

REVIEW

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Oxidative stress in cancer: from tumor and microenvironment remodeling to therapeutic frontiers

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Abstract

Oxidative stress is a pathological condition of redox signaling dysregulation and macromolecular oxidative damage arising from elevated ROS levels. Oxidative stress interacts with tumor cell growth regulation and tumor microenvironment remodeling, and has been a critical hallmark of cancer. Targeting oxidative stress has garnered great attention in cancer therapy development. However, it is still challenging due to the complexity and heterogeneity of oxidative stress regulation across different cancers, and this encourages a comprehensive understanding of the oxidative stress network in cancers to overcome this obstacle. Therefore, we introduced the oxidative stress generation and regulatory network within tumor cells and discussed their roles in both tumor cells and the tumor microenvironment. Subsequently, we summarized the current therapeutic strategies and highlighted emerging clinical applications, providing an up-to-date overview of oxidative stress-based approaches. Particularly, their cross-application with immunotherapy and nanomedicine has provided an excellent opportunity to integrate multiple effects, exhibiting surpassing advantages. This review elaborates on oxidative stress in cancer biology and its therapeutic implications. By integrating current knowledge and the emerging coordination with immunotherapy and nanomedicine, we underscore the potential of oxidative stress-targeting approaches. Future research on overcoming therapeutic resistance and developing compatible platforms to combine multiple approaches will pave the way to cancer elimination.

Keywords ROS, Antioxidants, Immunocytes, Immunotherapy, Nanomedicine

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Introduction

Oxidative stress is a pathological imbalance of redox signaling, accompanied by cellular macromolecular oxidative damage arising from excessive ROS (reactive oxygen species), which will lead to dysregulation of cellular signaling pathways and cell death. Elevated oxygen metabolism and mutations in related proto-oncogenes cause ROS accumulation during the early stages of tumor development, resulting in excessive ROS production in tumor cells. This cytotoxic process can lead to a series of dysregulated redox signaling pathways and molecular damage and participate in various pathological processes, including the occurrence of tumors [1], thereby forming a vicious cycle. Tumor metabolic reprogramming, along with the increased metabolic flux required for rapid cell division, is accompanied by excess ROS production. The corresponding antioxidative response is activated to protect cells from oxidative damage and promote their survival [2]. This cell-initiated series of protective anti-oxidation reactions that reduce ROS damage is called the adaptive responses to oxidative stress [3]. ROS also exerts bidirectional effects on cell growth, and the dynamic and complex regulation of the oxidative stress system contributes significantly to cancer progression. The $O_2\bullet^-$ (super-oxide anion) is an important source of ROS, primarily derived from the respiratory chain and some oxidases in cells that can damage macromolecules and contribute to disease onset [4, 5]. Various antioxidant enzymes can convert $O_2\bullet^-$ into H_2O_2 (hydrogen peroxide) with a concentration-dependent duality. The H_2O_2 modulates the cell signals at physiological levels while triggering cell damage under pathological accumulation [6]. The complex crosstalk between ROS generation and scavenging system significantly impacts tumor development. Targeting the key nodes that regulate oxidative stress represents a promising therapeutic strategy.

The TME (tumor microenvironment) is a specialized niche comprising abundant non-tumor cells, extracellular matrix, and aberrant vasculature, which are embedded within various biophysical gradients. Non-tumor cells in the TME mainly include fibroblasts, lymphocytes, and macrophages [7]. Tumor cells exert complex interactions with non-tumor cells to promote the stromal barrier remodeling, aberrant angiogenesis, and immunosuppressive cytokines release to survive and invade [8, 9]. Therefore, the TME cells play a pivotal role in tumor development [10]. CAFs (cancer-associated fibroblasts) are the key stromal cells in the TME and can secrete extracellular matrix components to form the physical structural scaffold and perform many other biological functions, such as promoting tumor cell proliferation and supporting angiogenesis [11]. It has been proven that CAFs located in both the tumor infiltration area and

normal tissue, and fibroblasts outside the tumor margin, can promote tumor proliferation and angiogenesis [12, 13]. Macrophages represent a predominant immunocyte population within the TME, constituting a significant proportion of the immunocyte compartment in some solid tumors [14, 15]. TAMs (tumor-associated macrophages) exhibit high heterogeneity across different tumors and populations, reflecting their strong adaptability to environmental changes [16]. They play a bidirectional role in tumor development, which stems from their adaptability to signals within the TME [17]. Undifferentiated macrophages can polarize into pro-inflammatory and anti-tumor M1 macrophages upon stimulation by factors such as IFN (interferon)- γ and lipopolysaccharide [18]. Conversely, IL-4 and IL-13 drive macrophage M2 polarization with anti-inflammatory and pro-tumor roles. In addition, various tumor-derived factors regulate TAM M1 and M2 polarization, affecting TME intercellular crosstalk and anti-tumor immunity [18]. Other cells, including MDSCs (myeloid-derived suppressor cells) and endothelial cells, are recruited by tumor cells to participate in immunosuppression and angiogenesis, thereby promoting tumor progression [19, 20]. Therefore, therapies targeting the high plasticity of microenvironmental cells can block their pro-tumor functions and reverse the local immunosuppressive status, thereby controlling tumor progression. ROS also plays an important role in the TME. ROS serves as a signaling messenger and is required for functional maintenance in anti-tumor immunocytes. For instance, T-cell activation relies on the transient generation of a physiological level of ROS and the ROS-dependent NF- κ B- and AP-1-related pathways [21]. CD8+ T-cells' 3D motility and infiltration into solid cancers require a sustained mitochondrial ROS level [22]. However, abnormal ROS elevation in TME impeded T-cell response [23] and remodels the TME through mechanisms such as TAM polarization and Treg recruitment. ROS can drive the polarization of TAMs toward the M2 phenotype, enhancing immunosuppression and tumor progression [24–26]. Additionally, TME ROS recruits and activates Tregs, further suppressing anti-tumor immunity and facilitating tumor growth [27].

Given the pivotal role of ROS in tumor progression, oxidative stress targeting has been developed as an effective therapeutic strategy to remodel the TME and inhibit tumor cells, thereby enhancing the efficacy of conventional treatments and immunotherapy in controlling tumors [28]. In this review, we summarized the mechanisms of ROS generation and regulation and their effects on tumor cells and the TME. We focused on presenting a series of therapeutic strategies and clinical trials and developing emerging clinical application fields based on ROS and tumor adaptive responses to oxidative stress.

The mechanism of endogenous ROS generation

The concept of oxidative stress was initially proposed in 1985 and has since been widely discussed. Its concept and connotation have also been updated [1] due to the complexity and the increasing understanding of oxidative stress. Some viewpoints suggest that oxidative stress could be reckoned as the sudden or prolonged increase in ROS that were originally at steady-state levels, disrupting cellular metabolism and other signaling pathways, which may eventually lead to macromolecular damage or cell death [29]. It has also been proposed that oxidative stress should include macromolecular oxidative damage with redox signaling and control disruption [30]. Meanwhile, oxidative stress should be emphasized as a pathological condition, while the physiological oxidant generation is considered as oxidative eustress [31]. Synthesizing these perspectives, oxidative stress could thus be comprehensively summarized as a pathological condition of either compromised redox signaling or macromolecular oxidative damage arising from dysregulated ROS elevation, leading to disruption of cellular signaling pathways and cell death. Mammals can generate ROS through various pathways [32]. One of the major sources of ROS is the mitochondrial respiratory chain [33]. The mitochondrial respiratory chain is primarily composed of four enzyme complexes, including Complex I, II, III, and IV [34]. Mitochondrial complex I contains an FMN (flavin mononucleotide) cofactor that can bind NADH (nicotinamide adenine dinucleotide, reduced form) and accept electrons from NADH. Additionally, it incorporates iron-sulfur (Fe-S) clusters within its protein subunits to facilitate electron transfer to Q (ubiquinone) by interconverting ferrous (Fe^{2+}) and ferric (Fe^{3+}) ions, thereby generating QH₂ (ubiquinol). Consequently, the mechanism underlying $\text{O}_2\bullet^-$ generation through complex I mainly involves two processes, with FMN serving as the mediator of electron transfer [35]. The first process generates $\text{O}_2\bullet^-$ by electrons from NADH oxidation at the FMN site. In contrast, the second $\text{O}_2\bullet^-$ -generating pathway involves RET (reverse electron transfer), which requires two critical conditions to drive electron flow in the reverse direction: an elevated proton motive force (Δp , composed of both proton concentration gradient and membrane potential) and a highly reduced ubiquinone pool (QH₂/Q ratio) [36–38]. In mitochondrial complex II, the electrons from succinate oxidation are accepted by FAD (flavin adenine dinucleotide) and subsequently transferred to Q via the Fe-S cluster [39]. The Q is then reduced to QH₂ once it receives electrons and protons. After the electrons flow from mitochondrial complex I- and II-derived QH₂ to cytochrome C in mitochondrial complex III, an unstable $\text{Q}\bullet^-$ species is generated and reacts with oxygen to produce $\text{O}_2\bullet^-$ [39]. The produced $\text{O}_2\bullet^-$ from mitochondrial

complexes I and III is generated in the mitochondrial matrix and intermembrane space, respectively [40].

In addition to the mitochondrial electron transport chain, the NOXs (nicotinamide adenine dinucleotide phosphate oxidases) are also critical in ROS generation [41]. The transmembrane NOXs are located in the nucleus, cell membrane, and ER (endoplasmic reticulum), generating $\text{O}_2\bullet^-$ directly in the nucleus compartment, mitochondrial matrix, and extracellular space [41]. The $\text{O}_2\bullet^-$ is less diffusible and has difficulty crossing the lipid cell membrane. Instead, they are transported via anion channels [42, 43]. Compared to $\text{O}_2\bullet^-$, NO (nitric oxide) is more stable and highly diffusible [44]. NO could react with $\text{O}_2\bullet^-$ close to the microdomains where the $\text{O}_2\bullet^-$ is generated. The reaction between these two species approaches the diffusion-controlled limit, rapidly producing ONOO⁻ (peroxynitrite) [45]. Thus, ONOO⁻ may directly damage macromolecules [10]. To neutralize cytotoxic ROS, the SOD (superoxide dismutase) isoforms are utilized for $\text{O}_2\bullet^-$ elimination that catalyze its dismutation into H_2O_2 . The SOD family exhibits distinct subcellular location: SOD1 widely localizes to the mitochondrial intermembrane space, cytosol, and nucleus compartment; SOD2 predominantly resides in the mitochondrial matrix; while SOD3 functions as a secretory isoform that is transported to extracellular space [41, 46]. In addition, H_2O_2 could also be generated in the ER and peroxisomes [33, 34]. Unlike other NOXs, the NOX4 in the ER can directly sense $p\text{O}_2$ and may generate H_2O_2 independent of internal $\text{O}_2\bullet^-$ dismutation [47]. Beyond the well-characterized NOX family, the ER harbors additional redox-active enzymatic systems contributing to ROS generation, including CYP (cytochrome P450) and ERO1 (endoplasmic reticulum oxidoreductin 1). CYP belongs to a family of heme monooxygenases capable of self-oxidation and is mostly present in the ER [48]. During the CYP reaction cycle, the uncoupling occurs with the incomplete substrate oxidation, which could generate $\text{O}_2\bullet^-$ and H_2O_2 in the ER [49, 50]. ERO1 can transfer electrons from reduced protein disulfide isomerase to oxygen, thereby generating H_2O_2 [51]. Peroxisome is involved in distinct metabolic pathways, and the metabolic enzymes, including acyl-CoA oxidases, D-aspartate oxidase, D-amino acid oxidase, polyamine oxidase, xanthine oxidase, L- α -hydroxy acid oxidase, L-pipecolic oxidase, and sarcosine oxidase (Fig. 1), are closely intertwined with ROS generation [52]. Specifically, acyl-CoA oxidases are responsible for initiating the β -oxidation of fatty acids. In contrast, D-amino acid oxidase and D-aspartate oxidase facilitate the catabolism of non-proteinogenic amino acids. Polyamine oxidase is involved in the metabolic processing of polyamines, whereas xanthine oxidase catalyzes the conversion of hypoxanthine to

