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Nanomedicine-based modulation of redox status for cancer therapy

Ping Jin[A,#], Lei Li[B,#], Edouard Collins Nice[C,*] and Canhua Huang[A,*]

For full list of author affiliations and declarations see end of paper

*Correspondence to:
Edouard Collins Nice
Department of Biochemistry and Molecular Biology, Monash University, Clayton, Vic. 3800, Australia
Email: ed.nice@monash.edu

Canhua Huang
State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China School of Basic Medical Sciences and Forensic Medicine, Sichuan University, and Collaborative Innovation Center for Biotherapy, Chengdu, 610041, P. R. China
Email: hcanhua@hotmail.com

#These authors contributed equally to this paper.

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ABSTRACT

Cancer has always been a major disease with an unfavorable impact on human health worldwide. Redox biology has a close and complicated relationship to the initiation and progression of cancer. Continuous work is being conducted to develop novel approaches for cancer prevention and therapy by modulating redox homeostasis, but problems in drug targeting, drug resistance, adverse effects and recurrence are persistent challenges. Nanotechnology is emerging as a powerful tool to achieve specific targeting, non-invasive therapeutics, high therapeutic efficiency and improved drug sensitivity for cancers by exploiting the features of their microenvironment, especially the redox properties. In addition, nanoplatform-mediated delivery of anticancer drugs or exogenous antioxidants/oxidants affords a promising prospect for cancer therapy. In this review, we will summarize recent advances in redox species-responsive nanoplatforms for tumor treatment. Current nanocarrier mediated strategies that manage redox status for cancer treatment will also be discussed.

Keywords: antioxidants, chemodynamic therapy (CDT), GSH-responsive nanoplatforms, H_2O_2-responsive theranostics, nanotechnology, redox, tumor, tumor microenvironment.

Introduction

Reactive oxidants, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), become abnormally high and cause oxidative stress.[1] Superoxide ($O_2^{\cdot -}$), hydroxyl ($OH^{\cdot -}$), alkoxyl ($RO^{\cdot -}$) and peroxyl ($ROO^{\cdot -}$) radicals are unpaired ROS that have higher reactivity since they can either give an electron or accept one from other molecules to reach stability.[2,3] Either endogenous or external factors can produce them. Endoplasmic reticulum (ER), peroxisomes and mitochondria are among the high oxygen-consumption organelles that are the main sources of endogenous ROS.[4] Other endogenous sources of ROS derived from reduced riboflavin include reduced flavin mononucleotide (FMNH2), reduced flavin adenine dinucleotide (FADH2), cytochrome P450 (CYP), monoamine oxidase, xanthine oxidase, cyclooxygenase (COX), glycolate oxidase, hydroxylate oxidase, aldehyde oxidase and amino acid oxidase.[5] Exogenous ROS sources include radiation, heavy metals, transition metals, narcotics, alcohol, tobacco smoke, pollution and industrial solvents. Nitric oxide (NO) and its peroxide derivative are components of RNS (OONO).[6]

Oxidants are counteracted by a robust antioxidant system which consists of antioxidant transcription factors, non-enzymatic reducing power and enzymatic antioxidants. Antioxidant transcription factors include nuclear factor erythroid-derived 2-like 2 (NRF2), forehead box class O (FOXO), activator protein 1 (AP-1), hypoxia-induce factor-1α (HIF-1α) and p53.[7] Non-enzymatic small molecules that can directly remove ROS include glutathione (GSH), bilirubin, α-tocopherol, ascorbate, CoQ, uric acid, α-lipoic acid, carotenoids and exogenous β-carotene, vitamin E, vitamin C and plant polyphenols. Enzymatic antioxidants include superoxide dismutase (SOD) for scavenging $O_2^{\cdot -}$, catalase (CAT) for converting H_2O_2 into H_2O and O_2, peroxiredoxins (Prxs) for reducing H_2O_2 to H_2O, glutathione peroxidases (GPXs), glutathione reductase (GR), thioredoxins (Trxs) and glutaredoxins (Grxs).[8] Importantly, cellular redox pairings

(NAD + /NADH, NADP + /NADPH and GSH/GSSG) ensure the transfer of cellular electrons by serving as coenzymes or substrates for these non-enzymatic and enzymatic systems.[9] In addition, non-classical antioxidant systems exist to cooperatively maintain the cellular redox homeostasis, which are mainly composed of metabolic enzymes, metabolites and antioxidant 'sacrificial' proteins, metalloproteins and other signaling proteins.[10]

All aspects of cancer are associated with redox biology. Non-transformed cells have low levels of ROS which act as intracellular signaling molecules responsible for maintaining signal transmission, the inflammatory response and autophagy.[1] Imbalance of redox homeostasis may drive abnormal cellular behaviour and promote the occurrence of cancer. Events such as DNA damage, oncogene activation and loss of tumor suppressor function lead to dysfunction of mitochondria, metabolism and hypoxia, which will further promote ROS production, resulting in higher concentrations of ROS in tumor cells than in normal cells.[11] Cancer cells develop a sophisticated ROS-scavenging machinery at the same time, which gives them a proliferative advantage but also leaves them vulnerable to excessive ROS.[12] On the one hand, adequate ROS levels can trigger the growth factor pathway, the mitogen-activated protein kinase (MAPK) pathway, the phosphatidylinositide 3-kinase/protein kinase B (PI3K/AKT) pathway, the nuclear factor kappa-B (Nf-κb) and the hypoxia inducible factor-1 (HIF-1) pathway, all of which are pro-tumor signaling pathways that could further promote the occurrence, development and metastasis of tumors. On the other hand, when ROS levels exceed the threshold that tumor cells can tolerate, related mechanisms will be triggered to destroy involved biomacromolecules including DNA and oxidized lipids, and eventually lead to apoptosis and necrosis.[13] Taken together, oxidative stress can bidirectionally activate the mechanism of cell proliferation and apoptosis depending on the degree of ROS excess and exposure time. Based on the dual role of ROS in cancer development, antioxidant and pro-oxidative strategies have attracted much attention in the development of antitumor strategies.[14]

