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Reactive oxygen species-dependent nanomedicine therapeutic modalities for gastric cancer

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Reactive oxygen species (ROS) play a double-edged role in gastric cancer (GC). Higher levels of ROS in tumor cells compared to normal cells facilitate tumor progression. Once ROS concentrations rise rapidly to toxic levels, they cause GC cell death, which is instead beneficial for GC treatment. Based on these functions, nano-delivery systems taking the therapeutic advantages of ROS have been widely employed in tumor therapy in recent years, overcoming the drawbacks of conventional drug delivery techniques, such as non-specific systemic effects. In this review, the precise impacts of ROS on GC have been detailed, along with ROS-based nanomedicine therapeutic schemes. These strategies mainly focused on the use of excess ROS in the tumor microenvironment for controlled drug release and a substantial enhancement of ROS concentrations for tumor killing. The challenges and opportunities for the advancement of these anticancer therapies are also emphasized.

1. Introduction

As a public health problem worldwide, gastric cancer (GC) caused over 1 million new cases and more than 760 000 deaths, ranking fifth and fourth among cancers, respectively.[1] Currently, the standard treatment for GC is surgical intervention supplemented by pre- and post-operative adjuvant radiotherapy (RT) and chemotherapy (CT).[2] Despite tremendous efforts, the 5-year survival rate for GC is approximately 30%.[3] Once distant metastasis occurs, the 5-year survival rate will be less than 5%.[3] The heterogeneity of GC, drug resistance, and non-negligible side effects hinder the applications of traditional therapeutic strategies.[4,5] It is urgent to find novel treatment methods for GC prevention and therapy.

Reactive oxygen species (ROS) are products of cellular redox processes that play vital roles in regulating a variety of physiological and pathological processes. They include free radicals with unpaired electrons, such as superoxide anions ($O_2^{\bullet -}$), hydroxyl radicals ($^{\bullet}OH$), and lipid radicals, as well as compounds with oxidizing abilities other than free radicals, such as hydrogen peroxide (H_2O_2), and hypochlorous acid (HOCl).[6,7] These small molecules are unstable and react easily with intracellular proteins, lipids, carbohydrates, and nucleic acids. Since the gastrointestinal tract is one of the organs that produces the most ROS, it is reasonable to discuss the role of ROS in the context of GC.[8,9] At low to moderate levels, ROS function as second messengers in information transduction, mainly promoting GC occurrence and progression while also regulating immune cell functions in the context of tumors.[10] When ROS levels substantially elevate, they can lead to cell death, which is instead beneficial for GC therapy.[11] The concentration-dependent functions of ROS imply that precise concentration modulations probably achieve a wide range of therapeutic benefits with unlimited possibilities. Due to the unique physiological roles of ROS, it is reasonable to construct ROS-based treatment approaches. However, ROS have short lifetimes and limited travel distances because of their hyper-responsiveness.[12] It is a challenge to control ROS accurately. Real-time regulation of the ROS level at close proximity is truly practicable for GC treatment, while uncontrolled ROS can harm non-tumor cells and organs, triggering hazardous adverse effects.

Recently, drug delivery employing the unique properties of nanoparticles has become a hot research topic, which is a solution for traditional administration drawbacks. Nanoparticle-based delivery has the capability of loading and protecting multiple drugs simultaneously, controllable drug release, and improving biodistribution. In addition to the enhanced permeability and retention (EPR) effect, nanoparticles accurately target destination organization through special modifications, which substantially reduce non-specific distribution.[13] Through design, nanoparticles can achieve more precise cellular or even subcellular localization.[14,15] Taking the high reactivity and short-range action properties of ROS into account, nanotechnology is a superior option for minimizing their toxicity and providing therapeutic benefits. Besides, the

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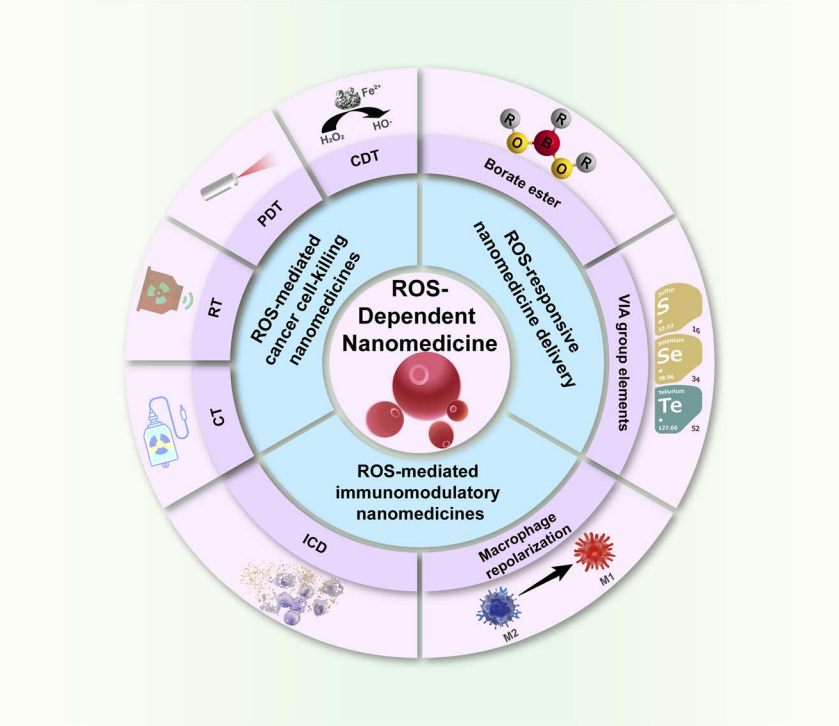

Fig. 1 Schematic illustration of ROS-based nanomaterial-assisted GC therapy strategies.

capacity of nanomedicines to mediate multiple treatment strategies concurrently enhances ROS-based therapy efficacy by improving ROS production or providing synergistic therapies, thus opening up new avenues for ROS-based treatments.

Currently, considerable research has been performed to reveal the relationship between ROS and GC, both favorable and unfavorable.[9] On account of this, a series of nanomedicines based on ROS for GC treatment have been designed and developed, including those that release drugs in response to ROS, scavenge inflammatory ROS, and trigger ROS-induced cell death. Herein, a series of articles demonstrating the physiologic role of ROS in GC have been integrated to prove the therapeutic potential of ROS. Additionally, we refer to a range of ROS-based nanomedicines (Fig. 1). Their design principles and anticancer properties are emphasized.

2. The relationship between ROS and GC

2.1 Overview of ROS

The gastrointestinal tract is one of the organs that generates the most ROS in the body. Large amounts of ROS can be produced by either endogenous or exogenous factors. In the organism, most intracellular compartments, and even extracellular spaces, are capable of generating ROS.[16,17] Among them, the mitochondrial electron transport chain (ETC) is the major pathway for ROS production in most mammalian cells.[18] $O_2^{\bullet-}$ derived from electron leakage of complexes I and III in the ETC during O_2 molecule reduction generates a variety of ROS intermediates for other ROS production.[19] In addition to mitochondrial ETC, reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOXs) in plasma membranes or phagolysosomes of intragastric phagocytes are activated during phagocytosis, consuming a large amount of O_2 and releasing $O_2^{\bullet-}$ into the extracellular space or phagolysosomes, which is known as respiratory burst.[20,21] Under physiological conditions, xanthine oxidase, lipoxygenase, myeloperoxidase, and nitric oxide synthase have the ability to generate partial ROS as well.[9]

Extrinsic factors also have the potential to cause oxidative stress in the gastrointestinal tract, which might impact the stomach. Fe and Cu in the normal diet can produce ROS through the Fenton reaction, as can trans fatty acids.[22,23] Cigarette smoke and ethanol are important sources of ROS generation, which are related to gastrointestinal dysfunction problems.[24] Ionizing radiation in tumor therapy can cause oxidative stress either directly by producing $^{\bullet}OH$ *via* H_2O radiolysis or through secondary reactions.[25] The stimulating effects of ROS produced during RT might cause damage to the gastrointestinal tract and result in severe gastrointestinal symptoms.