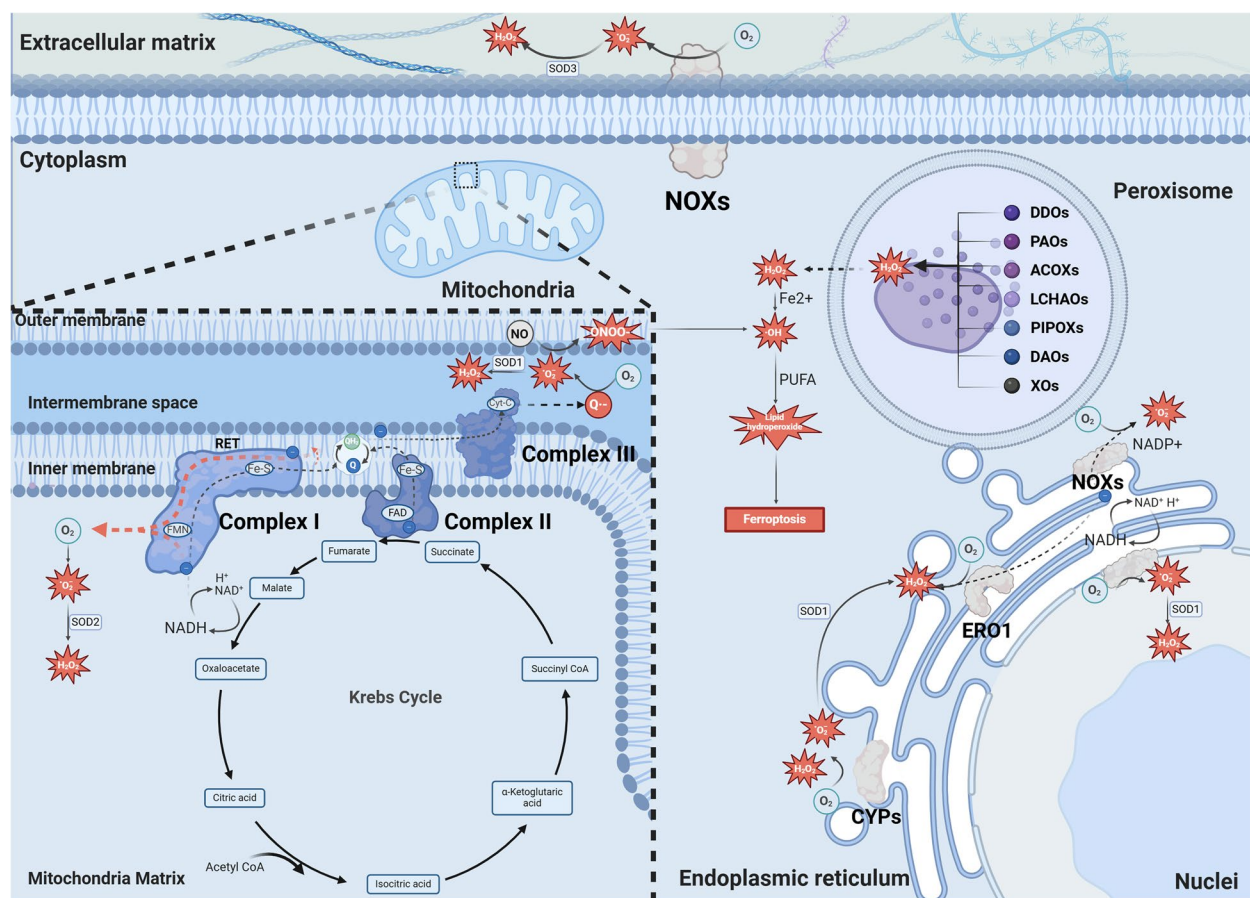


Fig. 1 Main processes of endogenous ROS production in eukaryotes. The diagrammatic sketch exhibits ROS production via the mitochondrial electron transport chain, the ER, the peroxisome, the nucleus, and the cytoplasm. The arrows and dashed arrows represent the activating effects and particle flow, respectively. The red dashed arrow refers to RET. ROS, reactive oxygen species. ER, endoplasmic reticulum. RET, reverse electron transfer. The figure was created with BioRender.com

xanthine and subsequently to uric acid. These enzymatic reactions generate ROS as a byproduct [41, 53]. In contrast to NOXs, which require assembly with regulatory subunits such as p22phox and Rac GTPases for activation, peroxisomal oxidases are mainly flavoproteins [52] with FAD or FMN cofactors intrinsically incorporated to enable direct reduction of molecular oxygen to generate H_2O_2 .

H_2O_2 can traverse cell membranes via simple diffusion and peroxiporin channel transportation. A notable example of its simple diffusion is that H_2O_2 penetrates human red blood cell membranes primarily through the lipid fraction independent of peroxiporins [54, 55]. However, peroxiporin-facilitated H_2O_2 transmembrane diffusion has been recognized as its primary transmembrane pathway [56]. The peroxiporins are a subgroup of AQP (aquaporins) and contain AQP0, 1, 3, 5, 6, 7, 8, 9, and 11 [57]. They facilitate the transport of H_2O_2 across membranes in addition to H_2O or glycerol transport.

These channels participate in redox signaling [58] and demonstrate elevated expression in human malignancies, promoting tumor cell proliferation and metastasis [59–61]. Notably, lower concentrations of H_2O_2 can selectively impact protein oxidation, thereby playing a pivotal role in signal transduction. Conversely, elevated H_2O_2 concentrations can cause oxidative stress-induced damage [62]. H_2O_2 can be converted to $\bullet OH$ (hydroxyl radicals). $\bullet OH$ is produced via the Fenton reaction of H_2O_2 with Fe^{2+} and the decomposition of $ONOO^-$ [63]. In the presence of PUFAs (polyunsaturated fatty acids), $\bullet OH$ can react with them to form distinct lipid peroxides, which induce various cell processes in a concentration- and composition-dependent manner, including ferroptosis, apoptosis, inflammation, and autophagy [64, 65]. These different forms of ROS may exhibit different functions and targets that contribute to cell fate control.

The network of intracellular ROS regulation

Excessive levels of $O_2^{\bullet-}$, $ONOO^-$, H_2O_2 , $\bullet OH$, and other ROS can damage cellular macromolecules, such as DNA, proteins, and lipids. However, tumor cells activate adaptive antioxidant pathways to maintain redox homeostasis under oxidative stress conditions [66].

The ROS-responsive transcription factors trigger antioxidant enzyme gene expression

The initiation of antioxidant defense primarily relies on transcriptional activation of antioxidant enzyme genes. A critical pathway for cells to erase ROS accumulation is the NRF2-ARE (antioxidant response elements) -antioxidant axis, which is activated in response to low and moderate levels of ROS. NRF2 is a well-known transcription factor for antioxidant reaction [67]. Under physiological conditions, the Neh2 domain of the NRF2 binds to the Kelch domain of the KEAP1 (Kelch-like ECH-associated protein 1) in the cytoplasm. KEAP1 is the substrate adaptor of Cullin3-based E3 ubiquitin ligase complex, and KEAP1's interaction with NRF2 to facilitates its ubiquitination and proteasomal degradation, thereby limiting its nuclear translocation and transcriptional activity through enhancer binding [68]. NRF2 activation upregulates various antioxidant enzymes, including HO-1 (heme oxygenase 1). The oxidative stress-controlled HO-1 could promote the displacement of BACH1 (BTB domain and CNC homolog 1) from the enhancer [69]. BACH1 is a competitor of NRF2, and they share small Maf proteins to form the heterodimer for ARE binding, thus repressing transcriptional activation of NRF2-mediated antioxidant gene expression [69]. BACH1 remains stable and blocks the binding between NRF2 and AREs under physical conditions, whereas, under oxidative stress, it undergoes E3 ligase HOIL-1-mediated degradation mediated by free heme derived from oxidized heme-containing proteins [70]. Also, heme decreases the DNA binding activity and promotes the nuclear export of BACH1, further suppressing its inhibitory effects on NRF2 [70]. Whereas, increased heme rapidly induces the HO-1 expression, which degrades heme and releases iron to promote ROS accumulation. ROS could oxidize the reactive cysteine residues in KEAP1 [71], inducing its conformational changes and inactivation, preventing NRF2 ubiquitination and degradation. Newly synthesized NRF2 then translocates to the nucleus and accumulates to activate the transcription of the target genes [72]. Therefore, these complex networks maintain a dynamic regulation of antioxidant response under oxidative stress. In addition to the KEAP1-dependent regulation, the stability of NRF2 is governed by GSK-3 β (glycogen synthase kinase-3 beta). The kinase GSK-3 β phosphorylates the serine residues of

the DSGIS motif located in the Neh6 domain of NRF2. This post-translational of NRF2 enables subsequent recognition by the β -TrCP-CUL1-based E3 ubiquitin ligase complex, targeting NRF2 for proteasomal degradation [73]. Meanwhile, since Akt phosphorylates and inhibits GSK-3 β [74], activation of the PI3K/AKT pathway suppresses GSK-3 β -mediated NRF2 phosphorylation, whereas PTEN-dependent AKT inhibition enhances GSK-3 β activity and subsequent NRF2 modification [73]. For instance, NRF2 inhibitors such as brucein D could block NRF2 activities by activating the PI3K/AKT pathway [75]. When NRF2 translocates into the cell nucleus and heterodimerizes with small Maf proteins, they bind to AREs to initiate the transcription of a series of antioxidant enzyme genes, including *GCLC*, *GCLM*, *GSTM1*, *GPX4*, *GSR*, *TXN1*, *PRDX1*, *SRXN1*, and *NQO1* [76–80], etc. Therefore, NRF2-mediated antioxidant transcriptional regulation is critical for tumor cells to counteract oxidative stress. Notably, NRF2 not only regulates the redox homeostasis but also directly affects the survival and proliferation of tumor cells [81].