Precise targeting of drugs to specific intracellular receptors or organelles unquestionably improves the therapeutic effect. Nanoparticles (NPs) are employed to delivery agents to achieve binding to targeted molecules and release compounds at the right time and right dosage, therefore achieving greater safety, high efficacy and low side effects.[15,16] The design of the wide range of nanosystems currently available is made according to the physiopathology and tumor microenvironment (TME) properties, such as vascular anomalies, oxygenation, pH, perfusion and metabolic states.[17] The advantages of nanomedicine over conventional platforms are as follows: (1) Nanomedicines can easily diffuse or absorb into the body due to their small size; (2) Specialized NPs can target specific TME components; (3) They concentrate in cancerous tissue as opposed to healthy cells as a result of enhanced permeability and retention (EPR) effects, abnormal lymphatic drainage and leaky vasculature; (4) They exhibit prolonged drug retention time and sustained or stimulus-triggered drug release. Notably, nanomedicine has been extensively applied to transforming the immunosuppressive TME into an immunosupportive environment thus re-sensitizing tumor cells to immunotherapy. Intriguingly, high levels of redox species in the TME are used as activators for theragnostic nanoplatforms.[18] Accordingly, redox-active nanomedicine such as H_2O_2 and GSH-responsive nanoplatforms have been exploited for selective and effective cancer treatment.[19] On the other hand, multiple NPs that function by neutralizing pro-tumor ROS or by augmenting intracellular oxidative stress have been documented to have outstanding anti-tumor efficiency.[20] Those NPs that elicit ROS levels beyond the threshold alone or simultaneously boost ROS production and deplete GSH, could lead to restructuring of the DNA architecture, inhibition of enzymes and activation of apoptosis.[21] Furthermore, there is growing interest in the idea of employing nanomaterials with inherent redox capacities or assembling complexes with medications or oxidants/antioxidants to obtain redox qualities for the purpose of eradicating malignancies.[22]

Here, we cover the most recent developments in the use of smart nanoplatforms that respond to redox species for effective cancer detection and treatment. Next, emerging strategies based on NPs for effective tumor elimination by modulating intracellular oxidative stress are discussed, with emphasis on ROS boosting, GSH depletion and antioxidants/oxidants delivery systems.

Redox species-responsive tumor-specific delivery nanoplatforms

The stable and robust characteristics of the TME including hypoxia, acidic nature, abnormal vasculature, high level of redox species and overexpressed enzymes make it an alternative target for cancer therapy.[23] A number of smart nanoplatforms have been created by using these characteristics as activators to produce accurate cancer targeted therapy, real-time imaging and effective cancer detection.[24] For instance, hypoxic TME offers the opportunity to use hypoxia-responsive nanoparticles for effective medication delivery to tumors, and a significant amount of data has demonstrated their great anti-tumor efficacy.[25] In addition, pH-responsive nanomaterials possess an overwhelming advantage for controlling controlled drug release.[26] Importantly, redox species are also well-recognized activators, exemplified by the development of H_2O_2 or/and GSH-responsive nanoplatforms (Fig. 1).

Redox species-responsive nanoplatforms for O_2 or other toxic ROS generation

Considered as a hallmark of malignancies, H_2O_2 which has high stability in the TME, has been employed as a stimulus

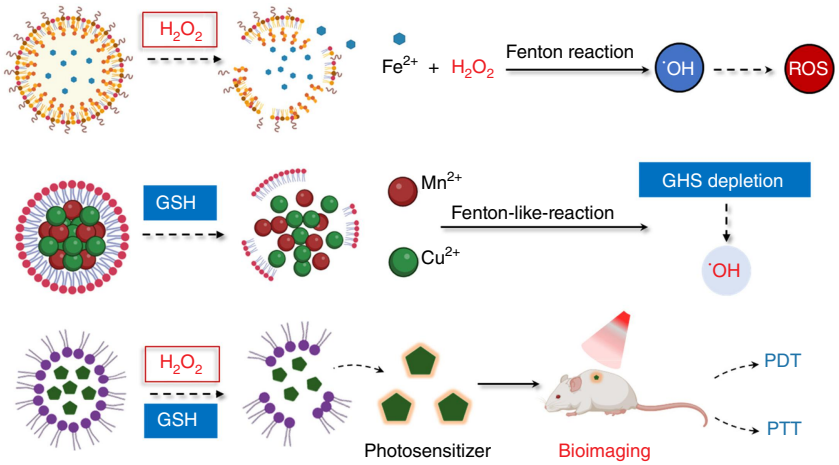

Fig. 1. Redox species-responsive tumor-specific delivery nanoplatforms. Redox species have been exploited as activators to develop a series of smart nanoplatforms to produce *in situ* O_2 or other toxic ROS generation, bioimaging, cargo release and prodrug activation for efficient cancer diagnosis and treatment.

in nanomaterial drug delivery systems. Meanwhile, GSH at high concentrations maintains the redox balance and can be used in the design of GSH-responsive nanoplatforms for cancer therapy. H_2O_2 not only functions as a signaling molecule to mediate cellular movements, but also can be decomposed to *in situ* O_2 or other toxic ROS under certain conditions, thus enhancing therapeutic efficacy. Depletion of GSH plays a significant role in redox stress elevation, relying on the Fenton reaction, due to its main function of scavenging ROS.[27] Additionally, redox species-sensitive nanoparticles cannot only achieve drug delivery but also offer bioimaging applications. In addition, many nanoparticles have been designed to respond to redox species to activate their function or release incorporated drugs.