The generated ROS are closely related to GC. Resident immune cells, intestinal flora, and dietary factors in the external environment of the gastrointestinal tract are potential ROS sources. The ingested substances and pathogens can enhance inflammatory factors secreted by epithelial cells, neutrophils, and macrophages, which further induce oxidative stress. The gastrointestinal tract is therefore vulnerable to ROS attack. When intracellular ROS levels are abnormally elevated compared to normal cells, ROS, as second messengers, promote the occurrence and development of GC. However, upon ROS being greatly elevated, they can lead to cell death, favoring tumor treatment (Fig. 2).

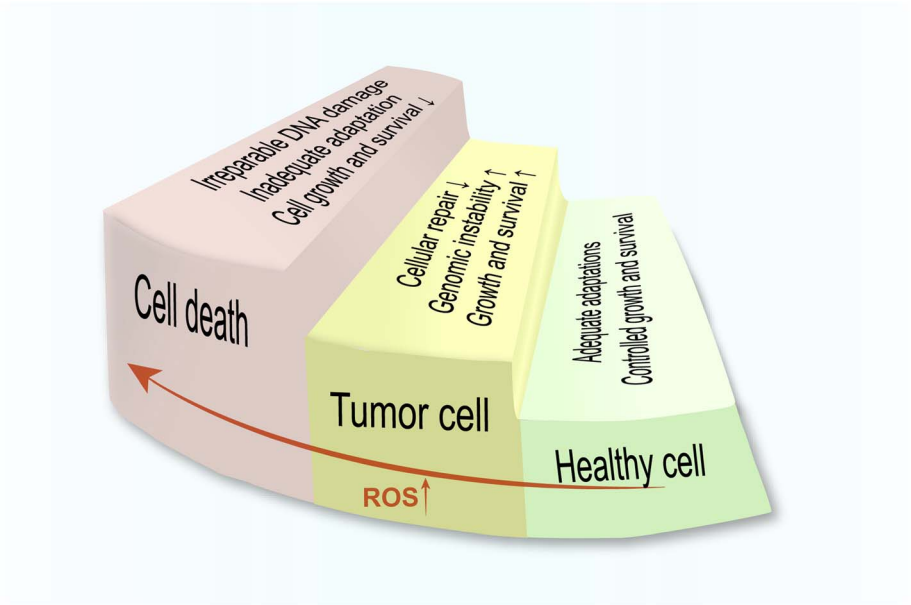

Fig. 2 ROS are balanced with adequate antioxidant systems in healthy cells. The metabolic activity of tumor cells generates high concentrations of ROS, which diminish cellular repair effectiveness, resulting in DNA damage and genetic instability, thereby increasing cell survival and proliferation. If ROS levels increase dramatically to toxic concentrations, oxidative stress causes irreversible damage, preventing appropriate adaptation and ultimately leading to tumor cell death.

As the two predominant ROS, the physiological roles of H_2O_2 and $O_2^{\bullet-}$ have been widely studied. In physiology, they are important redox signaling substances continuously generated at a controllable speed through the intra-mitochondrial NADH-dependent system, the extra-mitochondrial NADPH-dependent system, and other oxidative enzymes.[26] These ROS signals are closely related to various physiological processes, such as transcription and epigenetic regulation. ROS affect cellular signaling primarily by modifying redox-sensitive residues, including cysteine or methionine. The function, transport, and degradation efficiency of proteins whose surface cysteines or methionines are oxidized are therefore altered.[27,28] By oxidizing certain redox-sensitive transcription factors, such as nuclear factor erythroid 2-related factor 2 (NRF2), nuclear factor kappa-B (NF-κB), activator protein-1 (AP-1), and hypoxia inducible factor 1α (HIF-1α), ROS have an impact on the transcription of mRNAs and non-coding RNA.[29,30] In addition, ROS directly affect epigenetic modifications of histones and DNA by oxidizing cysteines of histone deacetylases and DNA methyltransferases, regulating gene expression efficiency.[31,32] As with other second messengers, ROS signals can also be amplified by triggering kinase cascade reactions or transmitted over long distances by converting themselves into more stable substances.[33] Recognizing the signal transduction events triggered by ROS and the physiological responses of these processes is critical to gaining a better understanding of GC, potentially lowering the risk of gastric carcinogenesis, delaying GC progression, or even curing GC.

2.2 ROS-induced gastric carcinogenesis

Prolonged ROS exceeding physiological levels induces strong inflammatory responses. Meanwhile, cells such as inflammatory cells and epithelial cells further produce ROS in the setting of chronic inflammation, causing DNA damage.[34] The development of oxidative stress and inflammation forms a vicious cycle, which may lead to cancer occurrence. Infectious diseases and chronic inflammation are estimated to account for about 25% of carcinogenic causes.[35] As gastric tissue is one of the organs exposed to high-dose ROS, oxidative stress greatly influences GC occurrence.[36] The large amount of ROS produced by symbiotic *Helicobacter pylori* (*H. pylori*) is associated with damage to gastric epithelial cells. *H. pylori* tend to generate $O_2^{\bullet-}$ to inhibit the killing effect of inflammatory cells on them. $O_2^{\bullet-}$ can be converted into H_2O_2 for direct oxidation or further converted into more toxic $^{\bullet}OH$ through transition metal-mediated Fenton reactions.[37] Cytotoxic factors released by *H. pylori*, such as vacuolating cytotoxins, cytotoxin-associated genes, urease, and outer inflammatory proteins, promote oxidative stress in gastric epithelial cells as well.[38,39]

In addition to *H. pylori* themselves, neutrophils, gastric mucosal cells, and vascular endothelial cells are also potential sources of ROS in *H. pylori*-infected gastric tissues.[40] Neutrophils engulf bacteria and kill them by NOX-generated ROS.[41] The NOX gp91phox catalytic subunit is activated and transfers electrons to O_2 with the aid of superoxide dismutase, converting O_2 to H_2O_2.[42] H_2O_2 is subsequently transformed into more hazardous ROS.[43] Sustained exposure to high levels of ROS interactions ultimately leads to DNA damage and cell death.[44,45] The phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR), Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3), and NF-κB/mitogen-activated protein kinase (MAPK) pathways

are three pathways frequently mentioned in oxidative stress-induced GC.[46]

Apart from *H. pylori*, chemicals like ethanol are able to cause GC through long-term ROS generation in the stomach. Cytochrome P450 2E1 would be overexpressed by ethanol induction, which is involved in the metabolism of some carcinogens. Ethanol also promotes ROS concentrations by suppressing the expression of antioxidant enzymes such as peroxidase and superoxide dismutase 1, as well as other cytoprotective proteins.[47] Accumulated ROS and electrophilic substances result in cellular DNA damage. GC development is driven by a vicious loop of inflammation and oxidative damage.[48]

Based on the pivotal role of ROS in GC development, removing *H. pylori* using quadruple therapy is the most common clinical measure to avoid chronic inflammation progression, thus reducing GC incidence.[49] Several clinical studies have been conducted on high-risk populations for GC, aiming to evaluate the antioxidant effects of vitamins on GC precancerous lesions, but no definite efficacy has been obtained yet.[50–52] Further explorations are needed on how to utilize antioxidants for excess ROS elimination, avoiding further persistence and deterioration of inflammation and tumorigenesis.

2.3 ROS-induced GC development

Due to the increased metabolic rate, gene mutations, and relative hypoxia, the production of ROS in cancer cells increases, resulting in higher ROS basal levels.[53] There have been studies indicating that ROS function as signaling agents at low to moderate concentrations, triggering proliferation, invasion, metastasis, angiogenesis, and drug resistance of malignant tissues.[54,55] As second messengers, ROS are involved in cellular signaling related to redox state changes, including interactions with oxidatively activatable kinases like MAPK, protein kinase C (PKC), and PKB.[56]

Tumor vascular proliferation plays a crucial role in tumor growth and metastasis by providing a steady supply of oxygen and nutrients while avoiding host immune monitoring. HIF-1α and HIF-2α, in particular, regulate tumor cell proliferation, metastasis, and angiogenesis through endogenous ROS production.[57] Intracellularly accumulated ROS lead to HIF-1α stabilization and activation as well as Sirtuin (SIRT) 3 degradation, resulting in an increased vascular endothelial growth factor (VEGF), lactate dehydrogenase A, and 3-phosphoinositide-dependent protein kinase 1 transcription, which promote angiogenesis and GC development.[58] After being treated with culture medium supernatant obtained from the coincubation of AGS cells and nicotine, endothelial cells showed a tendency to grow and form tubes mediated by elevated interleukin (IL)-8 mediated through ROS/NF-κB and ROS/MAPK (extracellular-regulated kinase (ERK) 1/2, p38)/AP-1 axis.[59]