In addition to the NRF2-ARE axis described above, several other antioxidant transcription regulations contribute to redox homeostasis. When oxidative stress surpasses the antioxidant capacity of the NRF2-mediated system, excessive ROS hierarchically activate other antioxidant transcription factors through distinct redox-sensing thresholds [82]. Elevated H_2O_2 induced AP-1 activation and it triggers the transcription of SODs. Besides, the antioxidant response can also be initiated through PPAR γ (peroxisome proliferator-activated receptor gamma), and NF- κ B (nuclear factor-kappa B), activating the transcription of genes such as *GSTs* and *SODs* [1, 20, 83, 84]. The ROS accumulation can also activate the AMPK (AMP-activated protein kinase) pathway to inhibit mTOR (mammalian target of rapamycin) and activate FOXO (forkhead box O) in tumor cells, promoting metabolic reprogramming to alleviate ROS accumulation [85]. Both AMPK and NRF2 pathways can respond to oxidative stress, and their complex interaction regulates ROS levels in tumor cells [86]. Meanwhile, the activated FOXO by upstream signals is also a critical redox transcript factor as already been recently summarized [87, 88]. Once activated and translocated into the nucleus, FOXOs bind to transcription regulators such as acetyl transferases to drive the acetylation of histones and FOXOs themselves, enhancing chromatin remodeling and DNA binding to trigger the transcription of their target genes, including *SOD2*, *SOD3*, *CAT*, *PRDX3*, and *SENP*. Furthermore, ROS-induced IKK (inhibitory kappa B kinase) induces I κ B (inhibitor of NF- κ B) phosphorylation, enabling NF- κ B nuclear translocation via the canonical pathway. This activated NF- κ B pathway subsequently

increases antioxidant gene expression, and thus alleviates oxidative damage [84]. The well-known tumor-suppressing transcription factor p53 exhibits bidirectional roles in redox homeostasis, demonstrating both antioxidant and pro-oxidant activities. P53 was found to upregulate the *GLS2* expression under oxidative stress or non-stress conditions, and the elevated *GLS2* (glutaminase 2) increases reduced GSH levels to enhance cellular antioxidant defence [89]. Meanwhile, p53 exerts a pro-oxidant effect by upregulating PIGs (TP53-induced genes) such as *PIG1–13* under severe oxidative stress conditions. These PIGs facilitate ROS amplification through redox-cycling quinones and p67phox-mediated activation of the NOX2 complex [90–93]. PIGs and antioxidant genes induced by p53 have opposite roles, with the former promoting ROS accumulation and apoptosis under severe stress, while the latter reduce ROS and protect cells under mild stress [90, 91].

The antioxidant enzymes compose distinct redox systems against oxidative stress

The transcribed mRNA of these genes encodes the corresponding enzyme proteins that participate in multiple antioxidative reactions (Fig. 2). The GSH-associated system is critical in antioxidative defense and contains various redox enzymes. *GCLC* and *GCLM* encode the catalytic and regulatory subunits of GCL (glutamate-cysteine ligase), which synthesizes γ -Glu-Cys from glutamic acid and cysteine. γ -Glu-Cys is converted into GSH (glutathione) by GS (glutathione synthetase), encoded by the *GSS* gene [94]. The generated GSH can directly scavenge ROS through the reductive activity of its thiol group [95] or function as a cofactor of antioxidant enzymes to reduce peroxides. GSH primarily reduces H_2O_2 to H_2O through the enzymatic actions of GPXs (glutathione peroxidases) or PRDX6 (peroxiredoxin 6), the latter being the peroxiredoxin family member exhibiting GPx-like activity [96, 97]. GSTs (Glutathione S-transferases) catalyze the conjugation of GSH via its thiol group to electrophilic centers on diverse substrates, thereby enhancing the compounds' water solubility. This biochemical

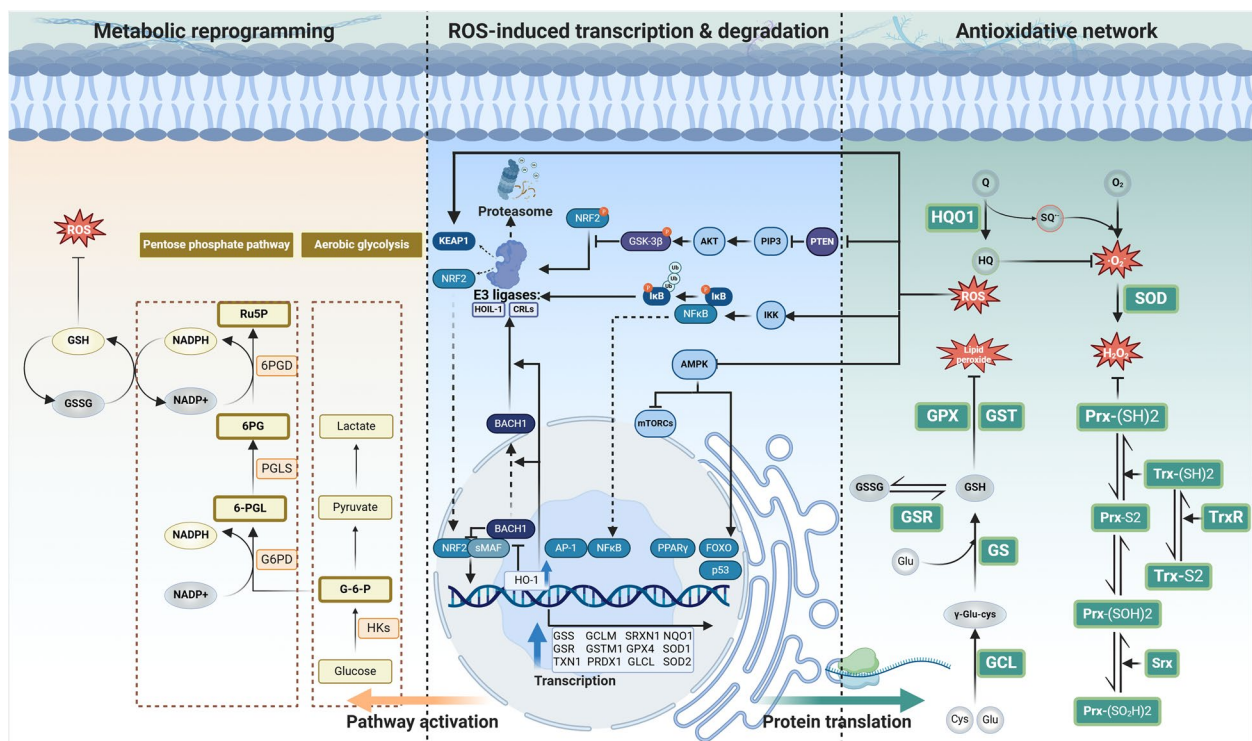


Fig. 2 Intercellular antioxidative network for ROS regulation. High ROS pressure triggers the translocation of transcription factors to initiate the expression of various antioxidant enzymes, which scavenge ROS when supplemented with antioxidants. Metabolic reprogramming is triggered to produce antioxidative substrates for ROS resistance. Arrows, inhibitory arrows, and dashed arrows represent activating or transforming, inhibitory effects, and translocation, respectively. The spherical symbols labeled 'P' and 'Ub' indicate phosphorylation and ubiquitination, respectively. The dual arrows indicate mutual transformations. ROS, reactive oxygen species. The figure was created using BioRender.com

mechanism facilitates the elimination of toxic endogenous compounds such as lipid peroxides [98, 99]. During the GSH-dependent reduction of peroxides, GSH is oxidized to its disulfide form (GSSG) [96, 97]. The GSR (glutathione-disulfide reductase), encoded by the *GSR* gene, can then reduce oxidized glutathione (GSSG) back to its reduced form (GSH) using electrons from NADPH (nicotinamide adenine dinucleotide phosphate), replenishing the cellular GSH pool [100]. Tumor cells exhibit the Warburg effect, indicating that they could undergo glycolysis under oxygen-rich conditions [101]. The Warburg effect triggers the PPP (pentose phosphate pathway) pathway for tumor cell nucleotide synthesis, and this process generates NADPH for GSH reduction and maintains redox homeostasis [85].

The Trx-Prx-Srx system is a hierarchically cooperative antioxidant network and is critical for peroxide elimination to maintain redox homeostasis. The Trx (thioredoxin) encoded by the gene *TXN1* is a key protein in the Trx system. It functions together with TrxR (thioredoxin reductase) to inhibit protein disulfide bond formation. TrxR can use NADPH as an electron donor to reduce Trx, thus restoring its ability to reduce oxidized proteins [102, 103]. Human Prx (peroxiredoxin) is encoded by gene *PRDX1* and possesses a conserved enzymatic cysteine known as the Cp (peroxidatic cysteine) at its N-terminus [104]. The Prx protein family catalyzes the reduction of H_2O_2 . During this catalytic cycle, the thiol group (-SH) of the Cp undergoes oxidation to form sulfenic acid (-SOH) [105]. The reduced Trx could transfer electrons to cytoplasmic Prx [106], facilitating the reduction of oxidized Prx. Srx (sulfiredoxin) is a unique enzyme for Prx reductive capability repair that reduces the sulfinic acid form of 2-Cys Prx [107]. Human Srx contains only a single cysteine residue, necessitating the involvement of external thiol (such as Trx or GSH) to regenerate its active site by reducing the thiosulfinate intermediate formed during catalysis [108]. The Srxs present functional convergence with Trx in regulating Prx redox homeostasis, for it reduces the hyperoxidized Prx, such as Prx-(SO₂H)₂, to Prx-(SOH)₂, which are further reduced by Trx [109], forming the Trx/Srx/Prx system to eliminate H_2O_2 .

NQO1 enzyme belongs to the NAD(P)H quinone oxidoreductase family and is activated by transcription factor NRF2 [80, 110]. It directly reduces quinones to hydroquinone and prevents the generation of SQ•⁻ (semiquinone radicals). SQ•⁻ can reduce oxygen to $O_2\bullet^-$, which can be eliminated by hydroquinone [111]. Some previously proposed viewpoints have classified $O_2\bullet^-$ as oncogenic and H_2O_2 as onco-suppressive ROS [112]. Varying the ratio of $O_2\bullet^-$ to H_2O_2 has been suggested to impact tumor progression. Although more convincing evidence is required to elucidate their precise roles in

the cancer process, this underscores the importance of regulating the $O_2\bullet^-$ -to- H_2O_2 ratio, representing a pivotal upstream factor in ROS dynamics to modify tumor fate. The SOD family is a critical antioxidant enzyme family that reduces the cytotoxic $O_2\bullet^-$ burden. SOD expression could be triggered by NF-κB [84]. This family includes three members with different subcellular locations: SOD1 and SOD2 are located in the cytoplasm and mitochondria, respectively, while SOD3 is secreted to the extracellular matrix. These SODs are efficient $O_2\bullet^-$ scavenger due to their capability to dismutate $O_2\bullet^-$ to H_2O_2 , which is then further eliminated by other enzymes as discussed above (Fig. 2) [82]. All the aforementioned antioxidant enzymes and substances constitute a complex regulatory network of the antioxidant response. Tumor cells utilize the antioxidant response to eliminate cytotoxic ROS and avoid ROS-induced cell injury and death.