To date, multiple nanoplatforms have been designed to decompose H_2O_2 to O_2 for alleviating hypoxia in the TME or converting H_2O_2 into highly toxic $^{\cdot}OH$ or $^1O_2$ for excessive oxidative stress. An H_2O_2-responsive degradable nanoplatform (MDSP NP) was created, for instance, by co-loading doxorubicin (DOX), aza-BODIPY (SAB) and a photosensitizer (PS) into MnO_2 NPs with a hydrangea structure.[28] In this system, MnO_2 can produce oxygen and alleviate tumor hypoxia by reacting with H_2O_2 and H^+ in the TME. The *in vitro* and *in vivo* data showed that MDSP NPs could be paired with laser radiation to produce an outstanding antitumor impact that was synergistic with chemo/photodynamic/photothermal treatment. Moreover, TME facilitates the generation of highly toxic $^{\cdot}OH$ converted from H_2O_2 in the presence of metal ions such as ferrous (Fe^{2+}) and cupric (Cu^{2+}) due to its mild acidity and overproduced H_2O_2. Fenton or Fenton-like reactions are what these are called. By using a hydroxide ion to coordinate H_2O_2 to Cu^{2+}, Lin *et al*. created a copper peroxide (CP) nanodot, for instance.[29] The release of Fenton catalytic Cu^{2+} and H_2O_2 as well as a Fenton-type reaction for the conversion of H_2O_2 into extremely poisonous $^{\cdot}OH$ were both enhanced by the acidic environment of endo/lysosomes in tumor cells. The resultant $^{\cdot}OH$ caused cell death via a lysosome-associated route by inducing lysosomal membrane permeabilization by lipid peroxidation. With the development of H_2O_2 responsive-nanoplatforms or nanomaterials with CAT mimicking activity, multiple antitumor strategies that require the presence of O_2 including photodynamic therapy (PDT), chemodynamical therapy (CDT) and sonodynamic therapy (SDT) have achieved better antitumor effects (the mechanism and effect of their action are described in detail below). Moreover, the generation of O_2 *in situ* by catalyzing H_2O_2 could overcome tumor hypoxia-associated drug resistance.

Developing nanoagents that can efficiently break redox homeostasis by reducing tumor GSH levels has also emerged as an efficient tumor therapy. Generally, multivalent metal ions such as Fe^{3+}/Fe^{2+}, Cu^{2+}/Cu^{+}, Mn^{4+}/Mn^{2+} and Co^{3+}/Co^{2+} exhibit GSH-responsive via a valence shift.[30] An illustration is a novel albumin-based multifunctional nanoagent for GSH-depletion that was created by co-growing CuO and MnO_X inside of albumin molecules and then conjugating the resulting nanoagent with a Pt^{IV} prodrug. Copper species can produce $^{\cdot}OH$ in weakly acidic conditions (pH = 6.5), whereas MnO_X can interact with GSH and deplete it, reducing the synthesis of GSH-Pt adducts and $^{\cdot}OH$ consumption. Thus, this system can inhibit GPX-4 expression and achieve better chemotherapy and chemodynamic therapy effects.[31] Gong *et al*. designed a nanomedicine by anchoring gold onto a carbon-dot (CAT-g), followed by conjunction with triphenylphosphine (TPP) and cinnamaldehyde (CA) on its surface to disturb mitochondrial redox homeostasis.[32] After the liberation of CA in response to the acidity of the endosomes, TPP-CAT-g quickly reacted with mitochondrial GSH and elevated ROS production. These data showed that MitoCAT-g treatment significantly inhibits tumor growth in subcutaneous and orthotopic patient-derived xenograft (PDX) hepatocellular carcinoma models, indicating that MitoCAT-g is a promising agent for anticancer applications.

Clearly, oxidative stress might be effectively increased to boost therapeutic effects in cancer treatment by simultaneously increasing ROS levels and depleting GSH.

Mesoporous copper/manganese silicate nanospheres (mCMSNs) coated with cancer cell membranes were developed by Liu *et al*. to convert endogenous H_2O_2 into O_2 and then react with O_2 to create harmful $^1O_2$.[33] While this is going on, Cu^+, Mn^{2+} and ·OH can be produced by the Fenton-like reaction that is catalyzed by the GSH-triggered degradation of mCMSNs. They showed that by converting endogenous H_2O_2 into O_2 and then reacting with O_2 to produce harmful $^1O_2$ when exposed to a 635 nm laser, mCMSNs might alleviate the tumor hypoxic microenvironment. For effective hydroxyl radical (·OH) formation, GSH-triggered mCMSNs biodegradation can simultaneously produce Fenton-like Cu^+ and Mn^{2+} ions and deplete GSH. This simultaneous hypoxia relieving and GSH depletion system disrupts the cellular antioxidant defense system, thus exhibiting exceptional anti-tumor therapeutic effects. Through the coprecipitation of upconversion nanoparticles (UCNPs) and AIE-active photosensitizers, followed by the formation of MnO_2 as the outer shell, Wang *et al.* created a GSH-depleting and near-infrared (NIR)-regulated nanoplatform.[34] UCNPs in this system cause the activation of AIE-active photosensitizers to produce ·OH under exposure to NIR irradiation. The MnO_2 shell was decomposed to Mn^{2+} by intracellular GSH, which efficiently depletes GSH and elevates intracellular ·OH. Notably, the resulting Mn^{2+} was subsequently capable of catalyzing intracellular H_2O_2 to ·OH. As a result, tumor growth was significantly inhibited by this triple-jump ·OH generation protocol with no noticeable side effects.

Redox species-responsive nanoplatforms for bioimaging

Redox species-sensitive nanoparticles cannot only deliver cytotoxic drugs but also provide bioimaging applications. The bioimaging of H_2O_2-responsive theranostics is mainly achieved by the quench of H_2O_2-sensitive fluorescent dyes. Nanomaterials containing metal ions,[35] arylboronic ester[36] and aryl oxalate ester[37] have been reported for bioimaging. An example is the Cu/CC NPs, which are synthesized by assembling a photosensitizer (Chlorine e6, Ce6) and modified carbon dots (CDs-Ce6) and Cu^{2+} and exhibit quenched fluorescence (FL) imaging and photosensitization. In addition, Cu^{2+} not only reacts with H_2O_2 to provide extra chemodynamic therapy (CDT) but also depletes GSH in tumors, thus enhancing the efficacy of ROS based therapy.[38] Recently, photoacoustic imaging (PAI) has emerged as a promising imaging modality for cancer diagnosis due to its good penetration into deep tissue and fine spatial solubility. A graphene quantum dot nanozyme (GQDzyme)/2,2′-azino-bis (ABTS) based exosome-like nanozyme vesicle was developed by Ding *et al.*[39] In the presence of H_2O_2, the GQDzyme effectively catalyzes ABTS into its oxidized form, which is an ideal contrast agent for PAI due to its strong NIR absorbance. Their research suggested that this exosome-like nanozyme vesicle, with excellent biocompatibility and blood circulation stealth ability, effectively accumulated and selectively triggered catalytic PAI in nasopharyngeal carcinoma (NPC). To further achieve imaging-guided tumor-targeted effective PDT, Zeng *et al.* reported a novel H_2O_2-activatable and biodegradable nanomedicine (BSA-MBPB) that encapsulates pro-photosensitizer (MBPB) into bovine serum albumin (BSA) with its photoactivity completely ablated within BSA.[40] H_2O_2 activates BSA-MBPB to not only produce the photosensitizer methylene blue for recovering its fluorescent for dual-modal imaging (photoacoustic and photosensitizing) and cytotoxic singlet oxygen ($^1O_2$) generation, but also provide adjuvant quinone methide to boost the $^1O_2$ by GSH-depletion.