Metastasis is the final step in cancer progression and the main cause of cancer mortality. Cell invasion and spread are facilitated by the intracellular redox state. Epithelial-mesenchymal transition (EMT)-related genes, including E-calmodulin, integrins, and matrix metalloproteinases (MMPs), are directly or indirectly regulated by intracellular ROS levels.[60] The conversion of mitochondria-generated superoxide to H_2O_2 has been suggested to be an important step in oxidative stress-mediated MMP gene expression, with subsequent promotion of angiogenesis and tumor cell invasion.[61,62] Increased intracellular ROS levels can enhance anti-nesting apoptosis and adhesion signaling, allowing metastatic tumor cells to survive. Oxidative stress also mimics autocrine adhesion signals and increases the apoptosis threshold, thus enhancing GC cell proliferation and metastatic potential.[63,64] Intravenous injection of H_2O_2-pretreated GC cells in mice promoted the metastatic process.[65] In addition, the ROS level in tumor cells with a metastatic tendency was higher than that in the remaining non-metastatic ones.[66] In summary, ROS have a profound effect on intracellular signaling, which is generally detrimental to tumor prognosis, potentially becoming a target for GC malignancy reversal.[67]

2.4 ROS-induced GC multidrug resistance (MDR)

Most tumor cells remain viable under higher levels of oxidative stress in the tumor microenvironment (TME). ROS overproduction induces DNA oxidation and double-strand breaks, leading to the accumulation of mutations that allow tumor cells to avoid apoptosis and transform into MDR.[68,69] In tumor treatment modalities, both CT and RT can generate large amounts of ROS, disrupting redox system balance and thus inducing cell death.[70,71] ROS-mediated MDR may be due to the activation of transcription factors sensitive to redox response, such as NF-κB, HIF-1α, and nuclear factor-like factor 2.[72,73] MDR tumor cells upregulated antioxidant enzymes along with ROS generated during CT, RT, and other treatments, which is brought about by the aforementioned gene activation.[74] Besides, ROS may advance MDR by converting cells from apoptosis to autophagy, avoiding cell cycle arrest, stimulating stem cell differentiation, and inducing metabolic reprogramming.[75–77] Several existing ROS modulators are already undergoing clinical trials to improve efficacy against MDR cells, including STA-4783, GKT137831, and APR-246.[78]

2.5 ROS-induced GC cell death

Although ROS promote the development of GC, GC cells are typically more sensitive to ROS than normal cells due to altered metabolic characteristics, defective DNA repair mechanisms, and inherently higher ROS levels.[79] Substantial increases in ROS concentrations lead to programmed cell death, including apoptosis, ferroptosis, NETotic cell death, and lysosome-dependent cell death.[80]

ROS interact with proteins of the B-cell lymphoma-2 (Bcl-2) family to activate various oxidoreductase-sensitive signaling cascades, such as endogenous apoptosis.[81] In parallel with Bcl-2 inhibition, ROS activate BCL2 associated X protein (Bax), which translocates to the outer mitochondrial membrane to form oligomers and promote cytochrome c release.[82,83] Released cytochrome c results in the assembly of apoptosis bodies from apoptosis protease-activating factor 1, which subsequently activates caspase 9 and 3, inducing apoptosis occurrence.[84]

Ferroptosis is an Fe-dependent, lipid peroxidation-induced programmed cell death form caused by membrane ROS and mitochondrial ROS (mtROS), which is characterized by peroxidation of polyunsaturated fatty acids in the plasma membrane and following lipid bilayer destruction-leaded membrane dysfunction.[85] Ferroptosis is connected to malignant progression reduction. Recent studies have also shown that cellular contents released during ferroptosis, such as damage-associated molecular patterns (DAMPs), facilitate immune response induction and enhancement.[86,87]

Therefore, killing GC cells by substantially elevating intracellular ROS levels is a feasible therapeutic option. In clinical practice, traditional non-surgical treatment methods for GC are RT and CT, both of which highly rely on ROS-dependent killing effects. However, there are issues such as poor response and significant non-specific toxic side effects. It is imperative to reduce the damaging effects of ROS on non-GC tissues while enhancing the killing efficiency on GC cells.

2.6 ROS-induced immune cell regulation in the GC TME

In addition to their effects on tumor cells, ROS modulate immune cells as well. Macrophages can be activated by ROS. Macrophage ROS levels facilitate the activity of MAPK, signal transducer and activator of transcription 1 (STAT-1), and NF-κB, leading to an overall increase in inflammatory signaling and promoting macrophage polarization toward the M1 type.[88] By oxidizing Cys residues of specific proteins, ROS can regulate downstream NF-κB and MAPK pathways to promote macrophage conversion from M2 to M1 type.[89,90] The mtROS are also important in the differentiation of hematopoietic or monocyte precursors into dendritic cells (DCs).[91] H_2O_2 and $O_2^{\bullet -}$ have the capability to induce DC maturation through an NF-κB-dependent mechanism.[92] By generating ROS to create an increased lysosomal pH, NOX2 in DCs avoids antigen degradation, thus promoting cross-presentation.[93] Moreover, the upregulation of mitochondrial ROS production is essential for major histocompatibility complex class I-mediated presentation of antigens to CD8 T cells.[94] T cell receptor stimulation is also commonly accompanied by ROS production, suggesting the potential role of ROS in oxidizing oxidizable Cys present in different signaling molecules for T cell activation.[95,96] NOX and mitochondrial oxidative phosphorylation would be activated in T cells upon stimulation of the T cell receptor, leading to an increase in ROS production, a process that enhances interleukin production.[97,98]

Apart from mediating anti-tumor immune responses, there is an immunosuppressive role for ROS. As a T cell subtype more resistant to oxidative damage, regulatory T cells (Tregs) are better adapted to the TME with high concentrations of ROS, where they exert their immunosuppressive effects.[99] NOX2-derived ROS facilitate the immunosuppressive effects of Tregs on $CD4^+$ T cells.[100] Produced by myeloid-derived suppressor cells (MDSC), ROS also restrict immunization by inhibiting T cell responses and promoting T cell death, which is one of the functions of these crucial immunosuppressive cells.[101] Intracellular ROS cause the oxidation of critical proteins in immune cells, especially T cells, which results in their dysfunction and cell death. ROS produced by dysfunctional mitochondria not only hinder antigen cross-presentation between DCs and T cells, but also lead to T cell exhaustion.[102] Increasing evidence has revealed the significant role of ROS in immune response regulation. ROS are not metabolic byproducts, but rather contribute to immunotherapy efficacy. However, the relationship between immunotherapy and oxidative stress has not been well-defined due to the lack of clinical trials. Immunotherapy based on ROS-producing drugs may boost immunotherapeutic effects on primary and metastatic tumors, which seems to be a promising anti-tumor strategy.

3. ROS-based nanoplatform for GC therapy

Based on the distinctive functions of ROS on GC, there have been numerous therapeutic modalities utilizing ROS for GC treatment. The high level of ROS in the TME provides exploitable conditions for TME-responsive prodrugs. Therapies such as RT, CT, photodynamic therapy (PDT), and chemodynamic therapy (CDT) increase the efficiency of ROS production by physicochemical or biological means, resulting in a direct killing effect on tumor cells. Some emerging CT methods could also modulate ROS to suppress tumors by intervening in the redox homeostasis within the TME. However, due to the hydrophobicity of most antitumor drugs, it is difficult to administer them directly. In addition, antitumor drugs tend to have adverse effects on normal tissues while treating tumors.[103] To overcome these limitations for better therapeutic efficiencies, various delivery systems have been developed.[104] Nanoparticles are promising anticancer drug carriers due to their controlled drug release characteristics and tumor selectivity.[105] Currently, a variety of nanomedicines are available, considerably extending clinical therapy possibilities. Herein, we have summarized ROS-based nanomedicine therapeutic approaches for GC, which mainly focused on the application of ROS-responsive controlled release nanosystems and ROS-enhanced nanomedicines (Table 1). Implementing a ROS-based treatment strategy for GC through the applications of nanomedicines is practical.

