, LPOs accumulation, increase ROS, downregulate P-gp, inhibit mitochondrial function; break the redox balance	[143]
Hollow mesoporous silica	DOX; Fe (VI); HE; PEG	Chemotherapy SDT	Saos-2	GPX4 inactivation, down-regulate expressions of hypoxia-inducible factor 1 α and P-gp, Fenton reactions	[144]
Co-assembling cisplatin (CDDP), linoleic acid (LA)-tailored IR820		PTT Chemotherapy		Alleviate hypoxia, oxidative stress-related peroxidized lipid accumulation	[145]
MOF	DOX; COD; CS	Chemotherapy	MCF-7/ADR	Produce $\cdot$ OH, reduce cholesterol, inhibit the synthesis of the pro-inflammatory enzyme COX, down-regulation of the anti-apoptotic protein Bcl-XL	[146]
Superparamagnetic iron oxide nanoparticles (SPIONs)	Poly(β -amino ester)s-PEG amphiphilic copolymer (rPAE), DOX	Chemotherapy Photothermal therapy	MB49	Promote iron overload-triggered macrophage polarization	[147]
Au/Fe-GA/	Sorafenib; DSPE-PEG2000	CDT; PTT	SMMC-7721	Downregulate the expression of P-gp, GPX4, and SLC3A2	[148]
I@P-SS-FRT	ferritin	PTT MRI	MCF-7/ADR	Substantive ROS and LPO generation, downregulation of GPX-4 activity, and evident TAM polarization	[149]
Copper-cysteamine (Cu-Cy)		Microwave dynamic therapy	HCT15	Deplete GPX4, enhance LPO and MDA	[150]
SPIONs			HuOCS	Accumulate ROS, induce oxidative stress	[151]
Arachidonic acid-conjugated amphiphilic copolymer	RSL3		NCI/ADR-Res, NAR		[152]
(2D) arsenene nanosheets	A cationic iridium complex (IrFN)	Chemotherapy PTT Immunotherapy		Ferroptosis-induced chemotherapy, PTT and immunotherapy	[153]
Photosynthetic microcapsules (PMCs)		RT, PDT	B16	Evoke lipid peroxidation, GPX4 suppression, GSH reduction	[154]
DOX, TA, FeCl ₃		Chemotherapy PPT	ER+ MCF7	ROS production, intracellular oxidative stress, reduce intracellular GSH	[155]
Mesoporous carbon nanoparticles (MCN)	FeCO, DOX	Gas therapy Chemotherapy PPT	MCF-7		[156]
SR780@Fe-PAE	GP2633	PDT	HepG-2	Generate hydroxyl free radical and lipid peroxide, deplete GSH	[157]
Superparamagnetic iron oxide	DOX, folic acid	Magnetohyperthermia	MDA-MB-231		[158]
MnO ₂	DHA, PolyMet, HA	Immunotherapy CDT	4T1		[159]

^aRefers to the additional components used for modification, including loaded drugs or substances that modify the surface of the material, in addition to the nanomaterials.

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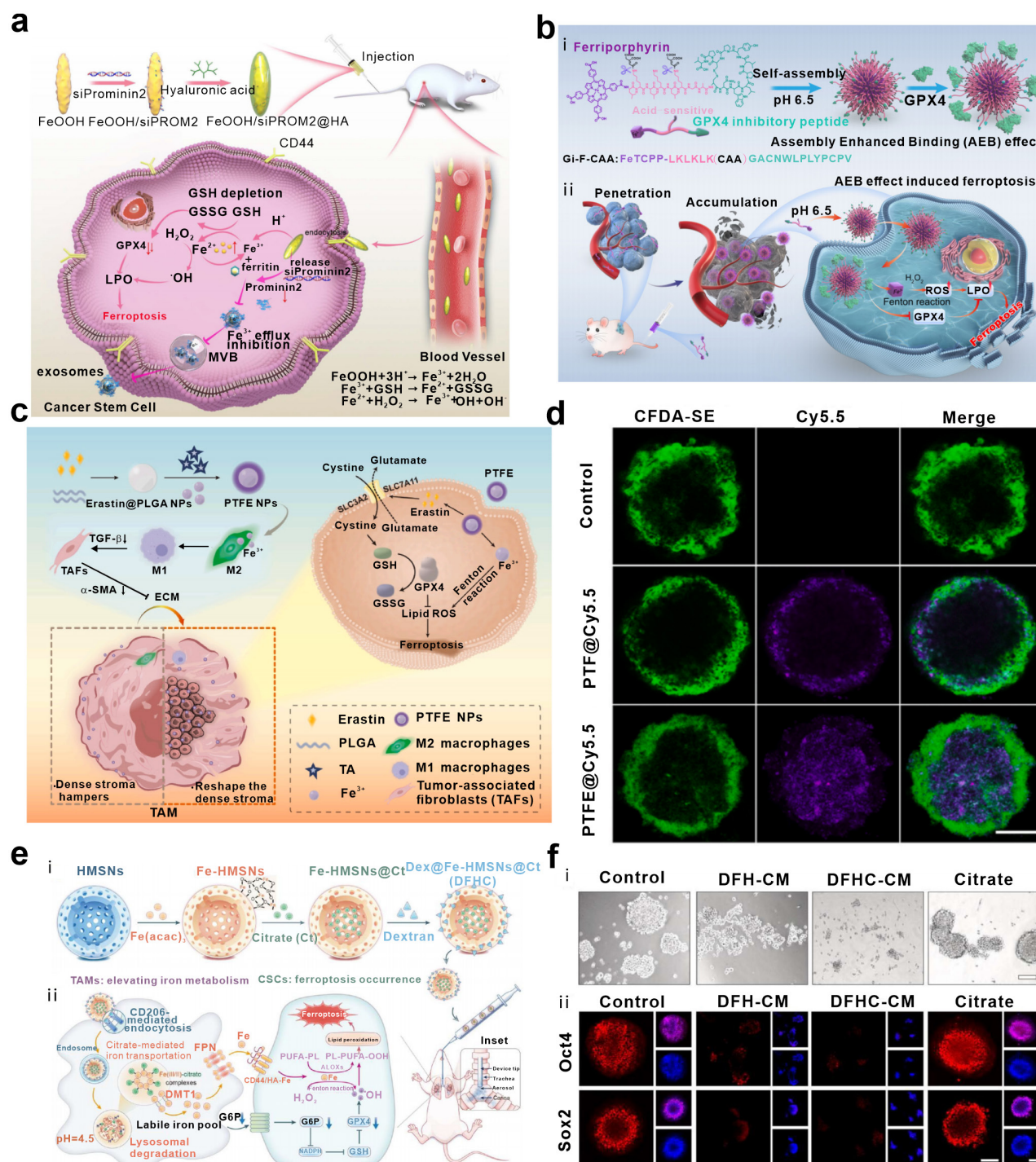


Figure 3 | (a) Schematic representation of FeOOH/siPROM2@HA-induced ferroptosis in BCSC. Reproduced with permission from Acta Materialia Inc., Copyright 2023 [82]. (b) The tumor microenvironment activates the specific peptide-ferritin conjugate (Gi-F-CAA) through enhanced binding effect assembly for ferroptosis treatment of bladder cancer. i) The process of drug self-assembly. ii) Drug delivery to the tumor site to exert therapeutic effects. The small-sized Gi-F-CAA can easily penetrate solid tumors and self-assemble into large nanoparticles in the acidic tumor microenvironment, enhancing the efficiency of endocytosis. Importantly, substantial inhibition of GPX4 activity is achieved through the assembly-enhanced binding (AEB) effect, enhancing the oxidative stress via the Fenton reaction of FeTCPP, and ultimately achieving significant anti-tumor properties through ferroptosis. Reproduced with permission from Nature Publishing Group, Copyright 2024 [93]. (c) Preparation process of PTFE nanomedicines and mechanisms of drug-induced ferroptosis and disruption of the ECM. PTFE disrupts the redox balance at

the tumor site and induces pronounced ferroptotic damage. (d) Demonstration of the effect of deep drug delivery using 3D cell spheres. (c) and (d) Reproduced with permission from Elsevier, Copyright 2024 [96]. (e) Schematic diagram of DFHC-regulated TAMs inducing CSC ferroptosis in the early stage of aerosolized treatment for primary lung cancer *in situ*. i) Synthesis of DFHC. ii) Mechanisms of action in TAMs following nebulization and the impact on CSCs through ferroptosis. (f) i) Inhibition of CSCs following various treatments. ii) Assessment of CSC markers after different treatments. (e) and (f) Reproduced with permission from American Chemical Society (ACS), Copyright 2023 [85].

DFHC is internalized by TAMs through the interaction of dextran with the CD206 receptor, releasing citrates and iron ions within the acidic lysosomal environment. These iron-loaded TAMs transport iron to CSCs *via* iron-CD44 interactions, leading to redox imbalance by downregulating glucose-6-phosphate (G6PD), ultimately inducing ferroptosis. Both *in vitro* and *in vivo* experiments demonstrated that DFHC-mediated regulation of iron metabolism in TAMs effectively inhibits the proliferation and stemness of CSCs. The nanoparticle inhibitory effect on tumor spheroid formation and suppression of stemness-related genes, such as OCT4 and SOX2, further underscore the efficacy against CSCs (Figure 3f). The study also explored aerosol therapy as a potential treatment for early-stage lung cancer *via* DFHC-mediated ferroptosis regulation by TAMs. Although promising results have been observed in animal models, further investigation into the long-term effects and potential toxicity of aerosolized nanomedicines is needed for clinical translation.

Despite the promise of ferroptosis-based therapies, several challenges remain, particularly regarding the use of iron in these treatments. One major issue is the stability of iron ions, which are highly reactive and prone to redox reactions within biological systems, leading to instability. This instability complicates predictions of behavior and effectiveness in inducing ferroptosis [160]. Another critical consideration is the biocompatibility of iron-based nanomaterials. The compatibility of these materials with biological systems is crucial, as poor biocompatibility could result in overactivated immune responses or other adverse reactions, limiting the clinical potential [161]. Furthermore, excess iron can be toxic, potentially causing cellular damage or death. Therefore, controlling the dosage and conditions under which iron-based nanomaterials are used is essential to avoid toxicity and ensure safe application [162]. In conclusion, while iron plays a vital role in inducing ferroptosis, challenges related to stability, biocompatibility, and toxicity must be addressed to maximize the therapeutic potential of iron-based nanomaterials.

In summary, these studies suggest that ferroptosis-based therapy holds promise for treating tumors, especially tumors resistant to conventional therapies. Although various nanomaterials have been developed to induce ferroptosis, clinical application remains limited, underscoring the need for further exploration and clinical trials to optimize use.