Studies have also suggested that the redox reaction between nanoplatforms and GSH provides bioimaging applications for diagnosis and treatment of cancer. Multiple imaging modalities with GSH-responsiveness such as MRI, computed tomography, optical imaging and upconversion luminescence (UCL) have been employed in the preclinic and clinic. For instance, He *et al*. reported on a drug delivery system that targets the mitochondria and is designated as CDs (DOX)@MSN-TPP@AuNPs.[41] This mesosystem worked as a promising fluorescent probe ($\lambda ex = 633$ nm, $\lambda em = 650$ nm) for targeted imaging of mitochondria using NIR fluorescence to increase therapeutic effectiveness and safety after being etched with GSH. In the meantime, mitochondrial depolarization and subsequent death can be induced in cells by the release of DOX in a GSH-dependent manner. Xu *et al.* designed a nanoagent based on the inherent UCL/CT/MRI abilities of upconversion nanoparticles (UCNPs) for imaging-guided therapy.[42] By rupturing the brittle Mn-O link and releasing Mn under acidic and high GSH conditions, the MRI effect was achieved. Additionally, this nanoagent was given numerous imaging capabilities to realize imaging-guided cancer therapy thanks to MRI/CT/UCL imaging produced from $Gd^{3+}/Yb^{3+}/Nd^{3+}/Er^{3+}$ co-doped UCNPs under 808 nm laser excitation. Overall, by combining monitoring tumor uptake and drug liberation on one platform, various imaging modality based nanotheranostic agents are anticipated to perform well in cancer therapy.

Redox species-responsive nanoplatforms for cargo release and prodrug activation

In addition to the above-mentioned applications, redox species can serve as a stimulus to activate the controllable release of drugs from nanosystems.[43] For instance, a ROS-triggered prodrug nanoplatform was created by pyropheophorbide-induced self-assembly of CTX-S-OA or CTX-Se-OA into nanoparticles (PPa).[44] CTX was selectively and rapidly released in response to not only H_2O_2 in tumor tissue, but also PPa generated ROS under laser irradiation. The tumor distribution and systemic circulation of both CTX and PPa were also greatly prolonged by this prodrug-nano combination, showing

promising synergistic therapeutic effects *in vivo*. Lee *et al.* have prepared PL-incorporated ChitoPEGse nanoparticles to target pulmonary metastasis of cancer cells by crosslinking selenocystine-acetyl histidine (Ac-histidine) with methoxy poly(ethylene glycol)-grafted chitosan (ChitoPEG) for delivery of piperlongumine (PL, a natural alkaloid).[45] In their investigation, PL showed superior anticancer and antimetastatic efficacy *in vitro* and *in vivo* and was released in response to H_2O_2 and acidic stimulation. Taken together, nanoplatforms containing H_2O_2-responsive moieties hold promise in stimuli-driven drug release.[46]

Nanoplatforms containing GSH-activated prodrug/cargoes have also been found to improve drug release and chemotherapeutic effectiveness. A pH/reductive dual-sensitive polymeric prodrug (P(OE DS-CP)) was created in 2019 by He *et al.* through condensation of cisplatin derivatives (Pt^{IV}) with an ortho ester monomer.[47] Prodrugs have the potential to self-assemble into micelles, load DOX and then form a synergistic drug delivery system. To release CDDP quickly and completely and DOX into tumor cells, the polymer backbone might be broken down at a low pH in the high GSH TME. *In vitro* and *in vivo* studies revealed that the DOX-loaded micelles could be triggered to release two drugs into tumor tissues which exhibited synergistic antitumor effects. Additionally, GSH has the ability to break numerous redox-sensitive chemical bonds, including disulfide bonds (–S–S–), diselenide bonds (–Se–Se–) and carbon–diselenide bonds (–C–Se–), resulting in the disintegration of nanostructures and the targeted release of drugs at the tumor site.[48] For instance, a stimulus-responsive silica nanoparticle (SNP) integrated with a disulfide crosslinker for GSH-responsive cargo release capability incorporating an imidazole-containing component for endosomal escape capability was reported.[49] Multiple cargos such as nucleic acids (e.g. DNA and mRNA) and CRISPR genome editors (e.g. Cas9/sgRNA ribonucleoprotein (RNP), and RNP with donor DNA) can be delivered by this SNP with excellent efficiency and biocompatibility to target cancer cells. Overall, these studies suggest an exciting strategy for specific drug release in the tumor.

Disturbing redox homeostasis by nanoparticles

Suppressing oxidative stress has long been regarded as a promising strategy for cancer therapy due to the crucial role that ROS play in cancer biology. On the other hand, recent research indicates that oxidative damage induction and programmed cell death can also be useful cancer treatment methods.[50] A significant amount of data has demonstrated that development of nanoparticle-based therapy holds huge potential to modulate redox homeostasis for cancer therapy (Fig. 2).

Nanoparticle-mediated suspension of moderate oxidative stress for cancer therapy

By promoting numerous biochemical processes including signal transduction, autophagy and proteolysis, moderate ROS has been shown to assist the physiological functions of various diseases, including cancer. Scavenging pro-tumor ROS in this situation has the potential to lower the risk of cancer and slow the spread of the disease. Obviously, direct delivery of ROS inhibitors such as *N*-acetyl-L-cysteine (NAC), sodium azide (NaN_3) and mannitol, as well as those agents that could inhibit ROS production by targeting related signaling pathways or node molecules possess huge potential to inhibit ROS for tumor suppression, and a plethora of studies have demonstrated their application.[51] Recently, nanocarrier loaded natural antioxidants, antioxidant enzymes or their mimics have attracted huge interest from investigators.