3.1 Nanomedicines for ROS generation inhibition

Inflammation is considered a hallmark of cancer development and progression. An increased ROS level leads to DNA oxidation while reducing DNA repair, resulting in cell death and abnormal DNA repair procedures.[156] The TME coordinated by inflammatory cells is an integral player in tumor development, proliferation, survival, and migration. Inhibiting inflammation for GC prevention is promising. However, the hotspot for inhibiting ROS to reduce inflammatory responses in the gastrointestinal tract is inflammatory bowel disease. There is no report on nanoparticles targeting ROS in the microenvironment of chronic atrophic gastritis to delay GC development. Reducing ROS has the potential to prevent the occurrence of gastric ulcers, but the indications were mostly acute gastric ulcers

Table 1 Summary of ROS-based nanomedicine therapeutic modalities for GC[a]

ROS function	ROS source	Nanomedicine name	Type of ROS	Ref.
TME-responsive delivery	TME	CMCh-BAPE-RGD@ICG	H_2O_2	106
		UA-based DPNS		107
		CPT-loaded micelle		108
Tumor killing	CT	Atranorin@SPION	Lipid peroxidation	109
		CJ-AuNP		110
		AuNR-PEG-Ab-DOX	Unspecified	111
		PD-PTLP		112
		P/T-NF		113
		TiO_2 NP		114
		Ptx/Tet-np		115
		PLGA@icaritin NP		116
		VN-AuNP		117
		MN-ZnONP		118
		CH-AuNP		119
		HA-G5 PAMAM-Au-METase		120
		CUR-NEM		121
	RT	miR-200c NP	Unspecified	122
		DOC-NP		123
		Ag@BSA		124
	PDT	Ni/Ni–P nanospheres	$^1O_2$	125
		CM/SLN/Ce6		126
		AuNR-$AlPcS_4$, Clip-$AlPcS_4$, F127-$AlPcS_4$		127
		FA-PLGA-Pba NP		128
		GNS@$CaCO_3$/ICG		129
		TPP-doped PFBT Pdot		130
		PPLA nanohybrid		131
		LNP(Er)AP,LNP(Tm)AP		132
		PPIX-LNP		133
		C-dots-Ce6		134
		Ce6-MNP		135
		E-NP	$O_2^{\cdot-}$	136
		OMCAPs@rBSA-FA@IR780	$^{\cdot}OH/^1O_2$	137
		Polphylipoprotein	Unspecified	138
		Oxygen tank		139
		Cy_{1395}-NP		140
		Exo-PMA/Au-BSA@Ce6		141
		CuS–NiS_2		142
		FA-Ser-Chol/IR780		143
		CFNP		144
		5-FU@SF-cRGDfk-Ce6		145
		Fe_3O_4-PEG_{2K}-FA@Ce6		146
		Nano-AE		147
		ICGm		148 and 149
		5-ALA-dMNT		150
	CDT	MPG NP	$^{\cdot}OH$	151
		PP@Mn NP		152
	CT/PDT	PTX@GO-PEG-OSA NS	$^{\cdot}OH/^1O_2$	153
Tumor killing/immune activation	PDT	CPT	$^{\cdot}OH/O_2^{\cdot-}$	154
	CT	HSA-Au	Unspecified	155

[a] Abbreviations: ROS: reactive oxygen radicals; TME: tumor microenvironment; CMCh: carboxymethyl chitosan; BAPE: 4-hydroxymethyl-pinacol phenylborate; RGD: Arg-Gly-Asp; ICG: indocyanine green; UA: ursolic acid; DPNS: dimeric prodrug-based nanosystem; CPT: camptothecin; NR: nanorod; PEG: polyethylene glycol; DOX: doxorubicin; NF: nanofiber; NP: nanoparticle; Ptx: paclitaxel; Tet: tetrandrine; SPION: superparamagnetic iron oxide nanoparticle; CJ: *Cirsium japonicum*; PLGA: poly(lactic-*co*-glycolic acid); VN: vitex negundo; MN: morus nigra; CH: *C. halicacabum*; HA: hyaluronic acid; CUR: curcumin; NEM: nanoemulsion; DOC: docetaxel; BSA: bovine serum albumin; PDT: photodynamic therapy; Exo: exosome; PMA: amphiphilic polymer; Ce6: chlorine6; OMCAP: mesoporous carbon nanospheres doped with small gold nanoparticles; FA: folic acid; CM: cell membrane; SLN: silica nanoparticle; Chol: cholesterol; Pba: pheophorbide a; 5-FU: 5-fluorouracil; SF: silk fibroin; GNS: gold nanostar; TPP: tetraphenylporphyrin; PFBT: poly[(9,9-dioctylfluorenyl-2,7-diyl)-*co*-(1,4-benzo-{2,1′,3}-thiadiazole)]; Pdot: polymer dot; AE: aloe emodin; PPLA: polyhedral oligomeric silsesquioxane; LNP: lanthanide nanoparticle; AP: aminopropyl; PPIX: protoporphyrin IX; 5-ALA: 5-aminolevulinic acid; dMNT: polyamidoamine dendrimer modified multi-walled carbon nanotubes; MNP: magnetic nanoparticle; CDT: chemodynamic therapy; OSA: oxidized sodium alginate; HSA: human serum albumin.

induced by stress or alcohol, which may not apply to GC caused by chronic inflammation.[157–160] Research on nanomedicines inhibiting gastric carcinogenesis by controlling ROS requires further exploration.

3.2 ROS-responsive nanomedicine delivery

Compared to normal cells, tumor cells tend to produce more ROS. Abnormally elevated ROS affect proteins that control redox homeostasis, leading to a further increase in ROS levels, especially H_2O_2.[161] ROS concentration in cancer cells can reach up to 100 μM, which is about 100 times higher than that in normal cells.[162] Therefore, it is feasible to utilize the high concentration of ROS in the TME for controlled drug delivery and onset of action.

Shao *et al.* designed and synthesized a novel nanoparticle named CMCh-BAPE-RGD@ICG loaded with indocyanine green (ICG) that enables ROS-responsive drug release.[106] The amphiphilic block nanoparticle consists of carboxymethyl chitosan (CMCh) as the hydrophilic shell with phenylboronic acid pinacol ester (BAPE) as the hydrophobic end. Arginine–glycine–aspartic acid (RGD) was conjugated to the shell, which allowed targeting capability to integrin $\alpha_v\beta_3$ highly expressed on GC cells. In the TME consisting of high concentrations of ROS, BAPE underwent hydrolysis as a boronic ester, causing nanoparticle disintegration and encapsulated ICG release. Through the tumor targeting effect brought about by RGD and the high ROS-responsive drug release, dual specificity tumor targeting could be achieved. In H_2O_2 solutions simulating the TME, the nanoparticle particle size increased due to disintegration, accompanied by the release of doxorubicin (DOX) characterizing drug release. Under the guidance of near-infrared fluorescence imaging, CMCh-BAPE-RGD@ICG enabled tumor-specific photothermal therapy (PTT). Mice bearing SGC7901 subcutaneous gastric tumors were mostly cured. In addition to boronic esters, there have been reports that C–S bonds of diethyl sulfide could be oxidized under high ROS levels, which facilitated TME-responsive drug release for anti-GC drug delivery.[108]

Apart from nanoparticle delivery system modifications, cargos themselves may utilize ROS-responsive chemical bonds to achieve tumor-specific killing functions. Most ROS-responsive prodrugs are based on borate ester structures responsive to H_2O_2.[163–165] There have been chemotherapeutic prodrugs developed based on the properties of VIA group elements, such as S, Se, and Te, oxidizing when exposed to ROS, which led to chemical bond breakage.[166–168] Ma *et al.* used nanoparticle-delivered thioketal-linked ursolic acid as a chemotherapeutic prodrug by taking advantage of thione's degrading properties in the presence of ROS.[107] Therefore, ROS-responsive nanomedicines can enable tumor-specific drug release, providing the possibility of reducing systemic responses.