The regulatory role of ROS and adaptive responses to oxidative stress in tumor cells

ROS elevation increases the risk of tumorigenesis and tumor cell growth

While causing macromolecule damage, ROS also functions as a critical mediator for tumor initiation and progression, and elevated ROS levels in tumors have been widely proven [113]. Genomic instability is commonly regarded as the main driving force of tumorigenesis and a major contributor of tumor heterogeneity [8]. Elevated ROS can cause direct DNA damage, disrupt replication and transcription, and impair the function of DNA repair enzymes. ROS can target nucleic acids to induce oxidized bases, such as 8-hydroxy-2'-deoxyguanosine (8-OH-dG) [114]. •OH directly damages DNA by oxidizing all four DNA bases [115]. These oxidized lesions impair polymerase activity. ROS-induced polymerase impairment as well as the DNA double-strand breaks both contribute to replication fork collapse [116]. Meanwhile, ROS promotes the dissociation of PRDX2 and TIMELESS protein, which also attenuates replication fork progression [117]. Besides, H_2O_2 extracts hydrogen atoms from deoxyribose, forming oxidized AP (apurinic/apyrimidinic) sites and DNA strand breaks [114]. ROS' DNA targeting can also induce DNA-protein crosslinks, potentially leading to chromosomal aberrations or breaks [118]. Current studies demonstrate that ROS can generate single- and double-strand DNA breaks in transcriptionally active regions, inducing R-loop formation and threatening genomic stability [119]. H_2O_2 induces significant ubiquitination of Rpb1, the largest subunit of RNA polymerase II. This process may depend on Ser-5 phosphorylation mediated by ERK1/2, consequently impairing transcriptional activity [120]. ROS also inhibits OGG1 (an 8-oxoG DNA glycosylase), blocking the initiation of

8-oxoG lesion repair [121]. These oxidized damages lead to genomic instability with increased risk of oncogenic mutations to promote cancer initiation and development [9, 122–124]. In the early stages of cancer, ROS can induce mutations in the proto-oncogene *RAS* and tumor suppressor gene *TP53*, thereby accelerating tumorigenesis [125]. Meanwhile, these mutations in oncogenes and tumor suppressor genes in tumor cells may alter metabolic signaling pathways, producing ROS accumulation [126–128]. For instance, the oncogenic mutation of *MYC* and *KRAS* can enhance glucose utilization and mitochondria-dependent macromolecule biosynthesis. This triggers the anaplerosis to supplement the substrates of the TCA cycle, which provides NADH to promote the mitochondrial electron transmission chain and ROS generation [128]. The inactivation of *TP53* can weaken the cell's antioxidative defense against ROS, further elevating the ROS burden. Additionally, *HIF-1* (hypoxia-inducible factor 1) can be activated under hypoxic conditions, regulating glycolysis and mitochondrial function, and thus affecting ROS generation and accumulation [127]. This may create a vicious cycle, maintaining relatively high ROS levels favorable for tumor progression.

The elevated ROS promotes the proliferation and survival of tumor cells (Fig. 3). ROS, a pivotal messenger, can activate the distinct signaling pathway via oxidation of specific amino acid residues, such as cysteine, in signaling proteins. H_2O_2 could oxidize the cysteine Cys215 in the catalytic domain of PTP1B (protein tyrosine phosphatase 1B), and the oxidized PTP1B promotes the clonal formation of hepatocellular carcinoma and epidermal cancer cells [129]. Moreover, the oxidized Cys215 in PTP1B has been found to cause significant conformational changes and block its substrate binding [130]. This might prevent the inhibition of the IRS-1-mediated PI3K/PDK1/AKT pathway and leptin-mediated JAK/STAT3, promoting cancer cell survival and proliferation [131, 132]. Similarly, H_2O_2 -oxidized PTPs also prevent the dephosphorylation of RTK (receptor tyrosine kinase) of EGFR (epidermal growth factor receptor) [133], activating EGFR-mediated signaling transduction. In addition to receptor activation, ROS can activate certain SFKs (src family kinases) and the subsequent ERKs (extracellular signal-regulated kinases) pathway [134–136]. Mechanistically, the redox-dependent SFKs activation is possibly triggered by ROS-mediated polymerization through S–S bond formation

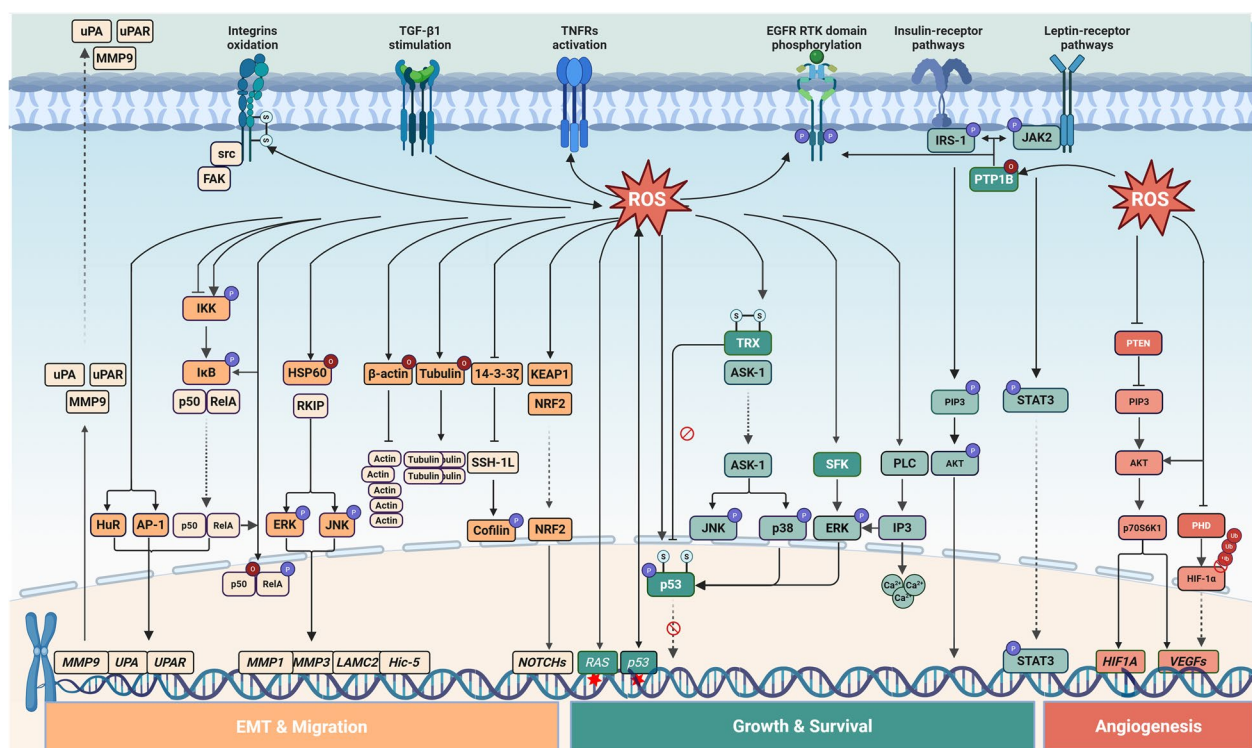


Fig. 3 Mechanical map of the role of ROS in affecting the malignant phenotypes of tumor cells. ROS exerts dual interactions with cell receptor activation and regulates the intracellular signaling pathways to control tumor cell EMT, migration, growth, survival, and angiogenesis. Arrows, inhibitory arrows, and dashed arrows represent activating, inhibitory effects, and translocation, respectively. The red forbidden symbol indicates blockage. The spherical symbols labeled 'P', 'O', 'Ub', and 'S' indicate phosphorylation, oxidation, ubiquitination, and thiol, respectively. Red star polygons indicate mutations. The figure was created with BioRender.com

or C-terminal cysteine oxidation [137]. Activation of the MAPK/ERK signaling pathway promotes cell proliferation and has an anti-apoptotic effect by influencing the activity of downstream cell cycle regulatory proteins and apoptosis-related proteins [138], and this process is facilitated by Trx-related ASK-1 regulation. ROS can directly activate the TNF (tumor necrosis factor) receptor and oxidize Trx, dissociating ASK-1 (apoptosis signal-regulating kinase 1) from Trx to phosphorylate and activate JNK (c-Jun NH₂-terminal kinases) and p38 pathways [134–136]. Besides, increased H₂O₂ levels were associated with PLC (phospholipase C)-gamma tyrosine phosphorylation, activating PLC-gamma-mediated intracellular Ca²⁺ release and activation of pathways like ERK [135, 139]. Elevated ROS in tumor cells inhibits cancer-suppressive PTEN (phosphatase and tensin homolog) and activates the Akt (protein kinase B). This mechanism involves the PI3K (phosphoinositide 3-kinase)/AKT signaling pathway to alleviate damage and promote tumor growth [140, 141]. ROS could oxidize p50 and phosphorylate RelA (also known as transcription factor p65) to affect their DNA-binding capabilities, resulting in highly complex effects [84]. ROS mediates the phosphorylation of p53 via various protein kinases, including p38α MAPK, ATM (ataxia-telangiectasia mutated protein), and ERKs. These processes disrupt two cysteine clusters within the DNA-binding domain of human p53 that are critical for the specific binding of p53 to its consensus sequence, thereby impairing p53's DNA-binding activity [91] and enhancing cell proliferation and survival [142, 143]. In summary, ROS has multiple upstream and downstream targets in these pathways. Their crosstalk might enable tumor cells to integrate the stress-adaptive pro-survival and pro-growth signals during tumor progression.

ROS contributes to tumor cell angiogenesis, EMT, and metastasis

Angiogenesis is a significant hallmark of cancers that supports their progression. In the TME, ROS induces the expression of VEGFs (vascular endothelial growth factors) to activate tumor angiogenesis [143]. Elevated levels of NOX-derived ROS in ovarian cancer cells activate the HIF-1α/VEGF pathway [144]. Similarly, mutant p53 promotes ROS accumulation and activates the HIF-1α/VEGF pathway to induce angiogenesis in HCT116 human colon carcinoma cells [145]. In ovarian cancer, H₂O₂ is also essential in the EGF-induced PI3K/AKT/p70S6K1 pathway activation, which induces VEGF mRNA expression through HIF-1α activation [146]. It also oxidizes the ferrous ion of PHD (prolyl hydroxylase) [137] to inhibit its catalytic activity, thus stabilizing HIF-1α [147], indicating the important role of H₂O₂ in angiogenesis. Meanwhile, ROS can also stabilize HIF proteins independent

of PHD, pVHL (von Hippel-Lindau protein), and p53 in kidney and liver cancer cells, but through neddylation of HIF-1α N-terminal site within amino acids 201 and 400 via NEDD8 [148]. However, increased angiogenesis was also observed in lung cancer cells after antioxidant treatment, for the reduced ROS increases BACH1 expression and promotes angiogenesis independent of HIF-1α, but rather in a BACH1-dependent manner [149].

Furthermore, elevated ROS can promote tumor metastasis. Tumor cell metastasis is a complex process that requires intracellular signaling and extracellular interactions. Tumor cell acquires the invasive capability through the EMT (epithelial-mesenchymal transition) process. EMT shifts tumor cells from epithelial-like to mesenchymal-like morphology and gene expression patterns [150] and interacts with redox homeostasis. TGF-β (transforming growth factor beta) is a classic EMT inducer [151]. TGF-β1 promotes the transcription of Notch4 and the activation of the Notch signaling pathway by activating the ROS/NRF2 pathway. The activated Notch signaling pathway then facilitates the development of EMT by directly activating the transcription of Snai1 [152]. In addition to NRF2/Notch axis, ROS also activates MAPK pathways to regulate tumor EMT [153–155]. The activated MAPK pathway increases the expression of transcription factors such as Snail and Slug, which play a crucial role in modulating the expression of genes associated with EMT, thereby facilitating the conversion of epithelial cells into mesenchymal cells [154].