3.2 Combining ferroptosis and chemotherapy for treating drug resistance tumors and CSCs

Relying solely on ferroptosis as a monotherapy often results in limited therapeutic efficacy. To overcome this limitation, researchers have explored combining ferroptosis with chemotherapy, which has shown enhanced therapeutic effects. Moreover, incorporating nanomaterials with chemotherapeutic agents not only reduces the required drug dosage but also minimizes toxicity to healthy tissues. This combination approach offers several advantages for treating drug-resistant tumors and CSCs. Combining nanomaterials with chemotherapeutic agents enhances efficacy by specifically targeting resilient CSCs, which are often responsible for tumor recurrence and treatment failure [163]. By combining ferroptosis inducers with chemotherapeutic agents, distinct cellular pathways can be targeted, helping to overcome multiple drug resistance mechanisms and reducing the likelihood of tumors developing resistance to both therapies simultaneously. Additionally, this synergistic approach allows for the use of lower chemotherapy doses, thereby minimizing toxicity and improving the quality of life. The induction of cell death through ferroptosis and traditional chemotherapy pathways may also result in more effective tumor regression, fostering the development of personalized treatment regimens based on biomarkers that predict sensitivity to ferroptosis. Furthermore, this combination can improve drug delivery and efficacy by disrupting the tumor microenvironment, providing a promising strategy for better outcomes in oncology [164].

For example, Chen et al. developed a nanopatform by conjugating camptothecin (CPT) with ferrocene (Fc) *via* a disulfide bond to form the small molecule prodrug (CPT-SS-Fc; Figure 4a). This prodrug was then assembled with the GPX4 inhibitor, RSL3, into nanoparticles, which were modified with DSPE-PEG-RGD for targeting. The nanopatform (RSL3@CPT-SS-Fc-RGD) remains stable in physiologic conditions but disassembles within the tumor microenvironment, where elevated GSH levels cleave disulfide bond, releasing CPT and promoting apoptosis. Simultaneously, Fc and RSL3 generate ROS and inhibit GPX4, thereby inducing ferroptosis. This formulation effectively overcomes chemotherapy resistance and enhances therapeutic efficacy through the synergistic effects of ferroptosis and apoptosis [116].

Similarly, gemcitabine (GEM) has reduced efficacy due to resistance in pancreatic ductal adenocarcinoma (PDAC). Yao et al. developed the prodrug, Nut@FSSG,

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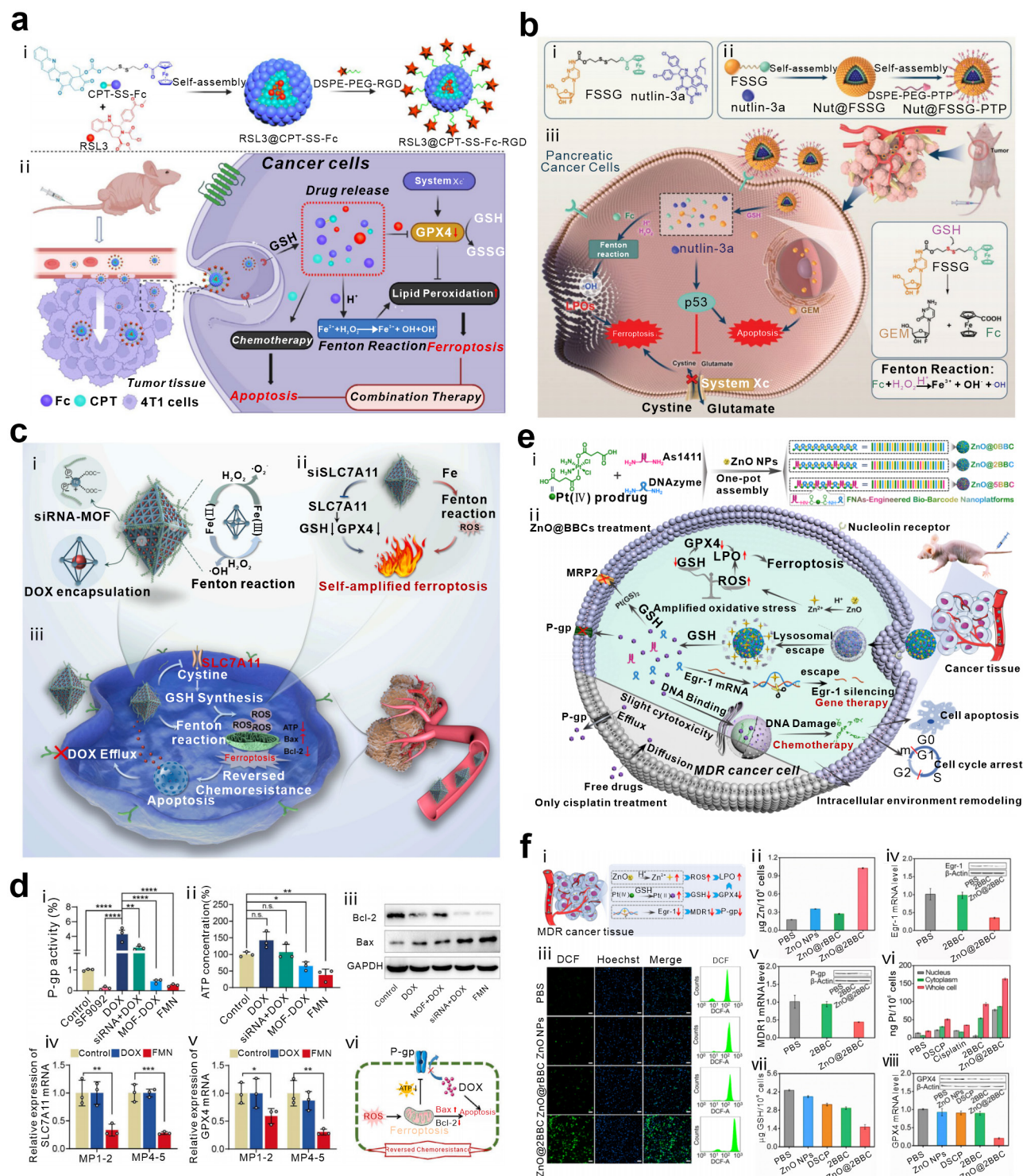


Figure 4 | (a) i) Synthesis of the RSL3@CPT-SS-Fc-RGD nanoplateform. ii) Schematic illustration of the role of nanoplateform in tumor therapy. Adapted with permission from Elsevier BV, Copyright 2023 [116]. (b) i) Structural formulas of self-assembled precursors. ii) Self-assembly synthesis process of the Nut@FSSG-PTP drug. iii) Mechanism of action of drugs at the tumor site. Adapted with permission from Wiley-VCH Verlag, Copyright 2023 [117]. (c) i) Design and structure of FMN. ii) FMN-enhanced ferroptosis via siSLC7A11. iii) Effective uptake of FMN by chemoresistant tumor cells triggers ferroptosis, inhibits ATP synthesis, impairs P-gp activity, and disrupts Bcl-2/Bax expression, reversing resistance. (d) i) Activity of P-gp following different treatments. ii) ATP concentration. iii) Western blot analysis of Bcl-2 and Bax expression. iv-v) Expression of ferroptosis marker

genes, SLC7A11 (iv) and GPX4 (v), in drug-resistant breast cancer cells. vi) Schematic representation of drug resistance reversal by ferroptosis. (c) and (d) Adapted with permission from Elsevier, Copyright 2023 [100]. (e) i) Construction of FNAs-engineered BBC-like nanomaterials. ii) Schematic representation of the mechanism of action of nanomaterials for targeted therapy of drug-resistant tumors. (f) i) Pathways of ZnO@2BBC action on drug-resistant tumor cells. ii) Zn content in cells across different groups. iii) ROS production following various treatments, assessed through confocal microscopy and flow cytometry. iv-v) Early growth response protein 1 mRNA (iv) and MDR1 (v) mRNA measured by qRT-PCR. vi) Pt contents in cells. vii) GSH content in cells following different treatments. viii) qRT-PCR and western blot analysis of GPX4 mRNA and protein expression. (e) and (f) Adapted with permission from American Chemical Society (ACS), Copyright 2023 [113].

comprised of Fc and GEM linked by disulfide bonds, along with nutlin-3a (Figure 4b) [117]. Nut@FSSG is encapsulated in plectin1 receptor-targeting lipid micelles (DSPE-PEG-PTP) to form Nut@FSSG-PTP. Upon drug release, nutlin-3a activates the p53 signaling pathway to enhance GEM-induced apoptosis, while Fc promotes ferroptosis *via* oxidative stress. This co-delivery system reduces gemcitabine resistance, promotes apoptosis, and significantly enhances therapeutic efficacy in PDAC. Notably, this formulation demonstrates selective tumor inhibition and good biosafety in various mouse models, including orthotopic and patient-derived xenograft (PDX) models, suggesting the effectiveness of this approach in overcoming chemotherapy resistance.

In another study, Yang et al. designed a ferrous metal-organic framework (MOF)-based nanomedicine (FMN) to reverse chemotherapy resistance. FMN consists of the ferrous MOF, MIL-101, SLC7A11-silencing siRNA (siSLC7A11), and doxorubicin (DOX). The MOF, rich in surface iron ions, serves as an intrinsic Fenton reagent to induce ferroptosis, while siSLC7A11 suppresses cystine uptake, reducing intracellular GSH levels. This strategy not only triggers ferroptosis but also inhibits P-gp activity, reducing DOX efflux and improving drug efficacy (Figure 4c) [100]. The FMN platform demonstrated significant therapeutic effects in MCF7/ADR tumor-bearing mice, confirming the ability of this nanomedicine to reverse multidrug resistance [MDR] (Figure 4d).

Remodeling the tumor microenvironment is essential for overcoming MDR. One strategy involves conversion of GSH to the oxidized form to mitigate GSH-mediated drug efflux *via* multidrug resistance protein 2. Zhi et al. constructed a functional nucleic acid (FNA)-based nanoplat- form utilizing the concept of biological barcodes (BBCs) for synergistic targeting treatment of MDR cancers. Zhi et al. synthesized a platinum (IV) prodrug, covalently linking two types of FNAs in a precise ratio to create a three-dimensional, BBC-like DNA nanoscale framework, alongside ZnO nanoparticles encapsulated *via* electrostatic interactions. In the acidic pH of lysosomes and the presence of overexpressed GSH, ZnO particles degrade into Zn²⁺ ions, generating ROS, while the platinum (IV) prodrug is reduced by GSH to release the active platinum (II) species for therapeutic DNA enzyme-based chemotherapy and gene modulation. The mechanism of action begins with GSH depletion, promoting downregulation of GPX4, which amplifies oxidative stress and increases lipid peroxidation,

leading to activation of ferroptosis. Furthermore, Zn²⁺-dependent DNA enzymes silence early growth response protein 1 mRNA, directly inhibiting the proliferation and migration of MDR cells, thereby further suppressing P-gp-mediated drug efflux (Figure 4e) [113]. This mechanism has been validated through western blotting and confocal microscopy, demonstrating downregulation of drug resistance-related proteins under the influence of this nanomedicine (Figure 4f). This innovative nanoplat- form demonstrates high stability, ease of synthesis, and low immunogenicity, presenting a promising approach for targeted cancer therapy and MDR reversal.