3.3 ROS-mediated CT nanomedicines in GC

A subset of chemotherapeutic agents has the potential to increase intracellular ROS generation, leading to irreparable damage and cell death. 5-Fluorouracil (5-FU) and mitomycin could trigger GC cell death through mitochondrial dysfunction and caspase activation mediated by excessive ROS and p53-dependent apoptotic pathways.[169] Similarly, as a chemotherapeutic applied in GC, DOX led to increased ROS production and oncogene p53 activation.[170] However, chemotherapeutic agents suffer from poor tumor specificity, damage to normal tissues, and MDR induction.[171]

To get around the issues of toxicity and lack of specificity, a range of nanomaterials have been employed to enhance therapeutic effectiveness and bioavailability. Paclitaxel (Ptx) is a commonly used chemotherapeutic agent for GC as a microtubule depolymerization inhibitor. To overcome Ptx resistance, Li *et al.* attempted to synergize its chemotherapeutic effect by employing tetrandrine (Tet)-induced intracellular ROS (Fig. 3).[113] Succinic acid (SA) was applied as the linker to connect Ptx and tumor-specific peptide RGD, whose product was named Ptx-SA-RGD. It subsequently self-assembled into nanofibers and encapsulated Tet to form Ptx and Tet copolymerized self-assembled nanofibers (P/T-NF). Upon administration, RGD directed P/T-NF to the tumor site and promoted its penetration, increasing tumor specificity while decreasing non-specific damage. After reaching the tumor site, the physically encapsulated Tet was first released, followed by Ptx because of the hydrolysis of the ester bond between Ptx and SA. Although Ptx alone induced intracellular ROS, the ROS level was dramatically enhanced by the synergistic functions of Tet. The sharply elevated ROS level in the P/T-NF group promoted GC cell endogenous apoptosis through the JAK2/STAT3 pathway, mediating optimal antitumor therapeutic capabilities.[172] Similarly, to enhance the killing effects of ROS generated by Ptx, Yu *et al.* utilized liposomal co-delivery of Ptx, the p-glycoprotein inhibitor, and the PD-L1 monoclonal antibody to reduce cellular drug efflux for Ptx cytotoxicity improvement.[112] There have also been reports of boosting 5-FU efficacy for GC treatment by nanoparticles.[114]

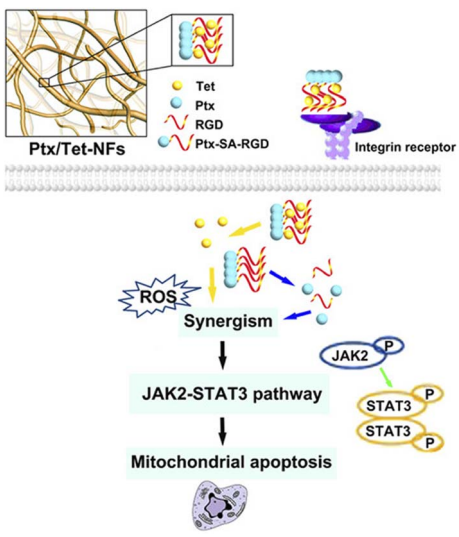

Fig. 3 Novel "Carrier-Free" nanofiber codelivery systems with the synergistic antitumor effect of paclitaxel and tetrandrine through the enhancement of mitochondrial apoptosis. Reproduced with permission.[113] Copyright 2020, American Chemical Society.

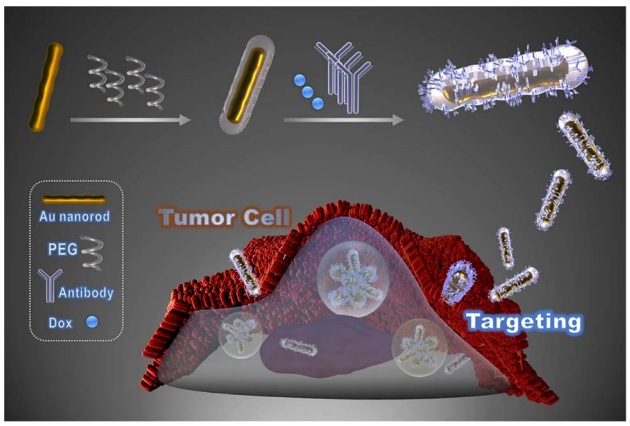

Fig. 4 The fabrication and drug delivery of AuNR-PEG-Ab-DOX. Reproduced with permission.[111] Copyright 2021, Springer Nature.

In addition to traditional chemotherapeutic drugs, there have been emerging drugs that achieved special physiological effects of ROS-dependent GC treatment through nano-delivery systems. As shown in Fig. 4, Fan *et al.* realized GC CT enhancement based on gold nanorods (AuNRs), a non-toxic and biocompatible metallic material.[111] AuNRs were connected with rimodulizumab (abbreviated as Ab in the text) and DOX *via* polyethylene glycol (PEG), which were referred to as AuNR-PEG-Ab-DOX. Ab was originally a clinically applied monoclonal antibody to vascular endothelial growth factor receptor 2 (VEGFR2) used for tumor vascular proliferation inhibition. It can also be utilized to specifically target SNU5 GC cells over-expressing VEGFR2 due to its antibody-binding effect.[173] On the basis of increased uptake, AuNR-PEG-Ab induced NOXS to produce ROS, which led to actin-dependent, lysosome-mediated programmed cell death. The ROS generation ability of Ab was only observed after AuNR loading, which represented a novel mechanism of interactions between Ab and AuNR. Ab might play a major role in the process of programmed cell death directly correlated with ROS by interfering with cellular redox homeostasis. This delivery system improved recognition, uptake, and accumulation efficiency *in vitro* and *in vivo* with the assistance of Ab, while also directly inducing GC cell death with minimal damage to normal gastric cells. As emerging chemotherapeutic agents, certain herbal extracts, such as curcumin, cardiospermum halicacabum extract, morus nigra extract, and icaritin, have also been reported to produce significant intracellular ROS and have been utilized in nano-delivery systems to improve anti-GC efficacy.[110,116–119,121]

3.4 ROS-mediated RT nanomedicines in GC

Radiation therapy, which uses ionizing radiation to destroy cells, is a popular antitumor therapeutic approach. Upon interacting with DNA, radiation can either directly harm DNA or indirectly cause DNA damage through the reaction of free radicals generated during RT with DNA.[174] Indirect DNA damage accounts for about 80% of radiation-induced DNA damage.[25] However, reducing the adverse effects while increasing radiation damage to tumor tissues is still a difficult undertaking to accomplish.

Radiosensitizers are expected to improve RT effectiveness by increasing tumoral radiation sensitivity while minimizing harm to healthy tissue by lowering necessary radiation dosage.[175] The most commonly used radiosensitizers in clinical applications are chemotherapeutic agents, among which docetaxel (DOC) has radiosensitizing effects on a wide range of malignancies.[176] To reduce nonspecific distribution and systemic adverse effects, Cui *et al.* used gelatinase-cleaving peptide-linked PEG and poly(ε-caprolactone) to encapsulate DOC as a radiosensitizer.[123] The outer shell of nanoparticles increased DOC solubility and *in vivo* circulation time. The peptide was excised by highly expressed MMPs in the TME after nanoparticles circulated to the tumor site, eliminating the stealth function of PEG and increasing drug uptake by tumor cells.[177] The sensitizer enhancement ratio of DOC-NPs was significantly elevated compared to the free molecules, taking advantage of features of the well-designed delivery system, which led to a large amount of ROS generation, G2/M arrest, increased nuclear double-stranded DNA breaks and apoptosis. Compared to GC cell lines with high MMP expression, GES-1 cells exhibited insufficient DOC-NP uptake due to the lack of MMPs, and the sensitizer enhancement ratio was similar to that of free DOC, which demonstrated minor radiotoxicity to non-tumor cells.