The tumor cell with EMT could obtain various malignant features, including elevated integrin expression, enhanced cell motility, and increased extracellular degradation capability. The integrin family comprises transmembrane glycoproteins located on the cell membrane, consisting of α and β subunits. Multiple studies have demonstrated that integrins play a vital role in TGF-β-induced cancer cell EMT, migration, and invasion [156]. Recent studies have demonstrated that integrins could trigger the EMT-stimulating capability of both activated TGF-β1 and latent L-TGF-β1 [157, 158]. ROS has been found to upregulate the expression of integrins in TSCC (tongue squamous cell carcinoma), thus facilitating TSCC tumor cell EMT and metastasis [159]. Tumor cell motility relies on the dynamic remodeling of the cytoskeleton. ROS oxidizes cytoskeleton components β-actin and tubulin cysteine to slow actin polymerization and facilitate tubulin tetramer formation, respectively [160]. Meanwhile, high-level ROS alleviates 14-3-3ζ-induced inhibition of SSH-1L to enhance cytoskeletal extension, which includes cofilin phosphorylation and lamellipodia formation [160], increasing cytoskeleton remodeling. Moreover, increased expression of proteases enables tumor cells to degrade the extracellular matrix. The NOX-derived

ROS could oxidize the cysteine of HSP60, the oxidized HSP60 could trigger the release of RKIP and subsequent ERK-JNK phosphorylation, activating the MAPK pathway and migration of hepatocellular carcinoma via MMP1, MMP3, LAMC2, and Hic-5 expression [161]. ROS also promotes HuR (human antigen R), NF- κ B, and AP-1 nucleus translocation to increase uPA (urokinase-type plasminogen activator) and uPAR (urokinase-type plasminogen activator receptor) expression, degrading extracellular matrix to facilitate tumor cell metastases. Additionally, ROS-induced NF- κ B [162], HIF-1 α , and TGF- β [163, 164] pathways increased uPA and MMP-9 for extracellular matrix reshaping, affecting the integrity of intercellular connections in tumor cells and activating the PI3K/AKT pathway to promote tumor cell mobility [165, 166]. However, some studies have demonstrated that elevated ROS levels can trigger TP53 activity to inhibit melanoma and glioma cell metastasis by altering the expression of metastasis-related genes such as *MMP2*, *MMP9*, and *TWIST* [167, 168].

Moreover, antioxidants may promote tumor metastasis under certain circumstances, primarily by affecting the interaction between NRF2 and BACH1. Antioxidants such as vitamin C, vitamin E, and NAC (N-acetylcysteine) can alleviate oxidative stress by scavenging ROS within cells. However, this process may lead to a decrease in NRF2 activation, subsequently impacting BACH1 degradation and increasing BACH1 stability. Furthermore, BACH1 activates the transcription of HK2 (Hexokinase 2) and GAPDH (glyceraldehyde-3-phosphate dehydrogenase), enhancing glucose uptake, glycolytic flux, and lactate secretion, thereby promoting lung cancer metastasis through a glycolysis-dependent pathway [169–171]. This accumulating evidence implies that the role of ROS in tumor metastasis is contingent on pathophysiological conditions. ROS can also regulate metastasis by affecting the intercellular crosstalk in the TME [172, 173], which is further elaborated in the next section.

Oxidative stress in tumor cell death and therapeutic resistance

Excessive ROS in tumor cells can cause DNA damage, lipid peroxidation, mitochondrial protein damage, and induce cell death [174]. For instance, GLS2 increases the generation of lipid ROS by converting glutamine to α -ketoglutarate, thereby inducing ferroptosis in hepatoma cells [175]. H_2O_2 treatment in prostate cancer cells activates TRPM2-Ca²⁺-CaMKII-mediated autophagy inhibition, leading to cell death [176]. However, apatinib-induced ROS/NRF2/p62 pathway could also trigger autophagy and apoptosis in lung cancer cells [177]. Similarly, quercetin 3-o- β -d-galactopyranoside

induces apoptosis in breast cancer cells by triggering the ROS-mediated NF- κ B signaling pathway [178]. These demonstrate that ROS is a critical mediator involved in drug-induced cytotoxic burden. ROS-targeting has been developed as a promising strategy to cause cell death, which will be discussed in detail in the subsequent section.

Tumor cells can counteract high ROS levels under oxidative stress with enhanced antioxidant synthesis or antioxidant enzyme expression [113], enabling tumor cell resistance to ROS-associated chemotherapy. Gastric cancer cells adopt PRDX2 (peroxiredoxin 2) to eliminate ROS and avoid apoptosis, acquiring resistance to cisplatin chemotherapy [179]. Also, overexpressed ROS-scavenger aldehyde dehydrogenase was observed in crizotinib-tolerant gastric cancer cells and was further shown to promote chemotherapeutic resistance in lung, breast, and colon cancer cells [180]. Recent studies have revealed that MFSD12 (major facilitator superfamily domain containing 12) is overexpressed in various cancers and promotes cystine storage in lysosomes, which can effectively buffer GSH depletion and tumor cell damage, leading to chemotherapy resistance in patients with breast cancer [181]. DDRGK1 (DDRGK domain-containing protein 1) [182] and iASPP (inhibitor of Apoptosis Stimulating Protein of p53) [183] can directly competitively bind to KEAP1, inhibiting the ubiquitin–proteasome-mediated degradation of NRF2 to resist ROS, promote cell growth, and inhibit chemotherapy-induced apoptosis. Furthermore, high ROS concentrations can activate the Aryl hydrocarbon receptor, allowing it to bind to PPP1R3C via sulfenylation, thereby enhancing glycogenolysis, PPP, and subsequent NADPH generation to achieve chemotherapy resistance [184]. These studies indicate that tumor cells possess various mechanisms to maintain redox homeostasis under chemotherapy-induced high ROS pressure, strengthening their therapeutic resistance capabilities.

Radiotherapy is also a critical therapeutic approach for many malignant cancers, and increasing evidence suggests that ionizing radiation exerts its antitumor effects by inducing the production of ROS, triggering cell death, such as lipid peroxidation-mediated ferroptosis [185] and immunogenic cell death [186] beyond the DNA damage effects. However, cancer cells have evolved adaptive mechanisms to counteract ROS damage, leading to resistance to radiotherapy. GBM (Glioblastoma) is the most common primary malignant tumor in the central nervous system. However, due to the therapeutic resistance mediated by GSCs (glioma stem cells), the standard non-surgical treatments such as radiotherapy and chemotherapy provide limited benefits [187]. Experiments have shown that the anti-proliferative protein PHB(prohibitin) is upregulated

in GSCs, and it binds to the mitochondria-specific PRDX3 (peroxidase peroxiredoxin 3), stabilizing the PRDX3 protein through the ubiquitin–proteasome pathway [187]. PRDX3 then reduces peroxide levels and protects cells from oxidative damage. Therefore, upregulated PHB in GSCs protects them from ionizing radiation-induced oxidative damage and promotes GBM radiotherapeutic resistance through PRDX3-mediated ROS scavenging [187]. Radiotherapy is also critical in hepatocellular carcinoma control, but dysregulation of the redox system can lead to radioresistance. The radiotherapeutic resistance of hepatocellular carcinoma cells could be enhanced by NUPR1 (nuclear protein 1) expression [188]. The interaction between NUPR1 and AhR (aryl hydrocarbon receptor) has been found to facilitate the degradation of AhR. This reduces AhR nuclear translocation via the autophagy-lysosome pathway, thereby attenuating CYPs-mediated ROS generation and promoting radioresistance in HCC (hepatocellular carcinoma) [188]. Additionally, radioresistance is a major obstacle to advanced head and neck squamous cell carcinoma treatment. Studies have shown that UBE2C (ubiquitin-conjugating enzyme E2C) may

be related to radioresistance, potentially regulating radioresistance through ROS signaling [189]. However, the mechanisms of UBE2C-mediated radioresistance remain unclear and warrant further experimental investigation [189]. In NSCLC (non-small cell lung cancer), microRNA-139 (miR-139) was found to be a novel radiosensitizer that functions by inhibiting NRF2 signaling [185]. In summary, tumor cells can utilize multiple pathways to reduce ROS burden and thus facilitate radiotherapy resistance. Sensitizing tumor cells to ROS damage is of great significance for overcoming radiotherapy resistance.

The above evidence implies that tumor cells harbor complex crosstalk between ROS and oncogenic signaling pathways, and this contributes to the tumor progression under a favorable ROS-rich condition. Notably, tumor cells also develop an adaptive antioxidant network to defend against cytotoxic ROS damage from either rapid cell metabolism or ROS-inducing therapies.

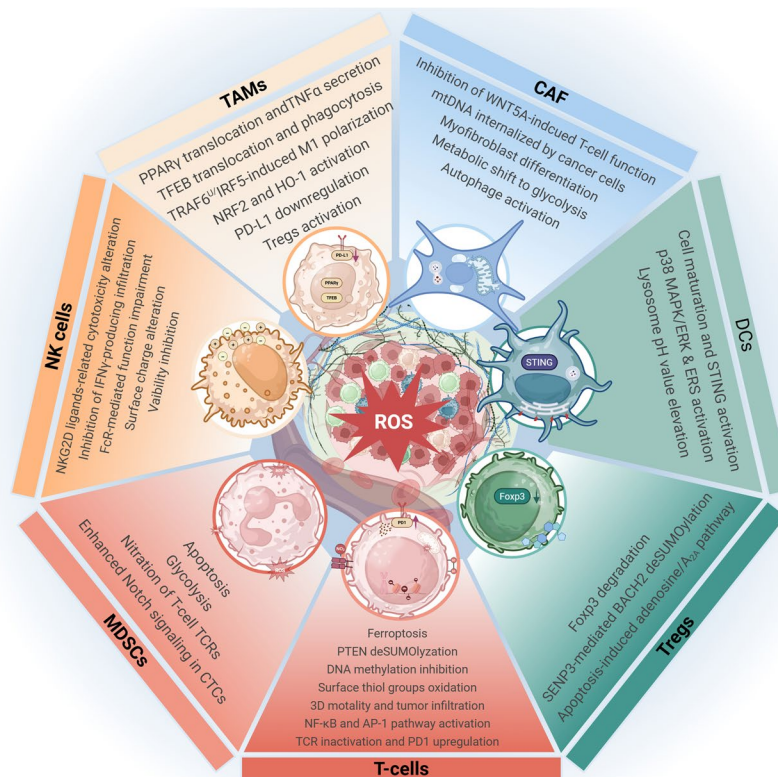


Fig. 4 The graphical summary of the effects of ROS on TME cells. ROS generated in the TME exerts multiple roles in regulating DCs, T-cells, Tregs, MDSCs, NK cells, TAMs, and CAFs to affect TME immunosuppression. ROS, reactive oxygen species. TME, tumor microenvironment. DCs, dendritic cells. Treg, regulatory T-cells. MDSCs, myeloid-derived suppressor cells. NK cells, natural killer cells. CAFs, cancer-associated fibroblasts. The figure was created using BioRender.com

The effects of ROS and adaptive responses to oxidative stress on the TME

In addition to tumor cell regulation, ROS and adaptive responses to oxidative stress play an important role in the interaction between tumor cells and their microenvironment, significantly contributing to tumor progression (Fig. 4) [190].