Nanoparticles also serve as sources of iron and delivery systems for ferroptosis inducers, facilitating tumor-targeted ferroptosis activation through the enhanced permeability and retention (EPR) effect. Increasing the circulation time or tumor-targeting ability of nanoparticles enhances accumulation in tumors, thereby promoting ferroptosis in tumor cells. For example, Peng et al. designed a multi-drug delivery nanoplat- form consisting of a Fe-based MOF nanoparticle loaded with pseudolaric acid B (PAB), a natural diterpenoid compound derived from cortex pseudolaricis, and coated with red blood cell (RBC) membranes. This design enables a combined treatment approach for MDR cancer through ferroptosis and apoptosis. The RBC membrane coating not only prolongs the circulation time of the nanoparticles but also reduces drug leakage. Furthermore, PAB depletes intracellular GSH *via* the p53-mediated system Xc⁻ pathway inhibition, inducing ferroptosis in glioma cells. Ferroptosis, driven by oxidative phospholipid damage, can downregulate P-gp expression, thereby reducing resistance [81].

In summary, combining ferroptosis with chemotherapy provides a multifaced approach to enhancing the efficacy of treatments for drug-resistant tumors and CSCs. This strategy improves tumor regression, reduces required chemotherapy doses, minimizes toxicity, and enhances CSC targeting. This strategy also paves the way for the development of novel, synergistic therapeutic strategies and provides mechanistic insights for the design of future cancer therapies.

3.3 Combining ferroptosis and sonodynamic therapy (SDT) for treating drug resistance and CSCs

In addition to combining ferroptosis with chemotherapy, SDT offers a unique and promising strategy for cancer treatment. SDT has garnered significant attention

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as a safe, non-invasive approach that uses ultrasound to activate sonosensitizers to generate ROS and to trigger drug release. By inducing localized oxidative stress and cellular damage, SDT enhances therapeutic efficacy while minimizing systemic toxicity. Given the ability to selectively target tumor cells, SDT presents a complementary treatment for overcoming CSCs and drug resistance [165, 166]. This rapidly evolving technique generates ROS that promote ferroptosis, further enhancing the effectiveness of treatments against both CSCs and drug-resistant tumors [167].

Recognizing that cancer cells often exhibit deficiencies in executing “pure” apoptotic cell death, Zhou et al. utilized a hybrid cell death strategy to address drug-resistant cancers by developing a composite liposomal nanodelivery system, co-loading the sonosensitizer protoporphyrin IX (PpIX) and the iron supplement ferumoxytol (Lipo-PpIX@Ferumoxytol). Ferumoxytol, an iron oxide nanoparticle, induces ferroptosis by supplying iron ions to cells, making iron ions more susceptible to SDT-induced apoptosis. The combination of SDT and ferroptosis synergistically enhances therapeutic outcomes by overcoming drug resistance and promoting complete tumor resection (Figure 5a) [122]. However, despite its promise, the application of SDT in clinical settings is still limited due to challenges in precisely controlling SDT activation and restricted efficacy in deep tissues, warranting further research to improve targeting and *in vivo* efficiency.

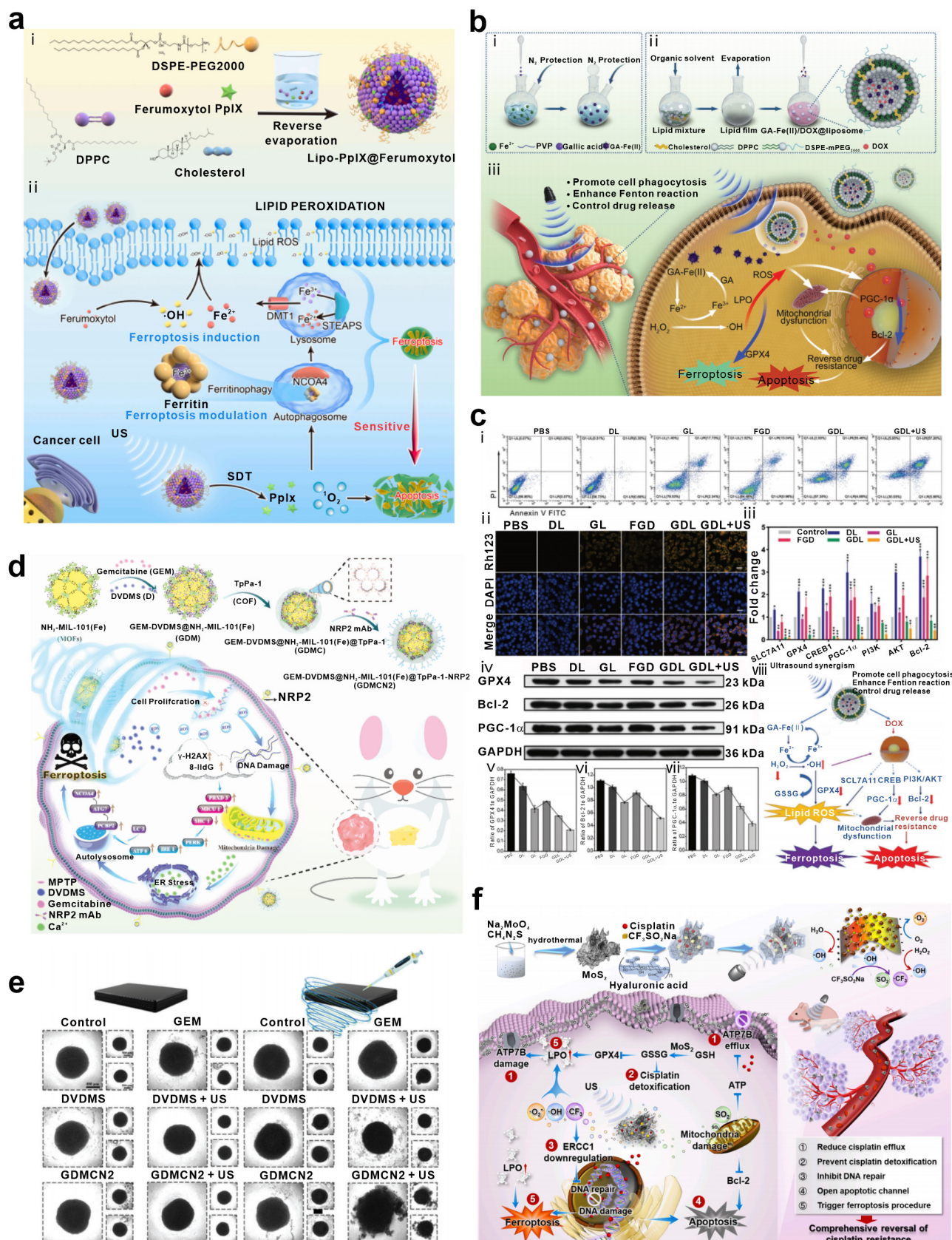
Similarly, Zheng et al. reported a gallic acid (GA)-Fe(II)-based liposomal nanodelivery system to enhance ultrasound-triggered nanocatalytic ferroptosis for reversing chemotherapy resistance (Figure 5b) [118]. This system encapsulates DOX and uses an ultra-small GA-Fe(II) nanoscale complex that catalyzes the conversion of H_2O_2 into $\cdot OH$ in the presence of ultrasound. The resulting ROS lead to lipid peroxidation and ferroptosis in DOX-resistant MCF-7/ADR cancer cells. Ultrasound-enhanced Fenton reactions also downregulate key survival proteins, such as PGC-1 α and Bcl-2, enhancing susceptibility of cells to DOX-induced apoptosis. Furthermore, apoptosis assays and assessments of ferroptosis-related genes confirm that the combination of ultrasound and ferroptosis significantly reverses tumor resistance and achieves favorable therapeutic results (Figure 5c).

The application of MOFs in cancer treatment is becoming increasingly common. However, several MOFs exhibit poor hydrophilicity, which adversely affects drug release and delivery *in vivo*. Recent studies indicate that covalent organic frameworks (COFs) synthesized *via* the Schiff base reaction of 2,4,6-trihydroxybenzaldehyde with para-phenylenediamine demonstrate remarkable hydrolytic stability when integrated with MOFs. In the context of overcoming GEM resistance in pancreatic cancer, Zhao et al. designed a novel nanocage system, GEM-DVDM5@MOFs@COF-NRP2 (GDMCN2), specifically targeting human GEM-resistant PANC-1/GEM cells. NRP2, a cell surface molecule prevalent in pancreatic

cancer, has a crucial role in tumor cell growth, migration, invasion, and angiogenesis. Researchers developed mouse monoclonal antibody (mAb)-modified GEM-DVDM5@NH₂-MIL-101(Fe) composites, thereby enhancing tumor targeting and facilitating rapid drug delivery to tumor sites. Under ultrasound, GDMCN2 generates substantial amounts of ROS, inducing mitochondrial and DNA damage. The ROS activate the mitochondrial permeability transition pore (MPTP), leading to the release of Ca²⁺ and triggering endoplasmic reticulum (ER) stress. This pathway activates microtubule-associated protein 1A/1B-light chain 3 (LC3), promoting lysosomal autophagy. With the upregulation of nuclear receptor coactivator 4 (NCOA4), this process further triggers autophagy-dependent ferroptosis. This strategy effectively integrates SDT with ferroptosis (Figure 5d) [120]. Additionally, experiments using 3D tumor spheroids demonstrate that the final treatment group effectively disrupts the tumor, achieving favorable therapeutic outcomes (Figure 5e).

In light of the limitations of conventional materials in cancer treatment, numerous studies have pursued innovations, such as piezoelectric materials (e.g., BaTiO₃, ZnO, BiFeO₃, and MoS₂). These materials are known for high efficiency in generating oxygen-free radicals and are widely utilized in catalysis, pollutant degradation, energy conversion, and tumor elimination, while exhibiting good stability. When combined with ultrasound, these piezoelectric materials facilitate electronic transfer to generate lethal radicals by. For example, Ge et al. developed an intelligent network integrating SDT with nanoparticles (HA@MoCF NPs) to overcome cisplatin resistance in ovarian cancer. MoS₂ serves as a sonosensitizer and nanoenzyme with trifluoromethane sulfonate (CF₃SO₂Na) as the CF₃ precursor and cisplatin functioning as the chemotherapeutic agent, while HA is a biocompatible shell. This system aims to reverse cisplatin resistance and enhance ovarian cancer treatment. Leveraging the nanoenzyme properties, MoS₂ can oxidize GSH to GSSG while generating significant ROS and lipid peroxidation, ultimately disrupting the efflux protein ATP7B and triggering ferroptosis (Figure 5f) [121]. The synergistic effects of these strategies markedly improve tumor treatment efficacy.