In addition to clinical chemotherapeutic agents, transition metals offer attractive properties for biological molecule engineering.[178] A variety of transition metals have been used for clinical RT sensitization. RT sensitization was achieved by forming albumin-coated Ag nanoparticles, which might be realized by Ag cation release and the high absorption of X-rays by high atomic number elements.[124] Similarly, Au nanoparticles can support GC RT sensitization as well, demonstrating the positive effect of nanomedicines on RT sensitization.[179]

3.5 ROS-mediated PDT nanomedicines in GC

Apart from traditional RT and CT, there are emerging therapeutic modalities utilizing ROS to kill tumors. PDT is a new noninvasive anti-cancer approach with high selectivity and low toxicity. In the presence of light and O_2, non-toxic photosensitizers within tissues produce a large amount of ROS, thereby achieving tumoral selective destruction.[180] In the early 1990s, PDT was approved in Japan for early GC foci that were not amenable to conventional endoscopic resection because of submucosal infiltration or the presence of ulcerative scars.[181] However, it is also plagued by issues such as narrow clinical indications, poor light penetration, and limited antitumor efficacy.[182,183]

To improve the tumor-specific targeting effect of photosensitizers for enhanced PDT effectiveness against malignancies, Ding *et al.* developed a novel cyanine thio-photosensitizer with self-assembly properties called Cy_{1395}-NP (Fig. 5).[140] The authors synthesized Cy_{641} based on the photosensitizer IR-813, using 1,2-ethanedithiol to replace its Cl atom. Cy_{1395} was subsequently synthesized by loading the maleimide of cRGD(fk)-3-

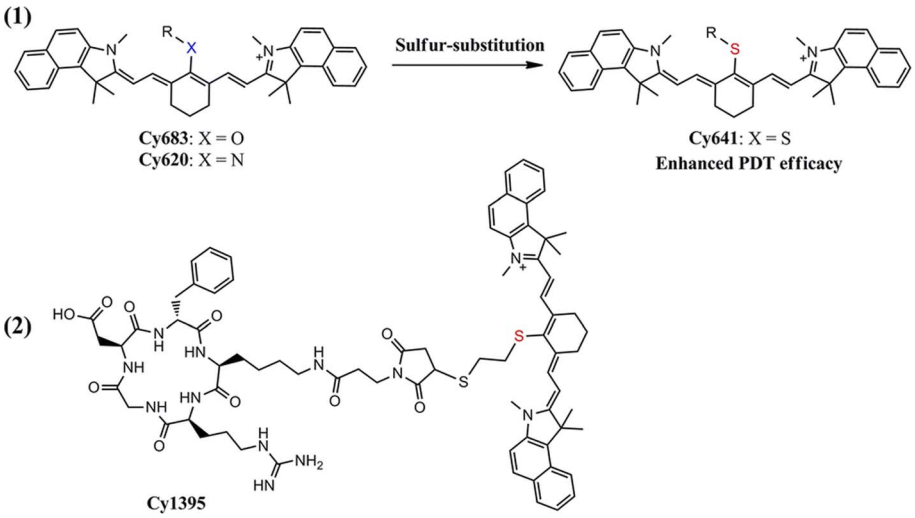

Fig. 5 (1) Sulfur-substitution strategy for designing the PDT agent; (2) the structure of the targeted PDT agent Cy_{1395}. Reproduced with permission.[140] Copyright 2022, Royal Society of Chemistry.

maleimide onto Cy_{641}. Since cRGD(fk)-3-maleimide is a hydrophilic molecule while Cy_{641} is hydrophobic, Cy_{1395} could self-assemble into nanoparticles with a hydrated particle size of approximately 115 ± 15 nm, facilitating *in vivo* delivery. Endowed with the binding characteristics of cRGD peptides to integrin $\alpha_v\beta_3$ highly expressed on MKN45 GC cells, Cy_{1395}-NP achieved GC-specific targeting, followed by mitochondrial accumulation.[184,185] Large amounts of ROS could be produced under light exposure because of the good PDT effect of Cy_{1395}. The cellular viability was significantly suppressed after administration and 40 s of light irradiation due to the toxic effect of ROS. Excellent anticancer effects were observed in the subcutaneous tumor model as a result of outstanding tumor targeting and PDT effects. By employing molecules specifically targeted to the tumor site, the tumoral photosensitizer uptake could be maximized, thus making full use of ROS while delivering a consistent dose. However, GC is characterized by heterogeneity. Therefore, there have been numerous attempts focusing on different GC targets for photosensitizer utilization improvement, including using RGDs to target $\alpha_v\beta_3$,[145,186] folic acid to target folate receptors,[128,137,143,146] epidermal growth factor (EGF) to target EGF receptors,[144] and GC cell membranes for their homologous targeting effects.[126] 5-aminolevulinic acid (5-ALA) could be converted to protoporphyrin IX (PPIX) (a photosensitizer) through cellular metabolism, which cannot be metabolized in tumor cells because of the lack of specific enzymes. Such a feature enables 5-ALA to be used as a prodrug for PPIX production and accumulation.[187] 5-ALA-based nanoparticles can utilize their inherent properties to provide tumor-specific ROS-killing effects.

Besides tumor-specific targeted delivery through nanoparticle modifications, nanoparticles also have the advantage of delivering multiple substances with distinctive capabilities simultaneously for synergistic effects, which may sensitize PDT. A common PDT sensitization strategy is the adoption of regimens to increase TME O_2 concentration. Most solid tumors are in a hypoxic state, where the lack of O_2 served as the raw material for ROS generation during PDT.[188,189] As shown in Fig. 6, in our previous work, we constructed a novel nanoparticle called Oxygen Tank for enhanced mitochondria-targeted PDT.[139] This nanosystem fused exogenous O_2 delivery, endogenous hypoxia relief, and mitochondrial dysfunction for PDT effectiveness improvement. Core–shell liposomes were applied for atovaquone (ATO), IR-780, and perfluorocarbon (PFC) encapsulation. Among them, ATO was an inhibitor of mitochondrial ETC complex III, which reduced O_2 consumption and increased ROS production; IR-780 was a cationic lipid-soluble dye with mitochondrial-targeting ability, which was used as a photosensitizer to generate ROS; and PFC was a common dissolved O_2 delivery vehicle. Wrapping another layer of the bionic erythrocyte membrane facilitated nanoparticle camouflage, further prolonging *in vivo* circulation time for a better tumor site accumulation effect. Combining the O_2-releasing role with O_2 consumption inhibition, Oxygen Tank possessed tumor hypoxia relief functions, which contributed to more IR-780-mediated ROS generation under 808 nm light irradiation on AGS GC cells. Due to the mitochondrial co-localization property of IR-780, the produced intra-mitochondrial ROS resulted in mitochondrial membrane depolarization and apoptosis. The anticancer function on subcutaneous tumors was optimized through the synergistic effect of exogenous delivery of O_2 and endogenous reduction of O_2 consumption. All the components in Oxygen Tank had good biocompatibility and safety, which boded well for clinical translation. Similarly, Yang *et al.* achieved TME hypoxia amelioration and an enhanced ROS generation rate during PDT using nanoparticles co-delivering metformin and photosensitizer.[190]

There have been several nanomedicines that enhance PDT efficacy by combining PDT with different therapeutic modalities, such as PTT and CT, relying on the multi-drug co-delivery properties of nanoparticles.[125,129,153] These PDT treatment