Oxidative stress is involved in immunosuppressive cell regulation

Immunosuppression is a critical hallmark in cancers [191]. The main cell components that contribute to TME immunosuppression include CAFs, MDSCs, TAMs, and Treg (regulatory T-cells) [192–194], which were highly plastic during cancer progression and could be recruited in the TME through abnormal ROS levels, causing immunosuppressive phenotype shift of tumors.

CAFs are a phenotypically and functionally heterogeneous population of mesenchymal cells highly engaged in intercellular crosstalk in the TME. They could remodel the ECM (extracellular matrix) to promote tumor growth, angiogenesis, metastasis, invasion, and even therapeutic resistance, and their pro-tumor effects are highly associated with ROS regulation. CAFs exhibit a myofibroblast-like phenotype and constitute critical stromal components of aggressive tumors. JunD-deficiency-derived ROS elevation enhances HIF-1 α accumulation and stimulates the CXCL12/CXCR4 pathway, which activates RhoA-GTPase to promote myofibroblast differentiation in TME, facilitating tumor metastasis [195]. A recent study discovered that MAOA (monoamine oxidase A) in stromal cells promotes their myCAF conversion, and MAOA inhibition prevented intracellular ROS accumulation, boosting WNT5A secretion to enhance the Ca²⁺-NFATC1 pathway in CD8+ T-cells, thus suppressing prostate cancer growth. However, the mechanism of ROS-mediated WNT5A secretion remains unclear [196]. Besides, the ROS generated by tumor cells can enhance the autophagy of CAFs, providing various nutrients for tumor cells [197]. ROS can also promote mitophagy and the release of mtDNA (mitochondrial DNA) from CAFs, and the mtDNA could be internalized by lung and breast cancer cells to promote their survival and metastasis [197]. Meanwhile, CAFs also affect tumor cell redox homeostasis. CAFs-secreted metalloproteases can trigger the Rac1b/COX-2-mediated ROS release in tumor cells, leading to tumor cell EMT and stem cell characteristics acquisition [198]. In addition, CAFs can reduce lipid-ROS accumulation in gastric and prostate cancer cells via exosomes, allowing them to acquire chemotherapy resistance characteristics [199]. This suggests that tumor cells can reduce ROS burden by relying

not only on their own antioxidant system but also on the involvement of non-tumor cell crosstalk.

MDSCs are a group of immunosuppressive myeloid cells. It is a precursor to DCs (dendritic cells), macrophages, and/or granulocytes, significantly suppressing immune cell function [200, 201]. Pathological expansion of MDSCs can trigger activation of the JAK/STAT3 (janus kinase/signal transducers and activators of transcription 3) pathway and NOXs, increasing ROS generation [201]. Accumulated ROS was also observed in human NSCLC MDSCs with downregulated LAL (Lysosomal acid lipase). LAL deficiency increased MDSC glycolysis and doubled ROS levels compared to those in LAL+/+ MDSCs [202]. ROS overload has been reported to contribute to MDSC apoptosis. The deficiency of NRF2 could increase ROS levels and sensitize the tumor-circulating or bone marrow MDSCs to apoptosis [203]. However, ROS-induced glycolysis in MDSCs appears to function as a feedback brake that curbs excessive ROS accumulation, thereby suppressing apoptosis. Glycolytic intermediates such as phosphoenolpyruvate possess antioxidative properties that mitigate excessive ROS generation. By sustaining optimal ROS levels, MDSCs are shielded from ROS-induced apoptosis, thereby promoting their expansion and accumulation in tumors [204]. Nonetheless, ONOO⁻ produced by MDSCs can nitrate TCRs on T cells, thereby modifying their peptide-binding specificity and resulting in a diminished responsiveness to antigen-specific stimulation [201, 205]. The ROS produced by MDSCs can also promote the proliferation and metastasis of CTCs (circulating tumor cells) via the NRF2/Notch1/Nodal signaling pathway. Specifically, the increased ROS produced by PMN-MDSCs upregulates Notch1 in CTCs through the ROS-NRF2-ARE axis, enabling CTCs to respond to ligand (Jagged1)-mediated and PMN-MDSC-driven Notch activation [206]. In summary, the MDSC-derived ROS signal is critical in promoting tumor cell metastasis and T-cell immunosuppression, contributing to tumor progression. Instead, inhibiting ROS generation can reduce the immunosuppressive effects of MDSCs in vitro [201, 205] and restore the proliferation of CD8+ T-cells [207].

TAMs are infiltrating macrophages in tumor tissues, mainly differentiated from monocytes. Extrinsic induction of ROS overload could promote the pro-inflammatory conversion of TAM. ROS elevation forced by a Cu_{2-x}Se nanoparticle could induce the ubiquitination-mediated TRAF6 degradation, and this triggered IRF5-mediated increase of CD80 and CD86 and suppression of CD206 and Arg1 expression, converting TMA from TM2-like to M1-like phenotype [208]. Vinblastine was reported to reset TAM towards the M1 phenotype. Vinblastine activated phosphorylated NF- κ B and

p22^{phox} protein, and the activated p22^{phox}-NOX2 complexes induced ROS generation, probably triggering ROS-dependent nuclear transcription factor EB (TFEB) nuclear translocation with enhanced phagocytic capacity [209]. However, the ROS-rich TME has been widely observed with few M1 macrophage infiltrations. The mechanism to explain the decreased M1 macrophages in ROS-rich TME might be attributed to the activated antioxidative response. The upregulated antioxidant gene expressions, including NRF2 and HO-1, are associated with attenuated M1 and enhanced M2 polarization macrophages in colorectal cancer [210]. Given the role of HO-1/BACH1/NRF2 axis in antioxidant response (Fig. 2), the upregulated NRF2 and HO-1 might limit macrophage ROS generation to reach pro-inflammatory levels, blocking M1 phenotype conversion. Besides, the ROS changes in tumor cells contribute to the TAM-mediated immunosuppression in TME. ROS can recruit TAMs into tumor tissues and enhance their M2 polarization [24–26]. Recent studies have indicated that eliminating ROS in ovarian cancer cells promotes the secretion of exosome-derived miR-155-5p, and this downregulates PD-L1 (programmed death-ligand 1) expression in macrophages [211]. Also, ROS can enhance TAM PPAR γ nuclear translocation to induce TNF- α release, thereby promoting tumor cell invasion [212]. Meanwhile, macrophage-induced Treg cell is ROS-dependent [27].

In Treg cells, ROS regulate transcription factor activities to affect their immune functions. transcriptional repressor SENP3 (SUMO1/sentrin/SMT3 specific peptidase 3) has been found to positively regulate their suppressive functions. ROS stabilizes SENP3 in Treg cells, thereby triggering BACH2 deSUMOylation. This mechanism modulates the nuclear localization and transcriptional activity of BACH2, ultimately maintaining the stability and suppressive functions of Treg cells [213]. ROS was also involved in TMED4-mediated Treg stability. TMED4 deficiency triggered HRD1/BIP-mediated ERAD (ER-associated degradation) of IRE1 α , XBP1 level reduction, and NRF2 inhibition, leading to ROS accumulation. The increased ROS then decreased Foxp3 stability and attenuated Treg suppressive function with boosted anti-tumor immunity in TME [214]. Besides, in the TME, Tregs can secrete large amounts of antioxidants such as Trx, making Tregs less susceptible to ROS-induced apoptosis [215]. However, Treg cells can undergo apoptosis in an excessively high-ROS environment, reducing the efficacy of PD-L1 blockade and producing excessive adenosine, thereby promoting A_{2A}-pathway-mediated immunosuppression [216]. These findings suggest that ROS plays critical roles in TMA-associated immunosuppression and malignant transformation.

Oxidative stress affects the functions of anti-tumor immunocytes

Apart from pro-tumor immunosuppressive cells, multiple anti-tumor immunocytes in the TME rely on a specific ROS level to maintain their anti-tumor immune functions. Importantly, ROS plays a vital role in T-cell activation. T-cell activation is triggered by mitochondria-derived ROS [217]. Transient generation of a physiological level of ROS is indispensable for T-cell activation via ROS-dependent NF- κ B- and AP-1-related pathways [21]. Meanwhile, a sustained mitochondrial ROS level is required for CD8⁺ T-cells' 3D motility and infiltration into lung cancers [22]. CD8⁺ T-cells can sense ROS levels via SENP7 (SUMO-specific protease 7). ROS-triggered SENP7 in the cytoplasm can deSUMOylate PTEN protein to promote its degradation, thereby maintaining its metabolic state and anti-tumor function [218]. These discoveries suggest that a physiological ROS level is required to maintain T-cell anti-cancer immunological functions. Meanwhile, it has been found in mice that blocking the generation of extracellular superoxide does not impair T-cell proliferation or other functions [219]. However, the abnormal ROS elevation in the TME can affect the anti-cancer function of T-cells [220]. The increased ROS via primary bile acids accumulation can lead to CD8⁺ T-cell death [23]. Elevated ROS also promotes T-cell ferroptosis with increased ferrous uptake through the CD36-mediated p38-CEBPB-TfR1 axis [221]. The ferroptosis of CD8⁺ T-cells could be prevented by lipid ROS elimination via adenosine A_{2A} receptor and GPX4 crosstalk [222]. When Treg cells contact CD8⁺ T-cells, they can release NOX2-containing microvesicles, increasing ROS levels and inhibiting CD8⁺ T-cell TCR activation [223]. ROS can also affect the redox status on T-cell surfaces, oxidize the cell surface thiol groups to S–S groups, thereby threatening T-cell survival, which is demonstrated in breast, colorectal cancer, and melanoma [224]. In renal cell carcinoma, CD8⁺ tumor-infiltrating lymphocytes have been found to produce increased ROS due to mitochondrial polarization and fragmentation, which decrease total DNA methylation and lead to activation defects that inhibit their anti-tumor functions [225]. In melanoma, TAMs-derived H₂O₂ reduces the activity of T-cells and NK (natural killer) cells [26]. Moreover, H₂O₂-treated microglia induce PD-1 (programmed cell death protein 1) expression in CD8⁺ T-cells [226], thereby promoting T cell functional inhibition and GBM progression. Since tumor-derived ROS also upregulate TAM PD-L1 expression [227], these results suggest that elevated ROS levels exhibit complex crosstalk with PD-1/PD-L-mediated immunosuppression in TME, escaping tumor

cells from immune attack. This might be another reason, in addition to immunogenic death, to explain why oxidative-stress-damage-based nano-acoustic dynamic intervention could achieve positive results when combined with anti-PD-L1 immunotherapy [228]. Nevertheless, the specific role of ROS in T-cell activities was context-dependent and warrants wider validation to confirm its significance to immunotherapy in different cancers.