Combining ferroptosis and SDT offers significant advantages in treating drug-resistant tumors and targeting CSCs but the combination also presents some disadvantages and future challenges. While this synergistic approach enhances therapeutic efficacy by inducing oxidative stress through ferroptosis and generating ROS *via* SDT, effectively eliminating resistant cells, a synergistic approach may also lead to unintended damage to healthy tissues due to the oxidative stress generated. Additionally, the precise regulation of ferroptosis is still not fully understood, which can complicate the therapeutic application. The effectiveness of this combination can be influenced by the tumor microenvironment, which may exhibit variability in response to treatment.



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Figure 5 | (a) Schematic of the preparation of engineered nanoliposomes and the synergistic therapeutic mechanism of ferroptosis targeting *via* SDT. i) Synthesis of Lipo-PpIX@Ferumoxytol. Lipo-PpIX@Ferumoxytol nanoliposomes, which possess SDT activation and ferroptosis targeting ability, were synthesized by a reverse evaporation method. ii) Role of nanomaterials in intracellular ferroptosis and ultrasound activation. The targeted delivery of iron oxide nanoparticles (aluminum glycolate) induces ferroptosis by introducing iron ions into cells. SDT, utilizing PpIX as a nanosensitizer, enhances the production of intracellular $^1\text{O}_2$ free radicals, which not only induce apoptosis of cancer cells but also modulate ferroptosis sensitivity by promoting cell-selective autophagy. Reproduced with permission from Elsevier, Copyright 2021 [122]. (b) Construction of GA-Fe(II)/DOX@liposome and the role in reversing tumor resistance combined with US irradiation-enhanced nanocatalytic ferroptosis. i-ii) Preparation of GA-Fe(II)/DOX@ liposomes. iii) Mechanism of ferroptosis and related effects following ultrasound activation of materials. The potential mechanism of GA-Fe(II)/DOX@ liposome-induced tumor nanotherapy, combining ferroptosis and apoptosis through ultrasound activation. GA-Fe(II) catalyzes ferroptosis by increasing intracellular Fe(II) levels, inducing LPO, depleting GSH, and inactivating GPX4. (c) i) Flow cytometry assay for apoptosis following different treatments. ii) Detection of mitochondrial damage. iii) Assessment of SLC7A11, CREB1, PGC, PGC-1 α , PIF-7, AKT, and Bcl-2 expression. iv-vii) Expression and quantification of GPX4, PGC-1 α , and Bcl-2 by western blotting. viii) Schematic illustration of the reversal of resistance to ferroptosis induced by ultrasound. (b) and (c) Reproduced with permission from Wiley-VCH Verlag, Copyright 2021 [118]. (d) Preparation of GEM-DVDMs@MOFs@COF-NRP2 nanomaterials and the reaction mechanism at the tumor site under ultrasound. (e) Morphologic analysis of three-dimensional tumor spheroids following various treatments. (d) and (e) Reproduced with permission from Wiley-VCH Verlag, Copyright 2023 [120]. (f) Synthesis of HA@MoCF₃Pt nanomaterials and the mechanism involved in the reversal of drug resistance. Adapted with permission from Elsevier, Copyright 2022 [121].

Moreover, optimization of dosing regimens and delivery methods for both therapies remains a challenge because achieving effective concentrations in tumor tissues while minimizing systemic toxicity is critical. Finally, there is a need for further research to understand the long-term effects and potential resistance mechanisms that may emerge from this combination strategy. Overall, while the interplay between ferroptosis and SDT holds promise for improving treatment outcomes, addressing these challenges will be essential for successful clinical translation.

In conclusion, while the synergistic use of ferroptosis and SDT holds significant promise for improving cancer treatment outcomes, addressing the challenges related to treatment precision, delivery, and long-term effects will be crucial for successful clinical translation.

3.4 Combining ferroptosis and PTT for treating drug resistance and CSCs

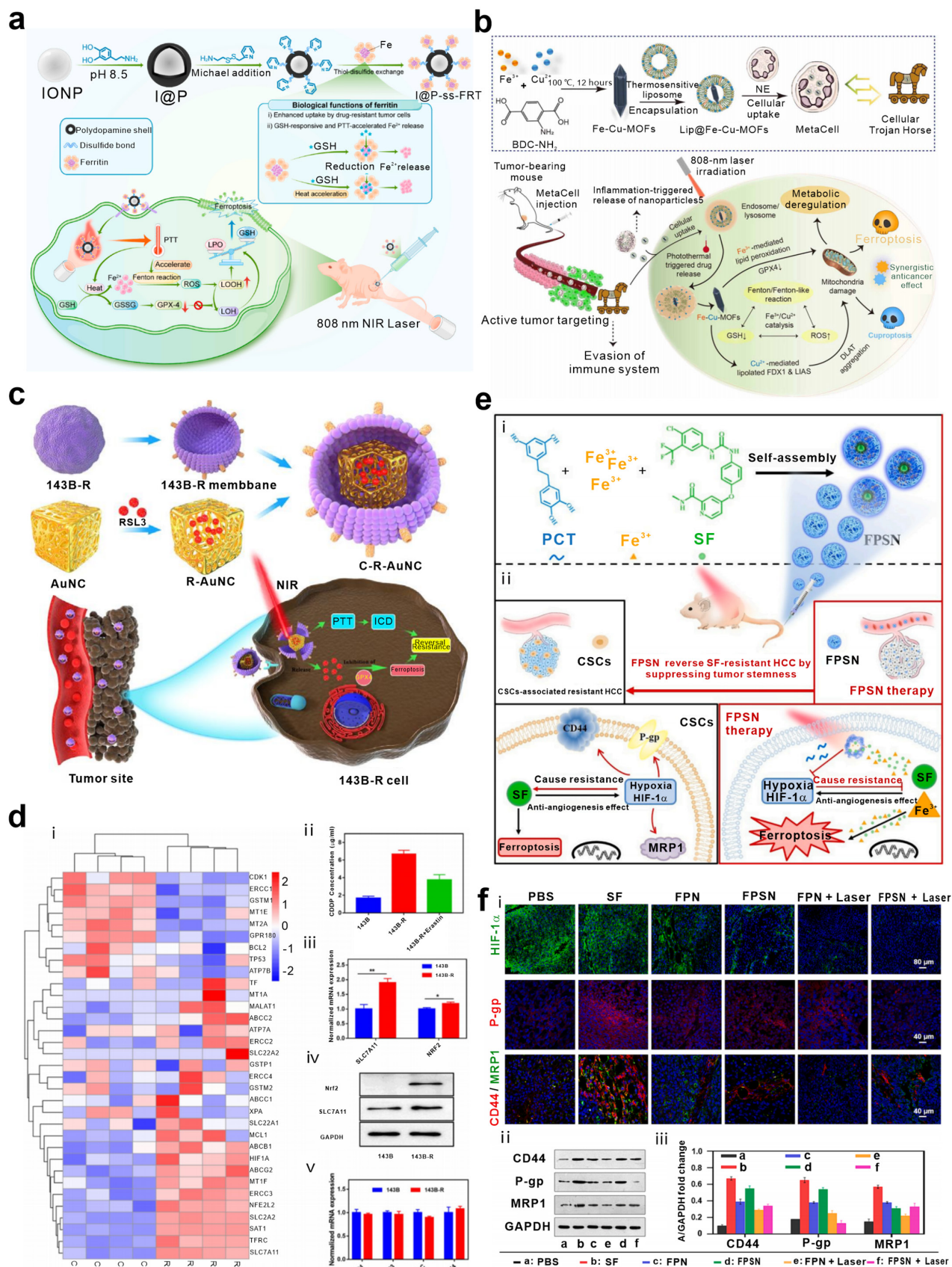
In addition to the unique advantages of SDT, photothermal therapy (PTT) has also garnered significant attention as a non-invasive, highly targeted treatment modality in cancer therapy. PTT utilizes near-infrared (NIR) light to induce localized heating within tumor tissues, which is primarily mediated by photothermal agents, such as nanoparticles or dyes. These agents absorb NIR light and convert it into heat, leading to tumor cell destruction, hyperthermia, and enhanced tumor vasculature permeability. The ability of PTT to focus heat on tumors while minimizing damage to surrounding healthy tissues makes PTT an attractive therapeutic option [168]. When combined with ferroptosis, chemotherapy, or SDT, PTT can yield synergistic effects, enhancing therapeutic outcomes and providing an effective strategy for overcoming drug resistance and targeting CSCs [169].

The elevated temperatures generated during PTT accelerate Fenton or Fenton-like reactions, involving iron ions and nanoparticles, leading to enhanced ROS

production and ferroptosis [170]. Concurrently, ROS generated during ferroptosis can degrade heat shock proteins induced by PTT, further reducing cellular heat resistance. This mutual reinforcement between PTT and ferroptosis suggests a synergistic effect, offering significant potential for treating drug-resistant tumors and CSCs.

As an example, Chen et al. reported a biomimetic nanoparticle (I@P-SS-FRT) that uses GSH-triggered and PTT-enhanced ferroptosis for the treatment of drug-resistant cancers (Figure 6a) [149]. Iron oxide nanoparticles were selected for an ability to release iron ions slowly and continuously in acidic environments, as well as the capability for photothermal conversion and magnetic resonance imaging. A polydopamine coating further enhances the photothermal effect and provides a reactive platform for subsequent ferritin modification due to the active catechol hydroxyl groups. Drug-resistant tumor cells exhibit more efficient nanoparticle uptake, mediated by ferritin, compared to non-resistant cells, thereby enhancing intracellular functionality. NIR-mediated hyperthermia promotes ferritin release, leading to ferroptosis through the depletion of intracellular GSH and the accumulation of ferrous ions. This interaction fosters a highly effective activation of ferroptosis, establishing a synergistic relationship between PTT and ferroptosis. The photothermal heating of I@P-SS-FRT induces ferroptosis, compensating for incomplete ablation caused by uneven heat distribution in PTT, thereby demonstrating potent synergistic effects against resistant tumors. Further *in vivo* studies focusing on cell enrichment and drug penetration would offer stronger validation of the drug therapeutic efficacy in solid tumors.