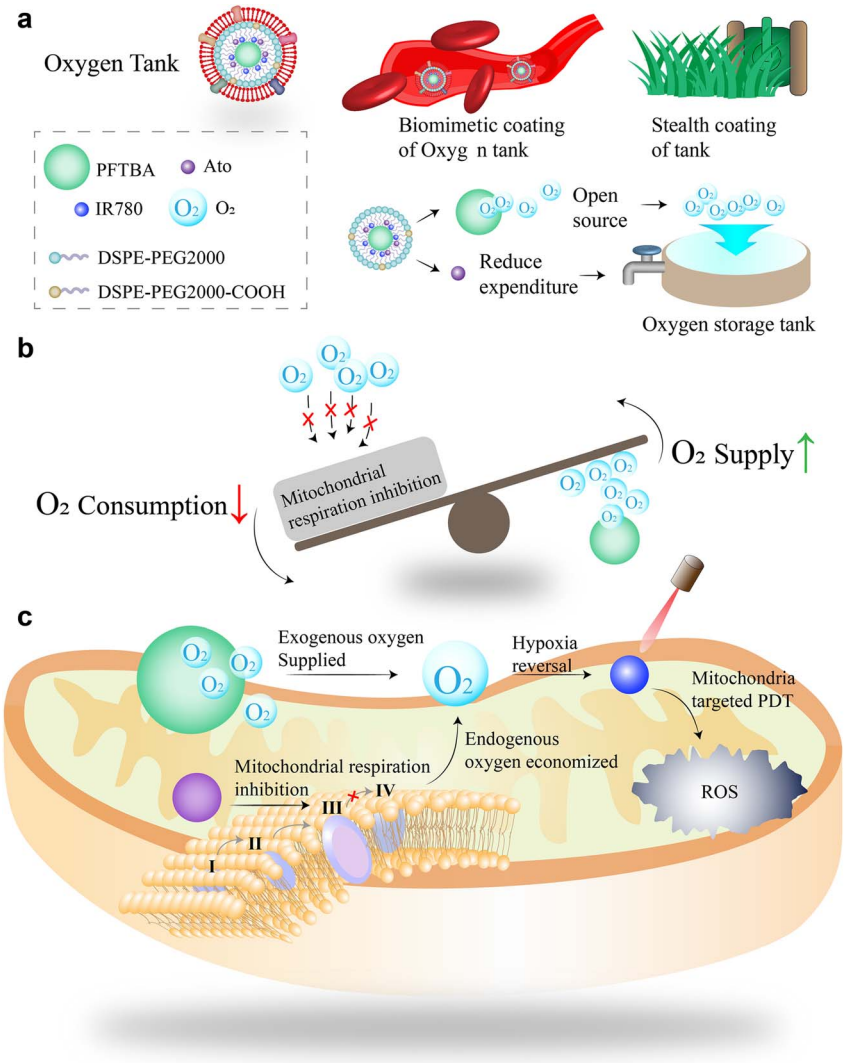

Fig. 6 Schematic illustration of the design, synergistic hypoxia reversal function, and therapeutic functions of the Oxygen Tank. (a) Design illustration of the Oxygen Tank. On the one hand, the biomimetic coating of the Oxygen Tank is similar to the stealth coating of a battle tank; on the other hand, the Oxygen Tank delivering oxygen and drugs to open source and reduce the expenditure of oxygen. (b) Oxygen Tank reduced oxygen consumption by mitochondrial respiration inhibition and increased oxygen supply by PFC to achieve synergistic hypoxia regulation. (c) Such synergistic hypoxia reversal and Mt-PDT strategy simultaneously supplied exogenous oxygen and inhibited endogenous oxygen consumption to manipulate the tumor hypoxia microenvironment and ultimately attack the mitochondria of tumor cells. Reproduced with permission.[139] Copyright 2022, Springer Nature.

regimens might achieve tumor cell death by ROS-induced upregulation of p21, promotion of the Bcl-2/Bax apoptotic pathway, activation of the MLKL/CAPG pathway, or assisting caspase-3-mediated apoptosis.[136,142,147]

3.6 ROS-mediated CDT nanomedicines in GC

CDT is a novel cancer treatment strategy that utilizes Fenton or Fenton-like reactions to generate ˙OH in the tumor region.[191] Fe and H_2O_2 undergo a complex chemical reaction that ultimately generates toxic ˙OH, a process known as the Fenton reaction.[192] Other metallic elements, such as Cu, Mn, and Co, can achieve ROS generation through Fenton-like reactions as well.[193–195] CDT has received a lot of interest because of tumor selectivity, low side effects, no reliance on external stimuli, and inexpensive treatment costs.[196]

Li *et al.* constructed a TME-responsive Mn_3O_4 nanoplatform (referred to as MPG NPs) for CDT on MDR gastric cancer cells (Fig. 7).[151] Polydopamine (PDA) was used to coat Mn_3O_4 nanoparticles for better biocompatibility. Then, GMBP1 was coupled on the PDA surface *via* photoclick chemistry, which ensured specific binding to the GRP78 receptor overexpressed on MDR tumor cells for cell-specific delivery.[197] After being internalized by MDR GC cells, Mn_3O_4 underwent a redox reaction with excess reduced glutathione (GSH), during which Mn^{2+} with Fenton-like activity was produced for subsequent conversion of endogenous H_2O_2 into highly toxic ˙OH. Apart from ROS generated *via* CDT catalyzed by Mn^{2+}, GSH consumed by Mn_3O_4 reduced ROS scavenging, leading to enhanced CDT efficacy. ROS levels were significantly increased in the SGC 7901 ADR DOX-resistant gastric cancer cell line, which induced apoptosis. PDA could

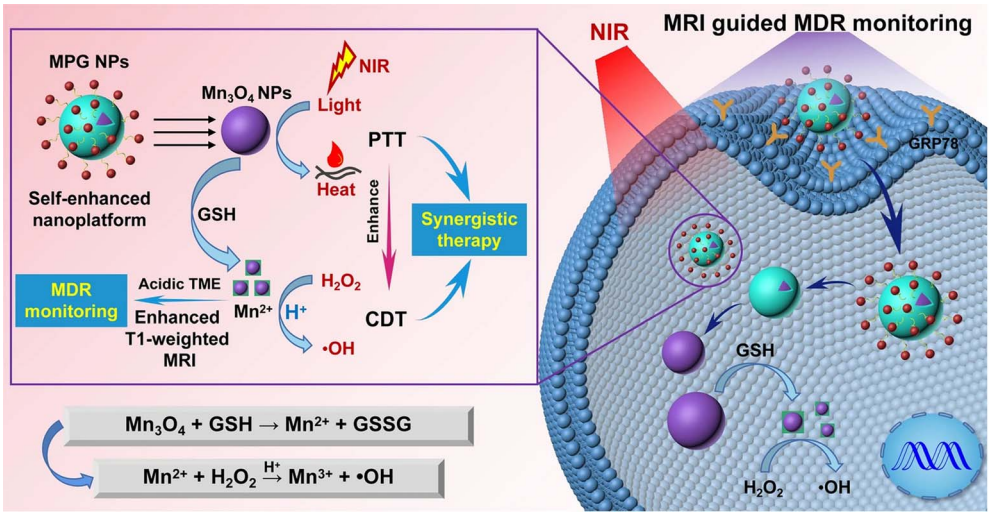

Fig. 7 The mechanism of pH/H_2O_2/GSH-responsive MPG NPs as a multifunctional self-enhanced nanoplatform for gastric cancer MDR monitoring and CDT/PTT synergistic therapy. After endocytosis, MPG NPs can react with intracellular GSH by a redox reaction to produce Mn^{2+}, which has Fenton-like activity and can convert endogenous H_2O_2 into highly toxic $^{\bullet}OH$ under HCO_3^- conditions. Mn^{2+} can enhance MRI for *in vivo* MDR monitoring. Under laser irradiation, MPG NPs can perform CDT/PTT synergistic therapy of MDR in gastric cancer. Reproduced with permission.[151] Copyright 2022, Springer Nature.

also generate heat when exposed to light and facilitate PTT as an adjunct to CDT. Chen also used a similar approach to exert anti-tumor effects *via* Mn^{2+}-mediated CDT.[152]

3.7 ROS-mediated immunotherapy nanomedicines in GC

Immunotherapy rejuvenates anti-tumor therapy. It employs the immune system of patients to destroy tumors and provide a long-lasting anti-tumor impact that avoids tumor recurrence. However, immunotherapy indications and efficacy are restricted due to the inherent characteristic of tumor cells to evade immune surveillance.[198] There is a need for novel broad-spectrum immunotherapeutic approaches. The tight relationship between ROS and anti-tumor immunity might pave the way for novel methods of clinical immunotherapy.

An increased local ROS level facilitates the release of tumor-associated antigens, DAMPs, and pro-inflammatory cytokines in addition to direct tumor ablation, a process known as immunogenic cell death (ICD).[199,200] It has been shown that the interactions of DAMPs such as calreticulin, high mobility group box 1 (HMGB1), and secreted adenosine triphosphate (ATP) with phagocytic, purinergic, and pattern-recognition receptors are required for ICD.[201,202] These antigens function as adjuvants to stimulate antigen-presenting cells (APCs), thereby eliciting an antigen-specific immune response against malignancies.[203] Based on this hypothesis, Zhu *et al.* constructed nanoparticles that elevated the ROS generation rate using PDT and activated ICD for immune response induction (Fig. 8).[154] Exosomes obtained from MGC803 GC cells were utilized to co-load the proton pump inhibitor pantoprazole and the aggregation-induced emission luminogen TBP-2 (known as CPT). Among them, TBP-2 had light irradiation-mediated ROS generation capability as a photosensitizer, which was the basis for ICD. Pantoprazole could inhibit glutamine transporter protein and glutaminase expression for glutamine metabolism blockage, which led to decreased GSH and ATP production rates, enhancing PDT efficiency. Tumor exosomes specifically delivered drugs to the GC site, thus facilitating subsequent PDT and immunotherapy. CPT-mediated therapy suppressed MGC803 GC cell viability by up to 90% and induced ICD *in vivo*, which was mainly manifested by increased expression of calreticulin on tumor cells. Unfortunately, the authors did not monitor changes in the *in vivo* tumor immune microenvironment. According to the research findings of others, organismic immunological response activation seemed inevitable. Similarly, liposome nanoparticles loaded with icariin could promote GC cell death through intracellular ROS production, as well as upregulating calreticulin and HMGB1 expression and ATP secretion, realizing ICD-implemented immunotherapeutic effects.[116]