In NK cells, the elevated ROS in TME could change their surface charge to anionic, and this prevents their adhesion to target tumor cells [229]. Meanwhile, the MDSC-derived NO impaired the FcR-mediated functions of NK cells, which include antibody-dependent cellular cytotoxicity, cytokine release, and signal transduction, thereby attenuating monoclonal antibodies therapeutic efficacy [230]. Similarly, Galectin-3-induced ROS increase derived from neutrophils could decrease NK cell viability and promote high-grade serous carcinoma progression [231]. In melanoma, NOX2 knockout or inhibitor could increase the IFN γ -producing NK cell infiltration into lungs with reduced melanoma metastasis [232]. As previously discussed, GSK-3 β could promote NRF2 phosphorylation and ubiquitin-dependent degradation (Fig. 2). The inhibition of GSK-3 β has been identified to increase breast cancer cell mitochondrial ROS, and this process decreases NKG2D ligands expression and suppresses NK cell function [233]. However, elevated NKG2D ligand expressions as well as increased susceptibility to NK cells were found to be probably induced by SFN- or IR-mediated ROS elevation in both breast and lung cancer cells [234], demonstrating the complex interaction between ROS and NK cell functioning.

ROS also contributes to DC cell activities. A Mn-LDH nanoparticle was designed to deplete the intracellular GSH in DCs, and increased ROS promoted DC maturation through activation of PI3K/AKT, NF- κ B, and STING (stimulator of interferon genes) pathways with the presence of Mn²⁺ [235]. Similarly, ROS in mouse DCs can promote SENP3 accumulation and deSUMOylate IFI204 (interferon-inducible protein), thereby activating their STING signaling and initiating anti-tumor immune responses [236]. ROS also activates p38 MAPK/ERK pathways and ERS (endoplasmic reticulum stress) to enhance DC maturation and increase lysosomal pH to maintain antigen conservation for antigen cross-presentation [237], thereby facilitating T-cell activation.

Antioxidative treatment to control cancer progression via ROS scavenging

Given that ROS plays a significant role in tumorigenesis and progression, applying antioxidants to prevent cancer is appealing [238]. Nevertheless, the cancer-preventive or

therapeutic potential of antioxidants remains controversial due to conflicting research outcomes. Though some studies suggest the anti-cancer roles, other research has presented the pro-cancer risk, such as tumor metastasis [239]. Furthermore, their role in chemotherapy remains controversial [240–242]. These discrepancies may stem from various factors, including variability in antioxidant types, dosage regimens, intracellular concentrations, experimental designs, and differential molecular mechanisms across biological systems. We summarize the current experimental evidence and clinical attempts to control tumors using different antioxidant strategies and better understand the involvement of oxidative stress in cancer prevention (Fig. 5).

Targeting cancers through non-enzymatic antioxidants

Non-enzymatic antioxidants have shown some potential in cancer treatment by influencing oxidative stress levels and regulating the redox homeostasis within cells. Current non-enzymatic antioxidants applied in cancers include vitamins, carotenoids, polyphenols, pyrazolinones, GSH, and benzoquinone derivatives, with distinct antioxidative activities determined by their chemical structures.

Ascorbic acid (vitamin C), an essential water-soluble vitamin, exists in three forms in vivo: reduced form (ascorbic acid, ASA), the radical intermediate (ascorbyl radical), and the oxidized form (dehydroascorbic acid) (Table 1) [243]. ASA directly neutralizes various ROS, converting itself into stable ascorbyl radicals that can be converted back to ASA via enzymatic processes involving NADH/NADPH-dependent reductases [244]. Low ASA concentrations exhibit antioxidant effects, while high concentrations paradoxically promote oxidative stress. High ASA concentrations can be catalyzed by ferric ions (Fe³⁺) and cupric ions (Cu²⁺) into ascorbic acid-free radicals and ROS [245], increasing intracellular ROS levels and causing cancer cell damage [246–249]. Intravenous administration of vitamin C produces plasma concentrations hundreds of times higher than those produced by the maximum tolerated dose (MTD) of oral administration of vitamin C [247]. A pharmacokinetic study of intravenous vitamin C in 21 healthy volunteers and 12 cancer patients showed that vitamin C exhibited first-order kinetics at doses ≤ 75 g. At doses up to 100 g, it was primarily excreted renally within 24 h, with 99% clearance in healthy subjects and 89% in cancer patients [250] (NCT01833351). This trial and many others have shown that high doses of intravenous vitamin C (at millimolar levels) have an excellent safety profile [250, 251]. Other clinical studies have also demonstrated the safety of intravenous vitamin C when used as monotherapy or in combination with chemotherapy drugs [251–255].

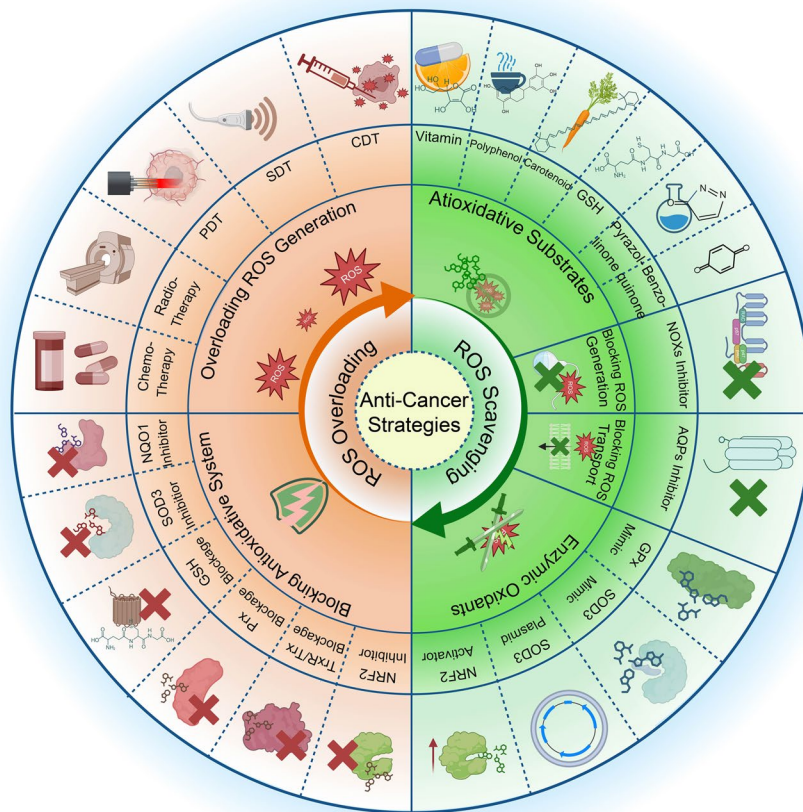


Fig. 5 Summary of oxidative stress-based strategies for cancer therapy. Current therapeutic strategies to control ROS can be divided into ROS overloading and scavenging approaches. The ROS-scavenging approach includes the addition of antioxidative substrates, enzymatic oxidants, and blockage of ROS generation. In contrast, the ROS overloading approach involves intracellular antioxidative system blockage and ROS overloading. ROS, reactive oxygen species. PDT, photodynamic therapy. SDT, sonodynamic therapy. CDT, chemodynamic therapy. The figure was created using BioRender.com

In Chen, Q et al.'s report, they evaluated the efficacy of ascorbic acid using mouse models of ovarian cancer, pancreatic cancer, and GBM xenografts. Ascorbic acid was found to reduce tumor growth and improve prognosis significantly with pharmacological concentrations of vitamin C achieved through intravenous administration [256]. The peak concentration reached by single dose administration is more than 30 mM, which is a similar plasma concentration easily achieved when human intravenous vitamin C is injected. In vitro experiments showed that its Effective Concentration 50 (EC₅₀) value on tumor cells is usually less than 10 mM, demonstrating a high potency of ascorbic acid [256]. Intravenous vitamin C administration also benefits electrothermic therapy in lung cancer patients. In a randomized Phase II clinical trial for patients with non-small cell lung cancer by Junwen Ou et al., one group ($n=49$) received intravenous vitamin C combined with modulated

electrothermic therapy plus best supportive care (BSC), and the other group ($n=48$) received BSC alone. After three months of treatment, the disease control rate in the combination treatment group was 42.9%, compared to 16.7% in the control group [257], suggesting a positive result. For more evidence, other phase II clinical trials are underway (NCT02905578 and NCT04033107). However, a double-blind, controlled study conducted by the Mayo Clinic failed to produce positive results for oral ascorbic acid administration [258]. This study used oral vitamin C in 150 patients with advanced cancers, including colorectal cancer, stomach cancer, lung cancer, breast cancer, and pancreatic cancer. All patients were divided into two groups, with one group receiving vitamin C (10 g per day) and the other group receiving a lactose placebo [258]. The results do not suggest a benefit of oral vitamin C therapy [258], likely due to its inability to achieve pharmacologically effective plasma concentrations.

Table 1 The ROS scavenging strategies in cancer control

Categories	Drug names	Mechanism	ROS	Effects	Tumors	References
Vitamins	Ascorbic Acid (Oral vitamin C, low concentration)	ROS neutralization, antioxidant activation, and antioxidant gene expression upregulation	Decrease	No impact	Colorectal cancer, stomach cancer, lung cancer, breast cancer, and pancreatic cancer	[258]
					Lung cancer, liver cancer	[259]
					Breast cancer	[260]
					Lung cancer	[149]
	Ascorbic Acid (Intravenous Vitamin C, high concentration)	Metal-catalyzed free radical generation	Increase	Anti-tumor	Mouse liver cancer, human bladder cancer, prostate cancer, breast cancer, liver cancer, endometrial adenocarcinoma	[261]
					Mouse ovarian cancer, pancreatic cancer, glioblastoma	[256]
					Human lymphoma, breast cancer, lung cancer, kidney cancer; mouse lung cancer, kidney cancer, colon cancer, melanoma	[262]
					Prostate cancer	[252]
					Pancreatic cancer	[254, 255, 263] NCT02905578
					Bladder cancer	NCT04046094
					Melanoma	[264]
					Multiple myeloma	[265]
Carotenoids	Vitamins A	Antioxidant gene expression upregulation, ROS neutralization	Decrease	No benefit	Lung cancer	[266]
					Non-melanoma skin cancer	[267]
					Breast cancer	[268]
					Head and neck cancer, lung cancer	[269]
	Vitamins E	ROS neutralization	Decrease	Pro-tumor	Lung Cancer	[270]
					Bladder, Breast, Colorectal, Esophagus, Lung, Oral and Pharynx, Ovarian, Pancreatic, Prostate, And Kidney Cancer	[271]
					Prostate Cancer	[272]
					Breast cancer	[273]
					nervous system, breast, and gastrointestinal cancers	[274]
					lung cancer and late age-related macular degeneration	[275]
Carotenoids	Asaxanthin	Electron donation for free radical neutralization	Decrease	Anti-tumor	breast cancer	[276]
	Lutein	ROS neutralization	Decrease	Anti-tumor	Prostate, gastric, colorectal cancer	[277–279]
Carotenoids	Lycopene	ROS neutralization	Decrease	Anti-tumor		

Table 1 (continued)