In another study, Chen et al. developed a multifunctional "Cellular Trojan horse" (MetaCell) designed to simultaneously induce copper-dependent and ferroptotic cell death (Figure 6b) [127]. MetaCell consists of



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Figure 6 | (a) Preparation of I@P-ss-FRT and the mechanism of action underlying enhanced ferroptosis under PTT. Reproduced with permission from Elsevier, Copyright 2024 [149]. (b) i) Design and preparation of the Trojan Horse (MetaCell). ii) Schematic representation of the anti-cancer effects of PTT and ferroptosis. Reproduced with permission from American Association for the Advancement of Science, Copyright 2024 [127]. (c) Schematic illustration of the design of C-R-AuNC and action at the tumor site. (d) i) Heatmap depicting resistance genes to cisplatin. ii) IC_{50} values following CDDP treatment. iii) mRNA expression of SLC7A11 and NRF2 in 143B and 143B-R cells measured by qRT-PCR. iv) Western blot analysis of SLC7A11 and NRF2 expression. v) mRNA expression of MDR1, P53, TFRC, and GPX4 in 143B and 143B-R cells. (c) and (d) Reproduced with permission from Elsevier, Copyright 2021 [124]. (e) i) Self-assembly of FPSN nanodrugs. ii) FPSN inhibits CSC stemness by suppressing hypoxia and acts synergistically through PTT and ferroptosis. (f) i-iii) Expression of CD44, P-gp, and MRP1 in tumor sections. (e) and (f) Adapted with permission from Elsevier, Copyright 2023 [123].

live neutrophils encapsulating thermosensitive liposomes loaded with bimetallic Fe-Cu-MOF (Lip@Fe-Cu-MOF). These frameworks are synthesized by integrating iron and copper ions with organic ligands to form highly porous structures. Compared to monometallic frameworks, these bimetallic Fe-Cu-MOFs offer enhanced stability, increased catalytic activity, and improved light adsorption capacity. Upon exposure to photothermal effects, the drug accumulates at the tumor site, triggering Fenton reactions that deplete GSH and amplify ferroptosis. MetaCell effectively eliminated solid tumors in tumor-bearing mice, preventing recurrence and significantly prolonging survival. This work highlights the potential of combining ferroptosis and cuproptosis therapies, offering insights into how metal homeostasis in tumors can be leveraged to circumvent drug resistance and enhance therapeutic efficacy.

PTT can induce immunogenic cell death (ICD), activating a robust anti-tumor response that further enhances the therapeutic effects of ferroptosis. For example, a gold nanocage coated with cancer cell membranes and loaded with RSL3 (C-R-AuNC) was designed to overcome chemotherapy resistance in osteosarcoma. These gold nanocages exhibit excellent biocompatibility, hollow interiors, porous walls, and efficient photothermal conversion in the NIR region, enabling effective PTT on cancer cells while facilitating controlled drug release at targeted sites. RSL3 induces ferroptosis by inhibiting GPX4, further enhancing the therapeutic effect. Moreover, PTT increases drug accumulation at tumor sites by generating heat that enhances blood flow and tumor vascular permeability. This effect is mediated through the modulation of protective genes and proteins, which sensitizes cancer cells to therapeutic drugs and impairs tumor ability to cope with oxidative stress (Figure 6c) [124]. The combination of ferroptosis with PTT offers a synergistic approach for treating resistant tumors. To better understand the therapeutic mechanisms in drug-resistant cells, the authors examined the levels and expression of relevant genes and proteins (Figure 6d).

Similarly, Lin et al. developed a pH-responsive, carrier-free nanosystem (FPSN) composed of silk fibroin (SF), paclitaxel (PCT), and Fe^{3+} , that was designed to effectively target SF-resistant hepatocellular carcinoma (Figure 6e) [123]. PCT has been shown to inhibit hypoxia inducible factor 1 alpha (HIF-1 α), a key

regulator of tumor hypoxia. Additionally, PCT targets CSCs by inducing apoptosis through activation of the caspase pathway and modulation of Bcl-2 protein and the p53 pathway. Moreover, PCT interacts with metal ions, such as Fe^{3+} , to form pH-responsive metal-phenolic networks that promote ferroptosis. This nanosystem facilitates the simultaneous release of SF and Fe^{3+} at the tumor site, enhancing oxidative stress and promoting ferroptosis. Furthermore, by harnessing the photothermal properties of PCT and HIF-1 α inhibition, FPSN alleviates tumor hypoxia and reduces hypoxia-associated CSC activity, thereby overcoming drug resistance (Figure 6f).

Combining ferroptosis and PTT presents a synergistic approach to enhance cancer treatment by effectively targeting drug-resistant cancer cells and CSCs. This combination improves therapeutic efficacy because ferroptosis induces cell death through oxidative stress while PTT utilizes localized heat to create additional stress on tumor cells [171]. Together, ferroptosis and PTT can overcome drug resistance mechanisms and selectively target CSCs, which are often more resistant to conventional therapies. The localized nature of PTT minimizes damage to healthy tissues and reduces systemic side effects while potentially activating an immune response against residual cancer cells. Additionally, nanoparticles designed for dual delivery of ferroptotic agents and PTT activators improve drug accumulation at tumor sites.

However, there are also disadvantages to consider. For example, the effectiveness of PTT can be limited by factors, such as tissue penetration depth and heat dissipation, potentially reducing its impact on deeper tumors. Furthermore, inducing ferroptosis can result in unwanted inflammatory responses or damage to surrounding healthy tissues. There is also a risk of developing resistance to ferroptotic agents over time. Future developments should focus on optimizing the design of nanoparticles to enhance the targeting ability and improve the delivery of ferroptotic agents and PTT activators. Research into combination strategies that further sensitize resistant cancer cells, as well as investigating biomarkers for patient selection, is crucial. Additionally, exploring the integration of immunotherapy with this combined approach may enhance anti-tumor effects and help overcome challenges associated with tumor

heterogeneity. Ultimately, continued innovation has the potential to significantly advance personalized cancer therapies and improve patient outcomes.

3.5 Combining ferroptosis and CDT for treating drug resistance and CSCs

In addition to other therapeutic strategies, chemodynamic therapy (CDT) has emerged as a promising approach in cancer treatment. CDT leverages the catalytic properties of specific agents to convert hydrogen peroxide (H_2O_2) into highly reactive hydroxyl radicals ($\cdot OH$) via Fenton or Fenton-like reactions [172, 173]. This process generates substantial oxidative stress within cancer cells, leading to cellular damage and ultimately triggering cell death. By exploiting endogenous H_2O_2 in the tumor, CDT offers a targeted and relatively safe method for selectively eradicating cancer cells, with several advantages, including efficient catalytic ROS generation, minimal dependence on external stimuli, deep tissue penetration, and resistance to drug tolerance [66]. Therefore, combining ferroptosis and CDT presents a powerful approach to overcoming drug resistance and targeting CSCs in cancer treatment. Ferroptosis, an iron-dependent cell death pathway driven by lipid peroxidation, bypasses the typical resistance mechanisms in drug-resistant cancer cells and CSCs, while CDT uses tumor-specific reactions to generate ROS that cause oxidative stress and cellular damage [174]. Combining ferroptosis and CDT creates a highly oxidative environment that disrupts cancer cell defenses, amplifying ROS, and enhancing treatment specificity [175]. This synergy effectively targets CSCs, reduces recurrence risk, and circumvents drug resistance by exploiting iron metabolism and the tumor redox imbalance, making ferroptosis and CDT a promising dual-modality therapy for aggressive cancers.

Materials based on the coordination of metal ions and phenolic molecules exhibit several attractive properties, including low cytotoxicity, high thermal stability, and pH responsiveness. Guo et al. developed Den-DOX-tannic acid- Fe^{3+} (DDTF) nanocomposites by loading DOX with dendritic macromolecules, which were then incorporated into tannic acid/ Fe^{3+} to metal-phenolic networks. This composite effectively combats MDR in cancer cells through a dual mechanism involving apoptosis and ferroptosis. The DOX-induced apoptosis increases ROS levels, thereby enhancing the sensitivity of cancer cells to ferroptosis induced by the Fenton reaction and improving the efficiency of CDT. Furthermore, DDTF circumvents drug efflux transporters on the membranes of resistant cancer cells, facilitating the efficient delivery of DOX into the cytosol and nucleus, where excessive ROS generated by both the Fenton reaction and DOX ultimately induces cell death (Figure 7a) [133]. While successful in *in vitro* studies, additional characterization such as spectroscopy and *in vivo* imaging provide a more comprehensive understanding of the nanomaterial therapeutic potential.

Building on the potential of CDT, Ma et al. used a top-down approach involving reflux ion exchange to produce high-quality ultra-thin 2D vermiculite (VMT) nanosheets from thermally expanded VMT crystals. Modified with polyvinylpyrrolidone (PVP), the VMT-PVP nanosheets undergo redox reactions with tumor overexpressed GSH to produce $Fe(II)$, catalyzing the conversion H_2O_2 into highly toxic $\cdot OH$. This reaction leads to lipid peroxidation and ferroptosis induction, significantly inhibiting tumor growth (Figure 7b) [135]. *In vivo* tests showed excellent biosafety and effective tumor inhibition, making vermiculite nanosheets promising candidates for dual ferroptosis-CDT nanomedicines.

While combining ferroptosis and CDT shows promise in targeting drug-resistant cancer cells and CSCs, some challenges remain. One major limitation is the potential for toxicity in healthy tissues because the high ROS levels and lipid peroxidation required for these therapies can sometimes affect surrounding cells. Additionally, the reliance on iron metabolism may result in inconsistent therapeutic outcomes due to variations in iron availability within different tumors. Achieving effective delivery of ferroptosis and CDT agents to deep-seated or hypoxic tumor regions also poses a challenge because hypoxia can limit ROS production, reducing therapy efficacy.

Future developments aim to address these limitations by creating highly targeted, tumor-specific delivery systems, such as nanocarriers engineered to release therapeutic agents in response to specific tumor microenvironment signals (e.g., acidic pH or specific enzymes). Additionally, combining ferroptosis and CDT with complementary therapies, like PTT or immunotherapy, could enhance ROS generation selectively in tumors and further reduce off-target effects. Advances in precision medicine and imaging techniques will also play a key role in refining these therapies, allowing for real-time monitoring and personalized treatment adjustments to maximize efficacy while minimizing toxicity.

3.6 Combining ferroptosis and photodynamic therapy (PDT) for treating drug resistance and CSCs

PDT is a minimally invasive cancer treatment that uses light-activated photosensitizing agents to induce cell death through the generation of ROS. PDT involves the administration of a photosensitizer—a molecule that becomes toxic when exposed to specific wavelengths of light, typically in the red or near-infrared range [176]. Upon activation by light, the photosensitizer undergoes a photochemical reaction that produces singlet oxygen and other ROS, which damage cellular components, such as lipids, proteins, and DNA, ultimately leading to cell death. Compared to traditional treatments, PDT offers several advantages, including minimal trauma, low toxicity, high selectivity, broad applicability, and a reduced likelihood of resistance.