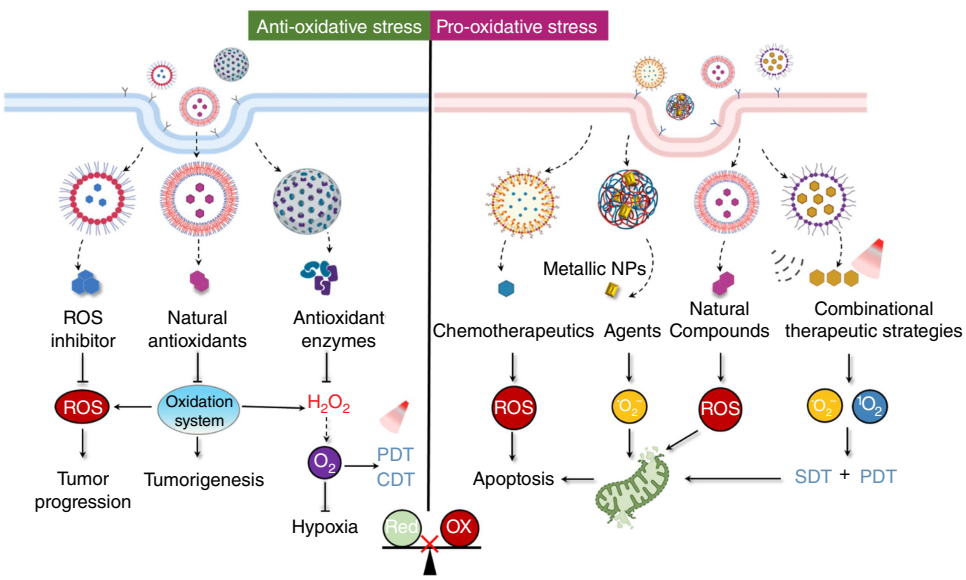

Fig. 2. Strategy and application of nanoparticle-mediated redox modulation for cancer treatment. A significant amount of data has demonstrated that development of nanoparticle-based therapy holds huge potential to modulate redox homeostasis for cancer therapy by direct delivery of ROS inhibitors/inducers, natural compounds and enzymes.

Natural antioxidants such as curcumin, resveratrol, polyphenols and flavonoids have been reported to counteract and neutralize ROS in the tumor or TME thereby inhibiting tumors.[52] Nano-antioxidants, referring to encapsulations of antioxidants into nanocarriers, antioxidant-derived nanoparticles, can achieve safe and efficient delivery of a high payload of antioxidants for eradicating cancer. One phytosterol found in a variety of food-producing plants, such as natural oils, nuts, and soy products, is called sitosterol. It has been shown to have therapeutic potential for decreasing cholesterol and low-density lipoprotein, scavenging free radicals and preventing cancer. Sitosterol-derived nano-antioxidant therapy employing alginate/chitosa nanoparticles (sito-Alg/Ch/NPs) was described by Afzal *et al.*[53] *In vitro* and *in vivo* results showed that these NPs exhibited higher cytotoxicity due to enhanced drug release patterns, improved bioavailability and antioxidant potential in breast cancer. Resveratrol, a type of polyphenol, is well-documented to function as an antioxidant for protecting the body from diseases including cancer. Increasingly studies have demonstrated that resveratrol inhibits cellular events associated with tumorigenesis and progression by inhibiting the activity of COX-1 and COX-2, impeding TPA-induced DNA binding of NF-kB.[54] Shi *et al.* recently created resveratrol-loaded Zein-SHA (low-molecular-weight sodium hyaluronate) nanoparticles. According to increased ABTS free radical scavenging ability and iron (III) reduction power, resveratrol in capsules has stronger antioxidant activity than free resveratrol. With IC_{50} values of 14.73 and 17.84 g mL^{-1}, respectively, this nanosystem also demonstrated more antiproliferative activity than free resveratrol in 4T1 murine breast cancer cells.[55] By encasing antioxidants in nanoparticles, researchers can increase the compounds' bioavailability, biodistribution and capacity to target specific tissues or receptors, resulting in a regulated release of chemicals over an extended period of time.

Recently, the delivery of antioxidant enzymes or their mimics is emerging as a method of reducing oxidative stress for tumor suppression. Mainstream research has been devoted to efficiently delivering CAT and SOD among numerous enzymes to mitigate oxidative stress for therapeutic purposes because the activity of other enzymes requires many co-factors and/or secondary enzymes for proper function. CAT and its mimics have been widely utilized to convert H_2O_2 into O_2 by taking advantage of the high levels of H_2O_2 in TME or inside tumors as described above. Recently, Wu *et al.* introduced a competent nanoplatform (denoted CSI@Ex-A) fabricated by encapsulating catalase (CAT) into silica nanoparticles (CAT@SiO_2) and then loading them with sonosensitizer indocyanine green (ICG), and further coating with AS1411 aptamer-modified macrophage exosomes.[56] In this approach, CAT@SiO_2 is dedicated to driving tumor hypoxia; the role of the macrophage exosomes is to cross the blood–brain barrier (BBB). After tumor cell endocytosis, this nanoplatform undergoes GSH triggered biodegradation and effective O_2 self-supply, thereby emerging as a promising therapeutic modality for glioblastoma (GBM). Additionally, a proliferation of nanomaterials with CAT mimicking action, such as metal–organic frameworks (MOFs), manganese dioxide (MnO_2) and cerium oxide (CeO_2) nanoparticles, has attracted significant interest in biological applications for the treatment of cancer.[57] Recently, a CAT@Pt^{IV}-liposome system was designed by encapsulating catalase inside cisplatin(IV)-prodrug-conjugated phospholipid formed liposome nanoparticles. This system shows outstanding enzyme activity to trigger decomposition of H_2O_2 into O_2 for hypoxia relief. After X-ray radiation, treatment of CAT@Pt^{IV}-liposome induces significant DNA damage in cancer cells, with potential for clinical translation.[58] Notably, studies were conducted to simultaneously encapsulate CAT and SOD in wind chime-like cyclodextrin (WCC) for efficient protein delivery.[59] By simply mixing with protein solution to create SC/WCC, the amphiphilic WCC may self-assemble into nanoparticles in aqueous solution and provide better encapsulation of these two antioxidant enzymes. This nanoparticle can integrate the synergistic impact of SOD and CAT to increase the elimination of reactive oxygen species (ROS) thanks to the safe and effective transport provided by WCC nanovehicles.