ROS can act as a second messenger to influence immune cell functions and thus enhance immunotherapy as well. Tumor-associated macrophages (TAMs) can exhibit either a tumor-killing M1 phenotype or an immunosuppressive M2 phenotype. Because of the inducing effect of ROS on macrophage polarization toward the M1 phenotype, nanoparticle-based ROS generation strategies have been developed. To modulate M2-like TAM in GC TME, Zhang *et al.* designed and synthesized a variety of Au 2-hydroxy-5-methylbenzaldehyde thiosemicarbazone compounds, which were encapsulated as 60.5 nm nanoparticles for loading and transport using human serum albumin.[155] Nanoparticles preferentially accumulated in M2-like TAMs and GC cells. In addition to directly leading to tumor cell death, ROS generated by Au compounds *via* redox effectively induced macrophage M1 toward polarization, as evidenced by upregulation of NF-κB and nitric oxide synthase and downregulation of Msr2 and STAT3. There was also a significant increase in tumor necrosis factor-α (TNF-α) and IL-

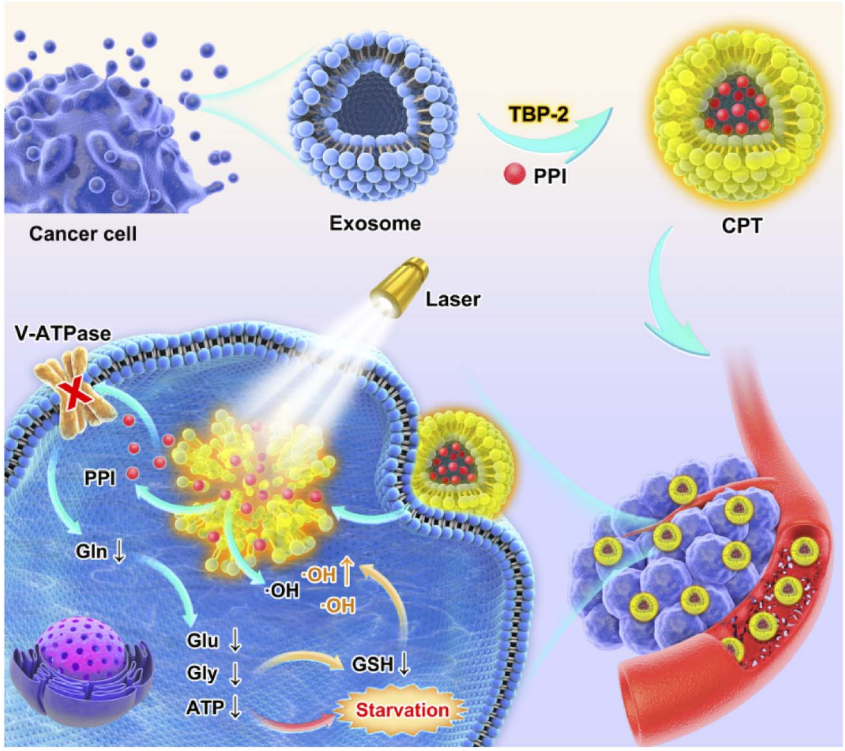

Fig. 8 Schematic illustration of tumor-derived exosomes co-delivering aggregation-induced emission luminogens and proton pump inhibitors for tumor glutamine starvation therapy and enhanced type-I photodynamic therapy. Reproduced with permission.[154] Copyright 2022, Elsevier.

12 secreted by macrophages *in vivo* or *in vitro*, as well as an upregulation of CD86 expression. *In vivo* TAM polarization activated $CD8^+$ and $CD4^+$ T lymphocytes and NK cells, thereby inducing tumor suppressive effects through enhanced immune responses. Therefore, ROS can exert an irreplaceable anti-tumor therapeutic effect by affecting immune cells.

4. Conclusion and outlook

The intricate relationship between ROS levels and GC is primarily dependent on the precise fine-tuning of ROS formation and clearance.[204] The widely differing observations on how ROS affect cancer formation reflect the numerous roles of ROS in inducing distinct cellular responses. In spite of the complexity, understanding the mechanisms governing ROS generation and response is essential to comprehending the ultimate fate of cancer cells. Cancer cells upregulate the antioxidant system while elevating ROS levels, achieving a precious balance between the two. As a result, tumor cells flourish in environments with greater ROS levels than healthy cells. For GC cells, moderately increased ROS levels are favorable for malignant progression. While detrimental to tumor prognosis, the property of high ROS levels can also make cancer cells more susceptible to external stimuli that further increase ROS production. A growing number of treatment approaches have been researched, most of which aimed at raising ROS levels and triggering oxidative stress, which is detrimental to cellular viability.[161,205]

Despite the potential of ROS in GC ablation, a number of issues remain. The dual role of ROS is not fully grasped. The ROS type and level are critical for their effects on cells. H_2O_2 possesses the ability to modify proteins and regulate signaling pathways, whereas highly active ROS are instead more likely to cause lipid damage and cell death. Once the concentration of H_2O_2 increases, it will similarly cause irreversible damage to cells.[206] The different localization of ROS also has an impact on their roles.[207] Further research to delineate distinct redox signaling pathways could facilitate the development of precision therapies based on them. Additionally, whether ROS may serve as targeted weapons to eliminate tumor cells rather than playing the dualistic role of indiscriminately harming normal cells is a key subject in the field of cancer redox biology. Although measures to globally raise ROS to lethal levels are supposed to kill cancer cells, as with traditional CT and RT regimens, these strategies often cause systemic damage, which may explain the contradictory findings of clinical trials and experimental investigations.[36] Furthermore, the role of ROS and its regulation is strongly influenced by the tumor type and stage. For various cancers, or tumors of the same type but at different stages, the same ROS-regulation technique may lose effectiveness or even encourage malignant growth.[208] A reliable and finely tuned ROS-based treatment approach is required.

Nanomedicines can partially overcome issues of ROS-based tumor therapies that rely on traditional delivery methods by precisely targeting tissues or cells. The utilization of unique *in vivo* capabilities of nanoparticles to target specific tissues, cells and even organelles has been extensively documented.[209–211] The potential systemic toxic effects of ROS will thus be avoided. Nanomedicines can be modified to target certain cells and exert

distinct effects on different cells in response to ROS activation. In this review, we have summarized the definitive effects of ROS on GC and a series of nanomedicines based on this, hoping to guide future research.

Substantial studies on the association between ROS and malignancies, along with preclinical applications, have been conducted; however, there is still a long way to go before adopting ROS-based nanoparticle-mediated therapy approaches in clinical practice. First, although it has been reported that cancer cells are more sensitive to ROS-producing agents than normal cells, the exact molecular and biochemical mechanisms responsible for this difference remain unelucidated. More research describing this phenomenon is essential to guide therapies that achieve precision tumor killing while avoiding damage to normal tissue. Second, since GC is intricate *in vivo*, the exact effects of different concentrations and types of ROS on distinctive cells in the TME remain uncertain. The elevation of ROS in the TME and the induction of cell death by excessive ROS are the most reliable research findings, on which most nanodrugs have been based for tumor treatment. Although preclinical experiments showed that lowering ROS in inflammation areas might inhibit carcinogenesis, clinical trial results seemed to be unsatisfactory, which was probably attributed to the complex physiological functions of ROS.[212] This calls for more in-depth fundamental investigations. Moreover, for nanomedicine, a thorough examination of the long-term biosafety is necessary. The majority of biosafety statistics included in articles were short-term mouse-based data. Considering the notable discrepancies between mice and humans, validation of long-term toxicity, pharmacokinetics, and pharmacodynamics is necessary.[213] Finally, most of the literature exploring the therapeutic role of ROS in GC focused on their effects on tumor cells. Even when effects on immune cells were considered, most attention was paid to the polarization-inducing effects on TAMs. Since there is already evidence that ROS play an integral role in the function of either DC or T cells, ROS-based nanoplatforms targeting these cells ought to be developed for anti-cancer immunotherapy. It is predictable that additional ROS-based nanomedicines will be produced in the future as a crucial component of GC therapy given the expanding knowledge of ROS effects in malignancies.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

The authors declare no competing financial interest.

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