Combining ferroptosis and PDT offers a promising strategy to combat drug resistance and target CSCs in

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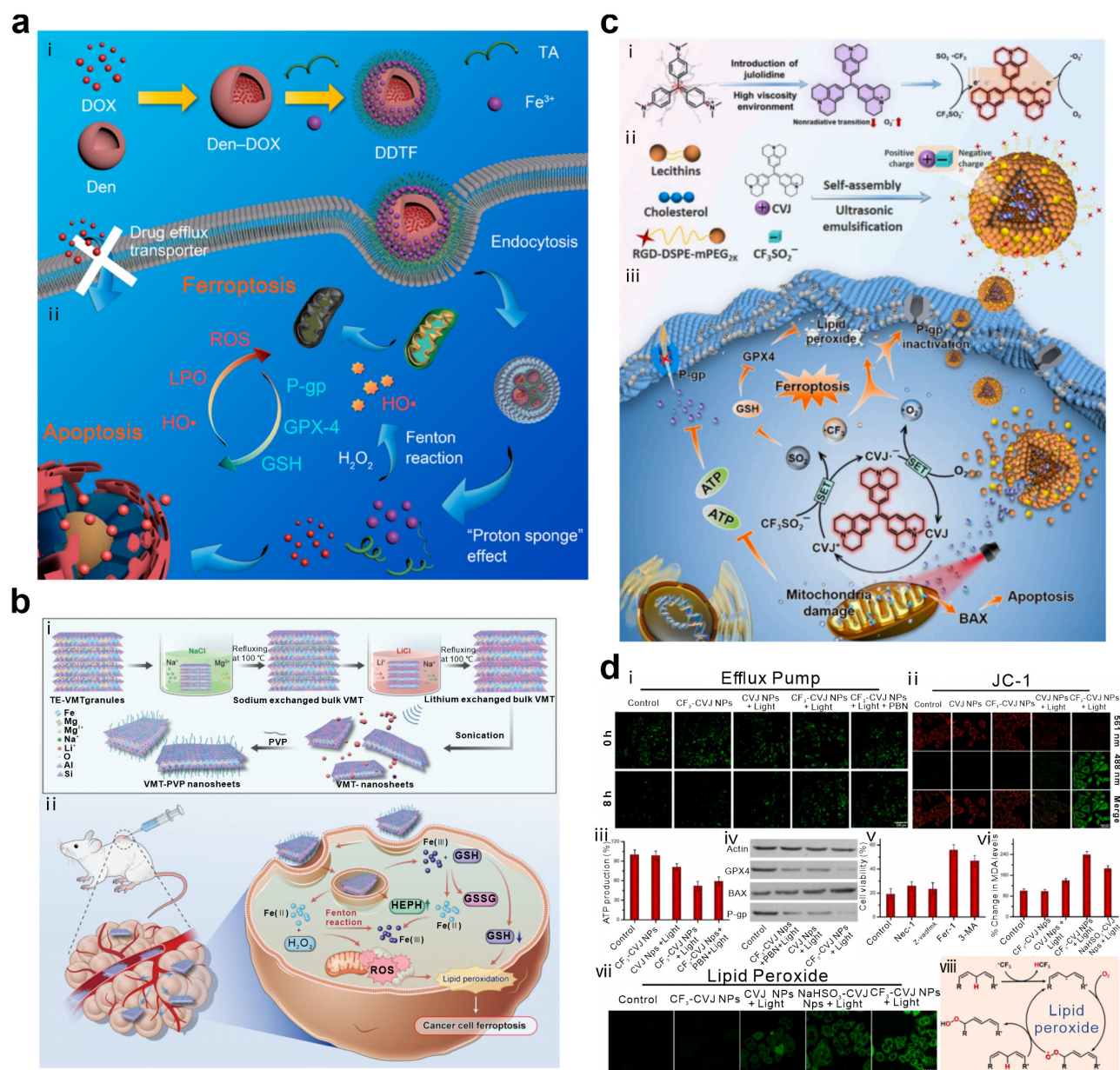


Figure 7 | (a) i) Preparation of DDTF nanomaterials. ii) Role DDTF in tumor treatment. Adapted with permission from American Chemical Society (ACS), Copyright 2019 [133]. (b) i) VMT nanosheet preparation process. ii) Schematic diagram of the therapeutic effects of VMT. Reproduced with permission from the Wiley-VCH Verlag, Copyright 2022 [135]. (c) i) Molecular structures of crystalline violet (CV) and juliside-modified crystalline violet (CVJ). ii) CF_3 -CVJ nanoliposomes induce ferroptosis under light irradiation. iii) Mechanism of ferroptosis promoted by CF_3 -CVJ NPs under photoirradiation. (d) i) P-gp efflux ratio detection in cells. ii) Detection of mitochondrial membrane potential. iii) ATP content. iv) Western blot detection of GPX4, P-gp, and BAX proteins. v) Cell survival after different treatments. vi) MDA content. vii) Lipid peroxidation detection. viii) Schematic representation of lipid peroxidation induced by $\cdot\text{CF}_3$. Reproduced with permission from the Elsevier, Copyright 2022 [137].

cancer treatment. Ferroptosis, an iron-dependent form of cell death characterized by lipid peroxidation, can effectively overcome the apoptosis resistance typically occurring in drug-resistant cancer cells and CSCs. PDT, in contrast, uses light-activated photosensitizers to

generate ROS that induce oxidative damage and kill tumor cells. By combining these two approaches, it is possible to enhance the production of ROS and further amplify oxidative stress within tumor cells, leading to synergistic cell death.

Zheng et al. developed a liposomal nanosystem based on triphenylmethane/ $\text{CF}_3\text{SO}_2\text{Na}$ ($\text{CF}_3\text{-CVJ}$) nanoplateform to overcome drug resistance. By introducing julolidine into the crystal violet (CV), a classic type I photosensitizer, Zheng et al. created CVJ. The large torsional surface of julolidine restricts the non-radiative transition capabilities of CV in the highly viscous tumor environment, thereby enhancing photocatalytic efficiency. The synergistic action of photodynamic and photocatalytic processes induces ferroptosis, effectively killing drug-resistant tumors. The catalytically produced SO_2 simultaneously inhibits GPX4 activity, further enhancing ferroptosis in tumor cells. Additionally, the photosensitizer upregulates pro-apoptotic proteins, reactivating apoptosis through mitochondrial damage in resistant tumor cells. Importantly, the photosensitizer efflux is inhibited by downregulating P-gp efflux proteins and mitochondrial ATP production, offering a novel strategy to overcome drug resistance (Figure 7c) [137]. The mechanism of action was validated through assessment of P-gp efflux, mitochondrial membrane potential, ATP levels, drug resistance proteins, and ferroptosis-related lipid peroxidation (Figure 7d).

In another work, Sang et al. designed a nanodevice aimed at enhancing ferroptosis induction. The photosensitizer is chemically linked to the lipophilic end of a polymer and is engineered to anchor to the mitochondrial membrane after disassembly. The sorafenib-loaded device, CSO-SS-Cy7-Hex/SPION/Srfrn, demonstrated redox-responsive characteristics and the ability to accelerate the Fenton reaction [136]. Upon light exposure, the device generates a substantial amount of ROS, depletes GSH, and produces significant lipid peroxidation. This system also mitigates invasion and metastasis, effectively overcoming drug-resistant tumors by combining ferroptosis and PDT.

The combination of ferroptosis and PDT amplifies the therapeutic effects, particularly in oxygen-rich and hypoxic environments, making the combination effective for both bulk tumor and CSC eradication. However, limitations, such as limited tissue penetration of light, off-target toxicity of photosensitizers, and hypoxia-related challenges, hinder the full potential of this combination. Moreover, the heterogeneity and resistance mechanisms of CSCs, like overexpression of antioxidant proteins, may reduce long-term effectiveness.

Future developments should focus on improving photosensitizers with enhanced tumor specificity and deeper tissue penetration, as well as incorporating nanocarriers to optimize delivery. Additionally, strategies to overcome tumor hypoxia, the design of dual-mode ferroptosis inducers, and combinations with immunotherapy or chemotherapy may enhance efficacy and help address resistance. Personalized approaches that tailor therapy to the unique tumor microenvironment could further improve treatment outcomes. Despite these challenges, continued innovation in these areas holds the potential to make ferroptosis and PDT a cornerstone of effective, targeted cancer therapy.

3.7 Combining ferroptosis and immunotherapy for treating drug resistance and CSCs

While several therapeutic strategies offer promise in cancer treatment, immunotherapy stands out due to a unique ability to harness the immune system to target and eliminate cancer cells. Unlike conventional treatments that directly target tumors, immunotherapy enhances the natural capacity of the immune system to recognize and eliminate cancerous cells [177]. This approach is particularly valuable for the potential to provide long-term and stable cancer control. Immunotherapy encompasses a variety of strategies, including immune checkpoint inhibitors, CAR T-cell therapy, cancer vaccines, and cytokine-based therapies, each amplifying the defense against cancer in distinct ways [178].

Combining ferroptosis and immunotherapy presents a compelling strategy for overcoming drug resistance and targeting CSCs. Ferroptosis, an iron-dependent form of programmed cell death driven by lipid peroxidation, enhances the release of tumor-associated antigens and damage-associated molecular patterns (DAMPs), thereby stimulating anti-tumor immune responses [179]. When paired with immunotherapy, this combination can amplify the activation and recruitment of immune cells to the tumor microenvironment, promoting more effective anti-tumor responses. This synergy can potentially overcome the resistance often posed by CSCs, known for the ability to evade traditional treatments and contribute to tumor relapse.

Additionally, the ferroptosis-immunotherapy combination can modulate the tumor microenvironment, shifting the tumor microenvironment from an immunosuppressive to an immunostimulatory state. This modulation enhances the efficacy of immune checkpoint inhibitors, enabling a more robust attack on cancer cells. By integrating these approaches, treatment can be tailored to leverage the immunogenic properties of ferroptosis while enhancing the durability and breadth of immune-mediated tumor control [180]. This strategy not only addresses drug-resistant cancer cell populations but also reduces the likelihood of recurrence driven by CSCs.