Nanoparticle-mediated amplification of oxidative stress for cancer therapy

While modest levels of ROS activate multiple pro-tumor signaling pathways, excessive ROS exert cytotoxic effects by oxidizing biomolecules such as nucleic acids and lipids. Consistent with the notion that the ROS levels of tumor cells are elevated compared to their normal counterparts, tumor cells are more vulnerable than non-transformed cells to pharmacological treatments that induce excessive ROS accumulation. In fact, many organic and inorganic substances have the ability to cross the ROS threshold and activate multiple signaling pathways, such as p53, tumor necrosis factor (TNF)-signaling, extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein kinase (MAPK), leading to oxidative damage and programmed cell death in a number of malignancies.[60] Recent advances in nanotechnology provide novel and powerful tools to specifically target tumors and enhance the performance of active compounds. Various NPs, particularly metallic NPs, can directly interact with the cellular membranes, organelles or macromolecules to induce oxidative stress.[61] In fact, a large body of research has shown that the toxicity of NPs is frequently linked to the creation of oxidative stress, which leads to genomic instability, protein malfunction and eventually deregulates enzyme activity, causing cellular dysfunction and cell death in cancer cells.[62]

Metallic NPs have improved potential to take advantage of the oxidative radicals generated by the metals for selective destruction of diseased cells, thus emerging as valuable and efficient diagnostic and anticancer agents.[63] Generally,

metallic elements function as charged vehicles and generate soluble cations to form complexes with natural cellular components.[64] Additionally, metal ions with a positive charge may regulate electron transport to help catalyze substrates and enzymes. According to certain studies, metallic nanoparticles can stimulate inflammatory cells like neutrophils and macrophages to produce more ROS. Certain metals, particularly transition metals, were discovered to promote the production of free radicals and lipid peroxidation (LPO). These metals include titanium dioxide (TiO_2), zinc oxide (ZnO), cerium oxide (CeO_2) and silver (Ag). For instance, it has been shown that ZnO NPs can produce excessive ROS production and activate mitochondrial-mediated apoptotic signaling, making them useful for anti-cancer research. The polymer-modified zinc peroxide nanoparticles (ZnO_2 NPs) that Lin *et al.* described are noteworthy because they combine endogenous and external ROS to intensify oxidative stress.[65] ZnO_2 NPs underwent disintegration after being ingested by tumor cells, leading to the regulated release of H_2O_2 and Zn^{2+}. Inhibiting the electron transport chain (ETC) could cause an increase in the production of mitochondrial $O_2^{\cdot-}$ and H_2O_2 which would have an additive effect on the anticancer effects of exogenously produced H_2O_2. Due to their good chemical stability and strong redox potential, TiO_2 and ZnO-based oxides have been most frequently used. In terms of their cytotoxicity, the majority of TiO_2 and CeO_2 nanomaterials (NMs) were only marginally cytotoxic and had no long-term impact on the effectiveness of colony formation. However, ZnO and Ag NMs had an adverse effect on cell survival and produced significant DNA damage at cytotoxic levels.[66] In a similar vein, another study found that TiO_2 nanoparticles at concentrations between 0.1 and 100 g mL^{-1} did not appear to be toxic to peripheral blood mononuclear cells, whereas ZnO_2 nanoparticles caused severe damage at concentrations of 1 g mL^{-1}, inhibited the production of interleukin-1 and interleukin at 6.5 g mL^{-1} and at higher concentrations promoted aggregation and degradation of malate dihydrogen.[67]

Several nanosystem-based therapeutic strategies that can selectively kill cancer cells by ROS generation have aroused enormous attention due to their advantages such as an excellent safety profile, minimal toxicity and non-invasiveness.[68] The most representative amongst them is photodynamic therapy (PDT), which employs a light excited photosensitizer (PS) to generate ROS in the presence of O_2 to selectively kill tumors.[69] In this process, the PS converts from the ground state into a singlet-excited state, and then a triplet-excited state upon absorption of photons to generate $^{\cdot}O^{2-}$ or $^1O_2$ by undergoing electron transfer with biomolecules. Obviously, the supply of sufficient quantities and the capability of photosensitizers for ROS production are robust tools for the enhancement of the therapeutic efficacy of PDT. In this sense, the use of biocompatible metallic nanoparticles, AuNPs and AgNPs, is particularly exciting, and numerous studies have shown the successful use of PDT in a variety of cancers, including colorectal, lung, cervical, liver and GBM malignancies.[70] For instance, a study by Dai *et al.* showed that g-C3N4 nanosheet coated with AuNPs could produce a lot of ROS when exposed to a 670 nm laser, considerably suppressing human non-small cell lung cancer, breast cancer and human cervical carcinoma both *in vitro* and *in vivo*.[71] Indeed, PDT has been available for more than 40 years with multiple formulations, including AuNPs, having been investigated in clinical trials[72] (NCT01679470, NCT00848042), and notably, several PSs, such as Photofrin, Foscan and Rada chlorin, have been used in the clinic.[73]

Chemodynamic therapy (CDT) is an emerging strategy that produces toxic $^{\cdot}OH$ independent of external light by undergoing a Fenton or Fenton-like reaction in the presence of excessive intracellular H_2O_2 in tumor tissues.[74] As is well known, $^{\cdot}OH$ possesses higher activity than $^1O_2$, thus providing better tumor-killing ability. So far, multiple investigations have demonstrated the promising efficiency of CDT in multiple tumors.[75] Recently, Zhang *et al.* summarized the development of CDT and their antitumor applications, with a critical discussion about the future development trend and challenges of CDT.[76] Another emerging strategy is sonodynamic therapy (SDT), which utilizes ultrasound to activate agents for ROS generation, thus inducing apoptosis in cancer cells.[77] For instance, by encapsulating the sonosensitizer chlorin e6 (Ce6) in the core and then conjugating anti-PD-L1 antibody (aPD-L1) to the interlayer, with a PEG coating, which could be sheddable at a low pH value (6.5) of the TME, Yang *et al.* created a lipid (LP)-based micellar nanomedicine.[78] With only mild immune-related side effects, this approach enabled tumor-targeting administration that triggered anti-tumor immunity (irAEs). A SDT activated by ultrasonic insonation also generates tumor-killing ROS in conjunction with immunity, resulting in a potent anti-cancer immunity and long-term immunological memory to successfully inhibit melanoma. Overall, these novel therapies offer fresh ideas for creating integrated anticancer drugs based on NPs that target and eliminate cancerous cells by raising their ROS setpoint with little invasion.

Interestingly, several natural compounds have recently gained significant attention as anti-tumor medicines due to their capacity of eliciting oxidative stress.[79] For instance, excessive doses of polyphenols can have pro-oxidant lethal effects by suppressing the Nrf2 pathway and antioxidative genes like GPX, heme oxygenase-1 (HO-1) and sirtuin-1 from being expressed (Sirt1). As a result, NP-based controlled drug delivery systems that are secure and appropriate have been utilized to assure effective administration of these therapeutic candidates into the tumor site. As an illustration, Shi *et al.* found that ZnO-PBA-Curcumin, a phenyl boronic acid (PBA)-conjugated and pH-responsive ZnO nanoparticles loaded with Curcumin (a polyphenol obtained from the herb *Curcuma longa*), can induce apoptotic cell death in MCF-7 human breast cancer cells by inducing

oxidative stress and mitochondrial damage.[80] Quercetin, a plant-derived bioflavonoid loaded into PBA-ZnO nanoparticles (referred to as PBA-ZnO-Q), caused apoptosis in MCF via enhancing oxidative stress and mitochondrial damage, as demonstrated by Sadhukhan *et al.*[81] Together, these significant findings suggest that phytochemicals hold potential to eradicate cancer cells by ROS-induced cell death and apoptosis, the nanoparticles ensuring their efficient transport and high efficacy against tumors.

Discussion

As known, cancer cells undergo metabolic reprogramming to boost ROS production as it is crucial for all aspects of cancer. Meanwhile, they have evolved a set of ROS-scavenging systems to avoid ROS-induced damage. The interaction of these two opposing systems raises the homeostatic ROS setpoint, which gives cancer cells an edge in terms of proliferation.[82] In that context, redox modulation represents a reasonable strategy for the prevention and treatment of cancer. On the one hand, neutralizing moderate ROS that is crucial for carcinogenesis would suppress a tumor by restricting cellular signaling transduction, physiological activity and the synthesis of biomolecules. On the other hand, because there is a larger level of ROS, cancer cells are more susceptible to an increase in ROS that will result in macromolecular harm and cell death.

While it is well demonstrated that parturition of the cellular redox balance provides promising therapy for eliminating cancer cells, their efficiency is limited not only by drug resistance and tumor relapse,[83] but also the properties of the drug itself and the targeting strategy. Most common chemotherapeutic medications frequently fail to eradicate tumors and may even trigger the development of therapy-induced cancers. Notably, selectively killing cancer cells with minimal toxicity and high safety are the primary challenges in cancer therapy. Drugs employed in standard chemotherapy often fail to discriminate between cancer and healthy cells. Additionally, unwanted side effects are common and can occur with any treatment, including those that are explicitly intended to target altered signaling pathways in cancer cells. Even though suitable natural antioxidants/pro-oxidants exhibiting tumoricidal effect alone or in combination with radiotherapy or chemotherapy have been identified, there is still a long way to go before these therapies enter the clinic. Their effectiveness is significantly hampered by drawbacks like non-specific tumor targeting, poor membrane permeability, short blood circulation times, complicated physiological processes and other challenges, and their clinical use for cancer therapy is constrained due to the paucity of conclusive human research data.

These issues can be resolved by the development of nanocarrier systems that efficiently deliver therapeutic candidates into the tumor site with little invasiveness. Redox species can function as essential 'regulators' or efficient 'targets' for antitumor therapeutics that integrate nanotechnology with redox modulating strategies (Table 1). On the one hand, excessive H_2O_2 in TME has been used to generate O_2 in the presence of CAT or other nanomaterials, with CAT simulating the necessary activity to treat hypoxia and make tumors more responsive to PDT, SDT, chemotherapy, radiation and other therapies. Additionally, H_2O_2 can be transformed into poisonous forms of OH, $^1O_2$, O_2 or RNS (NO), which can harm cancer cells by oxidation. High GSH-responsive theranostics have also been developed for the stepwise release of drugs or biomacromolecules, prodrug delivery and triggering of CDT by integrating GSH cleavable linkers such as S–S, Se–Se, C–Se and Au–S into nanocarriers.[18] Multimodal imaging that responds to H_2O_2 or GSH is another important use in nanomedicine. On the other hand, nanomedicines have been shown to be effective in cancer therapy by deleting pro-tumor moderate ROS or pushing cancer cells beyond their oxidative stress limits that can destroy them. Notably, nanocarriers coated with natural antioxidants/pro-oxidants are being used to enhance the efficacy of conventional treatments or to treat tumors by modulating redox status. Despite the significant advancements in nanomedicine, there still remain some problems in this area. Multiple biological processes, including NP–protein interactions, blood circulation, tumor tissue penetration and tumor cell internalization, as well as interaction with the TME, are involved in the systemic transport of NPs, which help determine the therapeutic outcome of NP-based treatments. Additionally, NP characteristics such as size, geometry, elasticity, stiffness, composition and targeted ligand might also affect the enhanced permeability and retention (EPR) effect (by which nanomedicine accumulates in the tumor) and the therapeutic results.[84] It should be noted that the ongoing use of multifunctional nanodrugs has been constrained by material restrictions, such as toxicities and inadequate drug loadings. Taken together, this means that the complexity and variety of the malignancies and the characteristics of the NPs necessitate rigorous patient selection to determine which patients will benefit from a particular nanotherapy.[68c] Their use requires a safety assessment based on biocompatibility, release, accumulation and metabolism.

Overall, modulating redox status by nanoparticles shows enormous potential in cancer therapy (Table 2). To expand their applicability in therapeutic settings, more study is required. The advancement of antioxidant therapy will be helped by the creation of more efficient nanodelivery technologies and extensive clinical research. Given that humans and animals differ greatly from one another, it is important to explore their compatible biocompatibilities, release, accumulation and metabolism. In addition to structural modulation, future research needs to investigate the treatment mechanisms, especially at the molecular level. We believe that nanomedicine based redox modulation therapy will bring new and more effective strategies for cancer therapy with significant breakthroughs in the near future.