Arachidonic acid (AA), a polyunsaturated fatty acid, is crucial in promoting lipid peroxidation and sensitizing cells to ferroptosis. Given the key role of cyclooxygenase-2 (COX-2) in AA metabolism, inhibiting COX-2 may elevate intracellular AA levels. Zhang et al. developed a carrier-free nanosystem composed of polyphenol COX-2 inhibitors, Fe^{3+} , DOX, and dopamine-modified HA (pHA-OH) for synergistic ferroptosis and immunotherapy targeting drug-resistant tumors. The pHA-OH component enhances nanosystem accumulation in tumor tissues via specific binding to CD44 receptors. Once in the acidic tumor microenvironment, the nanosystem degrades, enabling controlled release of DOX, COX-2 inhibitors, and Fe^{3+} ions. The released Fe^{3+} induces ferroptosis in drug-resistant GBM cells. Simultaneously, Fe_3O_4 nanoparticles and siPD-L1 are degraded by

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GSH, leading to the release of siPD-L1, which inhibits PD-L1 expression. The polyphenols selectively inhibit the COX-2 pathway, suppressing P-gp expression and increasing cancer cell sensitivity to DOX. Upregulation of AA promotes lipid peroxidation, enhancing Fe³⁺-induced ferroptosis. Additionally, the Fe³⁺-phenol complex exhibits notable photothermal properties, which further promotes ferroptosis and amplify the ICD effect, activating robust anti-tumor immune responses (Figure 8a) [129]. Western blot analysis confirmed COX-2 and P-gp protein downregulation (Figure 8b). Analysis of differentially expressed genes (DEGs) implicated in drug resistance and ferroptosis underscored the roles in resistance mediation and ferroptosis pathway activation (Figure 8c). Further investigation into the relationship between the characteristics of LNPs, such as size and surface modification. The *in vivo* biological distribution could significantly enhance tumor accumulation and improve tumor suppression efficacy.

Recognizing the synergistic effects of ferroptosis and immune response, Liu et al. synthesized a composite nanoplatform to overcome drug-resistant glioblastoma. This construct links PD-L1 siRNA (siPD-L1) with Fe₃O₄ nanoparticles via disulfide bonds and is further coated with microglial cell membranes (M-BV2) to create a brain-targeting platform (Fe₃O₄-siPD-L1@M-BV2). Once internalized by drug-resistant glioblastoma cells, Fe₃O₄ nanoparticles and siPD-L1 are released in response to GSH, inducing ferroptosis and inhibiting PD-L1, which in turn activates a cascade of immune responses (Figure 8d) [128]. Similarly, Cao et al. used a dual-strategy approach combining GSH depletion with ROS upregulation to counteract drug resistance (Figure 8e) [131]. Cao et al. designed a nanosystem (GL-EF@siPD-L1) featuring calcium phosphate core-lipid shell nanoparticles to co-deliver FdUMP, erastin, and siPD-L1 [131]. This strategy effectively induces ferroptosis and PD-L1 downregulation, which stimulates anti-tumor immune responses, including dendritic cell maturation and T cell proliferation.

While the combination of ferroptosis and immunotherapy shows significant promise, there are several challenges and potential drawbacks. One major disadvantage is the difficulty in precisely controlling ferroptosis within the tumor microenvironment to avoid off-target effects and unintended damage to healthy tissues. Additionally, the variability in patient genetic and metabolic profiles can lead to unpredictable responses to treatment, potentially reducing the efficacy and safety of the approach. The inflammatory response induced by ferroptosis could also contribute to adverse side effects, such as exacerbating autoimmune reactions.

Future developments could focus on improving the selectivity and targeting mechanisms of ferroptosis inducers to enhance tumor specificity while minimizing systemic toxicity. Advanced delivery systems, such as nanoparticle carriers, could be designed to optimize drug delivery and accumulation at the tumor site.

Furthermore, combining ferroptosis with more personalized immunotherapy approaches that are tailored to the specific characteristics of a patient tumor microenvironment may increase treatment efficacy. Research into predictive biomarkers for ferroptosis sensitivity and immune response will also be essential to refine patient selection and treatment protocols, ultimately advancing this combination therapy toward clinical application.

3.8 Combining ferroptosis and other therapeutic strategies or combined therapies for treating drug resistance and CSCs

In addition to the above-mentioned treatment strategies, several other therapeutic strategies, such as gas therapy or combined therapies, have been combined with ferroptosis to effectively combat drug-resistant tumors. For example, Guan et al. developed a multifunctional drug delivery nanosystem (TK-Fc/LAE) with ROS cascade amplification capabilities (Figure 9a) [143]. This system consists of a diblock copolymer (PTKPTX-b-PFc [TK-Fc]) and a stabilizer (lauroyl-arginine ethyl ester [LAE]) designed for reversal of MDR by gas therapy and ferroptosis. The authors reported that the delivered nitric oxide (NO) downregulated P-gp expression and inhibited mitochondrial function (Figure 9b) and ferroptosis-induced ferroptosis disrupted the redox balance within tumor cells, acting synergistically against the tumor. This synergistic effect enhances the therapeutic efficacy of paclitaxel (PTX) in drug-resistant tumors. This multimodal nanoplatform holds promise for reversing MDR. However, achieving maximum efficacy requires an understanding of how to optimize the synergistic effects of each modality to avoid interference.

Nanomaterials with capacities of controlled drug release and imaging are able to reduce side effects and monitor therapeutic progresses. For example, Fu et al. reported that the Fe(VI)/DOX-based nanoplatform, DFHHP, ameliorates DOX-associated resistance (Figure 9c) [144]. Ultrasound-induced mild hyperthermia triggers the release of DOX and Fe(VI) components. Fe(VI) not only catalyzes tumoral H₂O and H₂O₂ into O₂ but also transforms H₂O₂ into [•]OH and oxidizes GSH through cascade reactions, resulting in tumor hypoxia alleviation and ferroptosis activation. This process leads to P-gp protein inhibition and sensitizes cancer cells to chemotherapy. Moreover, DFHHP acts as a contrast agent for photoacoustic imaging and glutathione tracking. In another study, Wang et al. synthesized the Au/Fe-GA/Sorafenib@PEG platform to reverse drug resistance through combined ferroptosis, CDT, and PTT [148].

In another study, Tang et al. proposed a CSC-targeted nanozyme, MDPH, designed to address drug-resistant tumors through a combination of CDT, ferroptosis, and immunotherapy. PolyMet within the MDPH nanozyme alleviates tumor hypoxia by reducing oxygen consumption and inhibiting tumor growth through the AMP-activated protein kinase (AMPK)-mediated

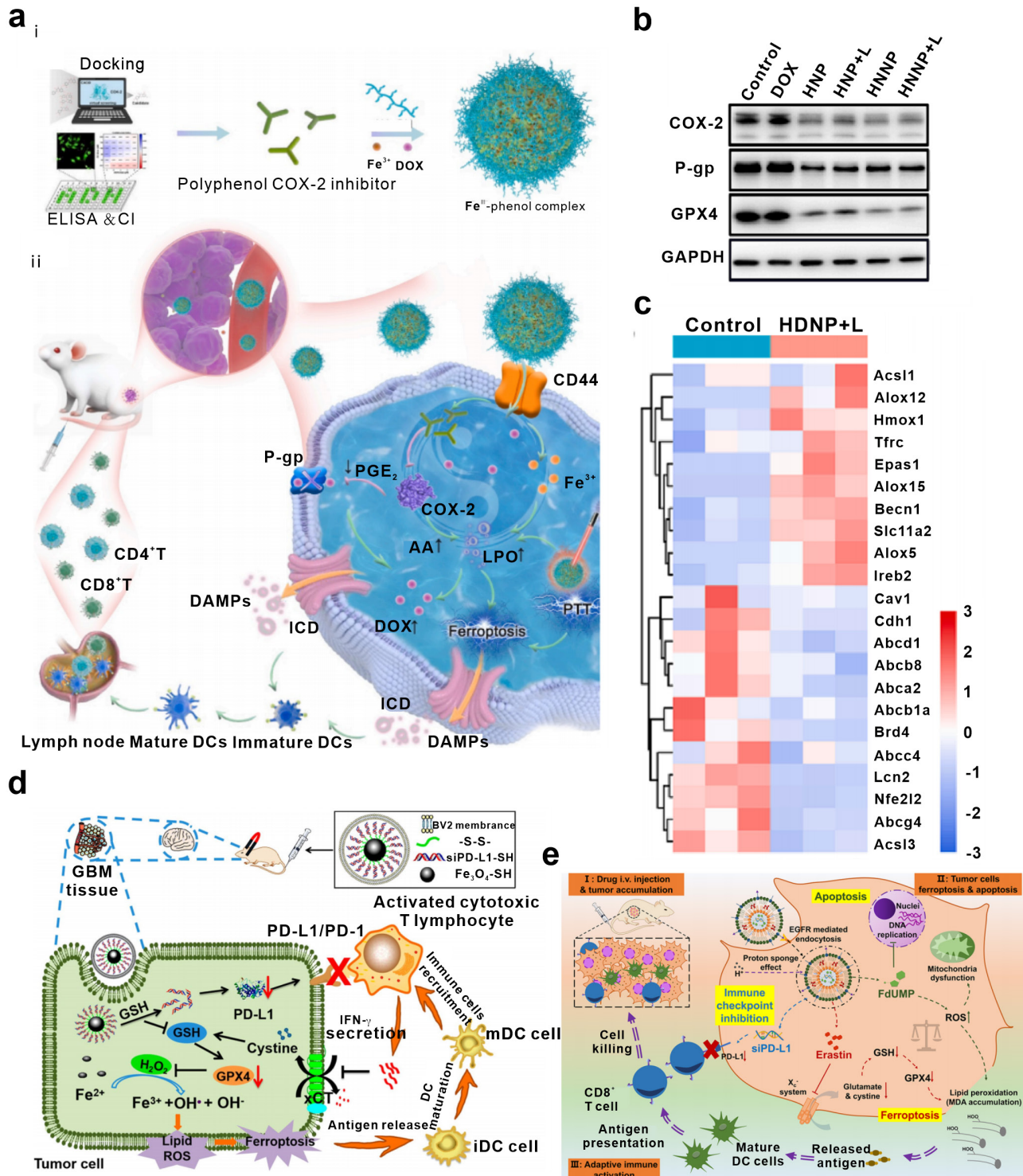


Figure 8 | (a) i) Preparation of carrier-free nanosystems. ii) Mechanism of overcoming tumor resistance through COX-2 inhibition and enhanced ferroptosis-mediated immunotherapy. (b) Western blot analysis of P-gp, COX-2, and GPX4 expression. (c) Heatmap illustrating DEGs related to drug resistance and ferroptosis in experimental and control groups. (a), (b), and (c) Reproduced with permission from Elsevier, Copyright 2024 [129]. (d) Schematic depiction of the Fe_3O_4 -siPD-L1@M-BV2 nanomaterial cascade for promoting ferroptosis and immunotherapy. Reproduced with permission from BioMed Central Ltd., Copyright 2022 [128]. (e) Schematic illustrating the therapeutic mechanism of GL-EF@siPD-L1 nanomedicine. Adapted with permission from American Chemical Society (ACS), Copyright 2024 [131].

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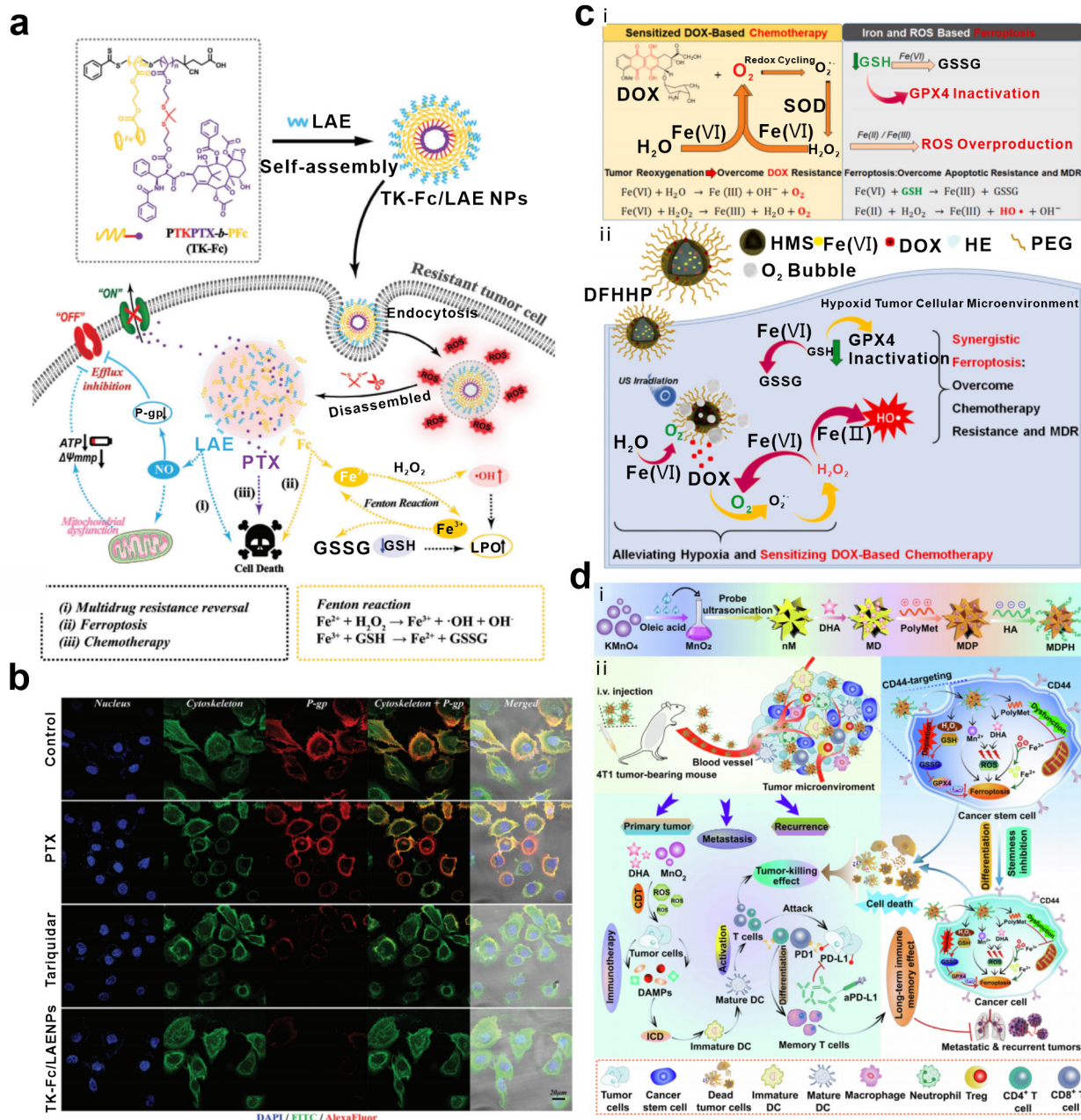


Figure 9 | (a) Multiple modality treatment pathways for TK-Fc/LAE. **(b)** Expression of P-gp after treatment in different groups. **(a)** and **(b)** Adapted with permission from John Wiley and Sons, Copyright 2023 [143]. **(c)** i-ii) Therapeutic Principles of DFHHP Nanomedicine. Reproduced with permission from Elsevier, Copyright 2020 [144]. **(d)** i) Preparation of MDPH nano-enzymes; ii) Schematic diagram of the anti-tumor mechanism of MDPH. Reproduced with permission from the Elsevier, Copyright 2024. [159].

pathway. The MDPH nanozyme also effectively targets 4T1 tumor cells and CSCs, generating intracellular ROS that induces ferroptosis and apoptosis in tumor cells while triggering mitochondrial dysfunction. This combination exerts a potent inhibitory effect on tumor cells and CSCs, further enhancing the therapeutic outcome. (Figure 9d) [159].

4. CONCLUSION AND PROSPECTS

In summary, current research indicates that the cure rate for cancer remains relatively low with significant challenges, such as drug-resistant tumors and the presence of CSCs, continuing to impede progress. However, the emergence of ferroptosis as a novel therapeutic

Table 2 | Relevant targeting strategies for CSC.

Targeting strategies	Relevant modalities
Specific surface markers	CD44, CD133, Sox2, Oct4, Nanog et al.
Related signaling pathways	Wnt, NF- κ B, Notch, and Hippo et al.
Induction of CSC differentiation	ATRA
Altering the microenvironment of CSC	ECM, Hypoxia

ECM: Extracellular matrix; NF- κ B: Nuclear factor kappa-B; ATRA: All-trans-retinoic acid.

approach offers promising prospects. Ferroptosis has demonstrated greater efficacy in tumor regulation compared to some traditional treatments. Recent advancements have led to the development of a range of nanomaterials designed to both induce ferroptosis and serve as delivery vehicles for small molecule drugs. These nanomaterials enhance targeting of tumor sites and also describe strategies to target CSCs (Table 2) through different nanodelivery platforms for better therapeutic effects in drug-resistant tumors, offering substantial promise for future development.

While ferroptosis has proven effective in cancer treatment, integration with other therapeutic modalities has yielded even more impressive results. This review highlighted the synergistic effects of combining ferroptosis with chemotherapy, SDT, PTT, CDT, PDT, immunotherapy, magnetic hyperthermia, and other approaches. These combinations significantly enhance therapeutic efficacy and treatment outcomes.

Despite the promising efficacy of these nanomedicines, continued development of novel drugs targeting drug-resistant tumors and CSCs remains essential for advancing cancer treatment. Evaluating the therapeutic effects of these nanomedicines in conjunction with other therapies underscores the potential effectiveness. Nevertheless, the safety of these materials must be rigorously assessed to ensure their suitability for clinical use, necessitating ongoing research and exploration.

In conclusion, ferroptosis represents a potent strategy for tumor treatment, particularly when combined with other modalities to capitalize on the synergistic effects and minimize side effects. Future research and innovation in cancer therapy hold the potential to significantly advance treatment and overcome the challenges posed by this formidable disease.

The clinical application of nanomaterials in ferroptosis, along with challenges, such as biocompatibility and targeting efficiency, is currently a hot topic in research. As a novel anti-cancer strategy, ferroptosis is a programmed cell death caused by an imbalance between oxidative damage and reductive protection, showing

significant anti-cancer potential. Nanotechnology offers new opportunities for ferroptosis-driven cancer treatment, especially with stimulus-responsive nanomaterials standing out due to their unique advantages [181]. Additionally, in the field of drug delivery systems, nanomaterial-based drug delivery systems demonstrate broad clinical application prospects and developmental value in oncology. These systems can achieve drug accumulation at tumor sites and exert synergistic therapeutic effects. Moreover, combining ferroptosis with traditional anti-tumor treatments can enhance treatment efficiency and reduce toxic side effects. For example, ferroptosis combined with phototherapy, chemotherapy, immunotherapy, and other therapies has made progress in related studies.

However, there are some severe challenges in the application of nanomaterials in therapy. First, the biocompatibility of nanomaterials is a major challenge in clinical application. Due to the unique physicochemical properties, nanomaterials may trigger immune responses or cytotoxicity, affecting treatment outcomes [182]. Second, the targeting efficiency of nanomaterials *in vivo* directly affects their efficacy. Currently, many nanomedicines struggle to precisely reach the lesion site, leading to reduced drug effectiveness and increased side effects [161]. Optimizing the targeting of nanomaterials to improve their aggregation at specific sites is key to enhancing therapeutic efficacy. Importantly, the potential toxicity of nanomaterials cannot be ignored in clinical applications. Long-term exposure to nanomaterials may cause cell damage and organ dysfunction. Comprehensive evaluation of the toxicity of nanomaterials, ensuring use within safe doses, is fundamental to patient safety. Furthermore, the long-term effects of nanomaterials are not yet fully clear. Continuous *in vivo* studies help reveal the long-term safety and effectiveness. Through animal models and clinical trials, monitoring the distribution, metabolism, and excretion of nanomaterials *in vivo* helps assess the long-term impact. Lastly, the application of nanotechnology in medicine involves numerous ethical issues, such as informed consent, privacy protection, and fairness. Establishing strict ethical norms to ensure patient rights and prevent social inequalities caused by technology abuse is essential for advancing nanomedicine.

Nanomaterials, due to the unique physicochemical properties, such as high specific surface area, tunable size and shape, and ease of surface modification, offer new possibilities for inducing ferroptosis. However, nanomaterials may trigger immune responses *in vivo*, depending on the surface characteristics, size, shape, and composition. Some nanomaterials might be recognized as foreign substances by the immune system, leading to inflammatory responses or antibody production. In terms of optimizing pharmacokinetics and biodistribution strategies, surface modifications can alter the biocompatibility and targeting ability of nanomaterials. For example, using polyethylene glycol (PEG) modification can enhance the

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stability of nanomaterials and reduce non-specific interactions. Moreover, designing controlled release systems ensures that nanomaterials are released at specific sites and times, reducing side effects on normal tissues and improving therapeutic efficacy.

In summary, while nanomaterials hold great potential in the clinical application of ferroptosis, nanomaterials also face multiple challenges, including biocompatibility, targeting efficiency, potential toxicity, long-term effects, ethical issues, immunogenicity, and pharmacokinetics. Future research needs to comprehensively consider these factors to ensure that nanomaterials have a safe and effective role in clinical treatment.

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CONFLICT OF INTEREST

The authors declare no competing interests.

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