Table 1. List of nanoparticles mentioned in this review.

Category	Nanoplatforms	Mechanism of action	Efficacy	Tumor type	Ref
H_2O_2 responsive	MDSP NP	Hypoxia relief; Chemo/photodynamic/ photothermal therapy	Reduce resistance to DOX; improve therapeutic efficiency	Colorectal cancer (HTC116)	[28]
	Copper peroxide (CP) nanodot	Fenton-type reaction; $^{\cdot}OH$ generation; lipid peroxidation	Cell death; tumor growth inhibition	Glioblastoma multiforme (U87)	[29]
	BSA-MBPB	Dual-modal imaging and $^1O_2$ generation; PDT	Antitumor without major side effects	Hepatocellular carcinoma (HepG)	[40]
	PPa@prodrug NPs	ROS generation	Antitumor	Breast cancer (4T1)	[44]
	ChitoPEGse nanoparticles	Apoptosis/necrosis	Superior anticancer and antimetastatic activity	CT26; A549	[45]
GSH responsive	P6 NPs	$^{\cdot}OH$ generation; GSH deletion; apoptosis	Inhibiting the growth of cisplatin-sensitive and -resistant cancer cells	Ovarian cancer (A2780)	[31]
	CDs(DOX)@MSN-TPP@AuNPs	Targeted imaging of mitochondria; apoptosis; membrane depolarization of mitochondria	Tumor inhibition	Hela; MCF-7; 4T1	[41]
	UCNCs-DOX	Chemo-photothermal therapy; MRI/CT/ UCL imaging	High anticancer efficacy	Cervical cancer (HeLa)	[42]
	MitoCAT-g	Elevated ROS production	Inhibits tumor growth	Hepatocellular carcinoma (HepG2)	[32]
	P(OE DS-CP)	Apoptosis	Excellent antitumor effect	Hepatocellular carcinoma (HepG2)	[47]
H_2O_2 and GSH responsive	mCMSNs	$^1O_2$ production; Fenton-like reaction; $^{\cdot}OH$ generation; tumor hypoxia relief	Inhibits tumor growth	Breast cancer (MCF-7)	[33]
	MUM NPs	Hypoxia relief; ROS generation; GSH-depleting; PDT; bioimaging	Inhibits cancer cell proliferation and damages tumor vascular tissues	Breast cancer (4T1)	[34]
	Cu/CC NPs	CDT; GSH deletion; fluorescence (FL) imaging; oxidative stress	Enhanced ROS-relevant therapeutic efficiency; antitumor with negligible adverse effects	Breast cancer (4T1)	[38]
	GQDzyme/ABTS nanoparticle	Photoacoustic imaging (PAI)	Cancer diagnosis	Nasopharyngeal carcinoma (CNE-2)	[39]

(*Continued on next page*)

Table 1. (*Continued*)

Category	Nanoplatforms	Mechanism of action	Efficacy	Tumor type	Ref
Suspending moderate oxidative stress	β-sito-Alg/Ch/NPs	Scavenging free radicals	Cytotoxicity	Breast cancer (MCF-7)	[53]
	Resveratrol (RES) loaded Zein-SHA	Antioxidant activity	Antiproliferative activity	Breast cancer (4T1)	[55]
	CSI@Ex-A	Hypoxia relief; SDT; antioxidant activity	Antitumor	Glioblastoma multiforme (U87)	[56]
	CAT@Pt (IV)-liposome	Hypoxia relief; DNA damage	Enhanced chemo-radiotherapy of cancer	Breast cancer (4T1)	[58]
Amplifying oxidative stress	ZnO_2 NPs	ROS production; oxidative damage	Killing cancer cell	Glioblastoma multiforme (U87)	[85]
	g-C3N4 nanosheet	ROS generation	Cancer cell-killing and tumor growth-suppressing	A549; MCF-7; and HeLa	[71]
	P-aPD-L1/C	Anti-tumor immunity activation; ROS generation; activation of cytotoxic T cells	Suppress melanoma growth and postoperative recurrence	Melanoma (B16–F10)	[78]
	ZnO-PBA-Curcumin	Inducing oxidative stress and mitochondrial damage	Cell death	Breast cancer (MCF-7)	[80]
	PBA-ZnO-Q	Oxidative stress and mitochondrial damage	Apoptotic cell death	Breast cancer cells (MCF-7)	[81]

Table 2. Clinical trials using nanoparticles that involve ROS-modulation for cancer therapy.

Drug	Nanoparticles	Status	Tumor type	Identifier
Doxorubicin	Doxil	Unknown	Lymphoma leukemia	NCT03975205
		Completed	Ovarian cancer	NCT00846612
	Lipodox	Recruiting	Breast cancer; ovarian cancer	NCT05273944
		Completed	Ovarian cancer recurrent	NCT03681548
	Myocet	Completed	Malignant glioma	NCT02861222
Paclitaxel	Lipusu	Unknown	Breast cancer	NCT02142790
	Abraxane	Terminated	Relapsed or refractory multiple myeloma	NCT02075021
	Genexol-PM	Terminated	Hepatocellular carcinoma	NCT03008512
		Completed	Bladder cancer; ureter cancer	NCT01426126
	Nanoxel	Unknown	Advanced breast cancer	NCT00915369
	Paclitaxel albumin-stabilized nanoparticle formulation	Withdrawn	Non-muscle Invasive Bladder Cancer (NMIBC)	NCT02718742
	NanoPac	Completed	Adenocarcinoma of the prostate	NCT03077659
Radiation; hafnium oxide	NBTXR3	Completed	Adult soft tissue sarcom	NCT01433068
Radiation; ferumoxytol	SPION	Recruiting	Liver neoplasms; hepatic cirrhosis; hepatic carcinoma	NCT04682847

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Author affiliations
[A]State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, West China School of Basic Medical Sciences and Forensic Medicine, Sichuan University and Collaborative Innovation Center for Biotherapy, Chengdu, 610041, P. R. China.
[B]School of Basic Medical Sciences, Chengdu University of Traditional Chinese Medicine, Chengdu, 610075, China.
[C]Department of Biochemistry and Molecular Biology, Monash University, Clayton, Vic. 3800, Australia.