Categories	Drug names	Mechanism	ROS	Effects	Tumors	References
Polyphenols	EGCG	ROS neutralization, ROS-producing enzyme inhibition, metal ions chelation, and NRF2 activation	Decrease	Anti-tumor	Pancreatic Cancer	[280]
			Decrease	Anti-tumor	Lung cancer	[281, 282]
					Fibrosarcoma	[283–285]
	Hesperidin				Lung cancer	[286]
	Naringenin				Lung cancer	[287]
	Luteolin				Bladder cancer	[288]
					Colon cancer	[289]
					Lung cancer	[290]
	Apigenin				B-cell lymphoma	[291]
	Anthocyanins	Labile aroxyl radical formation, NOX activation, mitochondria destruction, GSH depletion	Increase	Anti-tumor	B cell chronic lymphocytic leukaemia	[292]
	Emodin				Colon cancer	[293]
	Gingerol				Lung cancer	[294]
	Isoliquiritigenin				Human glioblastoma	[295]
	EGCG				Cervical cancer	[296]
	Hesperetin				Colon cancer	[297]
	Quercetin				Breast cancer	[298]
					Colon cancer	[299]
					Liver cancer	[300]
					Breast cancer	[301]
					Cervical cancer	[302]
	Isoflavone daidzein				Bcr-Ab(+) chronic myeloid leukemia	[303]
	7,3',4'-trihydroxyisoflavone				Ovarian cancer	[304]
	Chlorogenic acid				Prostate cancer	[305]
	Oligomeric proanthocyanidins				Colon cancer	[306]
	Hydroxychavicol				Prostate cancer	[307]
	Curcumin				Colon cancer	[308]
	Hydroxytyrosol				Lymphoma	[309]
	Resveratrol				Lung cancer	[310, 311]
	NAC	GSH generation	Decrease	Anti-tumor	Triple-negative breast cancer	[312]
				Pro-tumor	Lung cancer	[270]
Benzoquinones					Melanoma	[313]
	MitoQ	Mitochondria targeting	Decrease	Anti-tumor	Breast and pancreatic cancer	[314]
			Decrease	No benefit	Melanoma and lung cancer	[315]
	SkQ1		Decrease	Anti-tumor	Fibrosarcoma and rhabdomyosarcoma	[316]
			NA	No benefit	Pancreatic cancer	[317]

Table 1 (continued)

Categories	Drug names	Mechanism	ROS	Effects	Tumors	References
NOX family Inhibitors	DPI	FAD complexation	Decrease	Anti-tumor	Epithelial ovarian cancer	[318]
					Colon cancer	[319]
SOD Mimics	GKT136901/GKT137831	NOX1,2,4,5 Inhibitor	Decrease	Anti-tumor	Mouse melanoma, Lewis lung cancer	[320]
		Unclear	Increase	Anti-tumor	Acute myeloid leukemia	[321]
	MnP	H ₂ O ₂ generation	Decrease	Anti-tumor	Breast cancer	[322]
					Clear-cell renal carcinoma	[323]
NRF2 Activators	NDGA	ROS-damaged phenylalanine scavenging	Decrease	NA	Glioblastoma	[324]
		GPx and GR activity improvement	Decrease	Anti-tumor	Skin cancer	[325]
	Enzastaurin	GSK-3 phosphorylation inhibition	NA	Anti-tumor	Colon cancer and glioblastoma	[326]
	Poly-Nitroxide Albumin	H ₂ O ₂ generation	Decrease	Anti-tumor	Triple negative breast cancer	[327]
	Omaveloxolone (RTA 408)	KEAP1-binding-mediated NRF2 stabilization	Decrease	Anti-tumor	Squamous cell carcinomas	[328]
	DMF	Alkylation of KEAP1 cysteine residues and nuclear export of BACH1	Decrease	Anti-tumor	Pancreatic carcinoma	[329]
AQP3 Inhibitors	Auphen-derived organogold compounds	H ₂ O ₂ influx reduction, intracellular ROS accumulation	Decrease	Anti-tumor	Primary effusion lymphoma	[330]
					Melanoma	[331]
AQP7 Inhibitors	Z433927330	Endofacial AQP7 binding	Decrease	Anti-tumor	Acute promyelocytic leukemia	[332]
AQP1 Inhibitors	AqB011	Intracellular loop D of AQP1 binding	Decrease	Anti-tumor	Colon cancer	[333]
	bacopaside II	Cell cycle arrest and apoptosis induction	Decrease	Anti-tumor	Colon cancer	[334]

ROS reactive oxygen species, EGCG epigallocatechin gallate, NRF2 nuclear factor erythroid 2-related factor 2, KEAP1 Kelch-like ECH-associated protein 1, NOX NADPH-oxidase, GSH glutathione, NAC N-acetylcysteine, DPI diphenyleneiodonium, FAD flavin adenine dinucleotide, MnP Mn porphyrin, SOD superoxide dismutase, NDGA nordihydroguaiaric acid, DMF dimethyl fumarate, AQP aquaporin

Vitamin A is enzymatically converted from plant-based provitamin A carotenoids and animal-derived preformed vitamin A. Recent research suggests that preformed vitamin A exhibits direct antioxidant activity [335]. Its metabolite ATRA (all-trans retinoic acid) can activate gene expression, including *TRX* and *GCLC*, after binding to nuclear receptors, thereby influencing the Trx antioxidant system and GSH production [335]. Vitamin E can scavenge lipid peroxyl radicals, resulting in the formation of lipid hydroperoxides and vitamin E radicals. Vitamin E plays a role in protecting PUFAs in cell membranes. An animal study conducted by Pierpaoli et al. revealed that administering 100 mg/kg of annatto-T3 to HER-2/neu transgenic mice resulted in a delayed onset of mammary tumors, a reduction in both the number and volume of these tumors, and a decrease in the size of lung metastases [273]. Although the mechanisms of vitamins A and E are clarified, clinical investigations regarding the association between these vitamins and cancer occurrence are inconsistent [242, 267–269, 271, 272, 336] (NCT00006392). Unlike their theoretically desirable anti-tumor effects demonstrated in preclinical studies, vitamin A and E supplementations may paradoxically increase cancer risk in certain contexts according to several clinical reports [266, 267, 270]. Omenn et al. 's trial involved 18,314 smokers, former smokers, and asbestos-exposed workers, with the treatment group receiving a combination of 30 mg of beta-carotene and 25,000 IU of vitamin A per day [266]. The results showed that the relative risk of lung cancer incidence was 1.28 in the treatment group compared with the placebo group, and the overall mortality was 17%, suggesting that the combination of vitamin A and beta-carotene exhibited no preventive effect, but increased lung cancer incidence and death risk [266]. Similarly, in the study by Sayin et al., 0.1 g/kg or 0.5 g/kg of vitamin E was used on mice with lung cancer models induced by KRAS G12D and BRAF V600E mutations. The results showed reduced levels of ROS within tumor cells, but with significantly increased cancer progression and decreased survival [270]. In a randomized controlled trial by Zandwijk et al., no statistically significant difference in overall survival or event-free survival was observed between lung and head and neck cancer patients treated with vitamin A (300,000 IU daily for 1 year followed by 150,000 IU for the 2nd year) and the placebo group [269]. A prospective study by Lippman et al. using 400 IU/day of vitamin E in a relatively healthy male population after approximately five and a half years of intervention showed that this did not prevent prostate cancer and did not improve prognosis [272]. Consequently, a consensus on their preventive utility has not been reached, which could be attributed to their complex interaction with other molecules within the human body.

Carotenoids could facilitate the addition of lipid peroxyl radicals to the carotenoid polyene chain or the electron transfer from radical to the carotenoid polyene chain to scavenge ROS [337]. The carotenoids include alpha- and beta-carotene, lutein, astaxanthin, and lycopene. etc. For some tumors, such as bladder cancer and prostate cancer, the results with no association found between dietary intake of these carotenoids and decreased cancer risk were previously reported [338, 339]. Besides, an RCT (NCT00064298) enrolling 134 head and neck cancer patients with multiple FV concentrates diet showed that patients in the diet group had significantly higher serum lutein as well as α -carotene, β -carotene, but did not differ significantly in biomarkers of risk for developing second primary tumors [340]. However, recent studies have provided positive results regarding carotenoids' role in cancer control. Astaxanthin is a natural C40 carotenoid and was reported to exhibit higher free radical inhibitory activity than α -tocopherol, α -carotene, β -carotene, lutein, and lycopene [341]. Copat et al. have reviewed the current research of astaxanthin in cancers, and many of the studies demonstrated its efficacy across distinct tumors, including nervous system, breast, and gastrointestinal cancers [274], though human-based evidence is lacking. In addition to astaxanthin, lutein exhibited a lower risk of developing lung cancer and late age-related macular degeneration compared to beta-carotene [275] and has shown inhibitory potential to breast cancer cells [276]. Lycopene is a natural carotenoid that has been discovered to exhibit anti-cancer efficacy, and it harbors higher antiproliferative effects on human cancer cells compared to other carotenoids, including alpha- and beta-carotene [342]. A systematic review summarizing the cancer incidence, improvement in treatment outcomes, and the mechanisms of lycopene action from 72 human and animal studies, and most of the in vivo anti-cancer effects were confirmed, with most of the research focusing on prostate cancers [343]. Previously, 79 patients with non-metastatic prostate cancer enrolled in an RCT (NCT00433797) were tested by nutritional intervention with tomato products containing 30 mg lycopene per day or other components. As a result, patients with the highest elevation in lycopene alone exhibited decreased PSA [277], indicating their inhibitory effects on prostate cancer progression. Meanwhile, a recent phase I trial (NCT0149519) involving 24 cases was conducted to evaluate the MTD, safety, pharmacokinetics, and effects on IGF-1 signaling and angiogenesis of synthetic lycopene in metastatic prostate cancer patients, the results indicate that the synthetic lycopene has significant effects on angiogenesis and IGF-1 signaling with low toxicity (pulmonary embolus in one out of 12 participants) [344]. In addition to prostate cancers, Lycopene also presents

therapeutic potential in gastrointestinal tumors, including gastric cancer [278] and colorectal cancer [279], implying its promising potential in cancer control.

Polyphenols harbor distinct chemical structures, but contain at least one aromatic ring and hydroxyl group [345], exhibiting strong antioxidant properties and can be divided into non-flavonoids and flavonoids [346]. A widely reported non-flavonoid polyphenol is resveratrol. Resveratrol is a natural compound that exists in many foods and exerts an antioxidant bioactivity. Its anti-cancer roles have been widely investigated and confirmed in more than ten cancer types [347]. Current clinical evaluation of resveratrol intervention on cancers has obtained periodic results. A phase I RCT (NCT00920803) enrolls 9 participants [348] with colorectal cancer and hepatic metastases, who received oral administration of resveratrol at 5.0 g once daily for 14 days, and has been completed. This study found that resveratrol was well tolerated and it increased cleaved caspase-3 by 39% in malignant tissues compared to placebo-treated patients, suggesting it promotes colorectal cancer cell death. In breast cancers, a pilot phase I trial studied the role in of resveratrol in systemic sex steroid hormones of postmenopausal women with BMI ≥ 25 kg/m² (NCT01370889), the results showed that resveratrol did not affect serum concentrations of estradiol, estrone, and testosterone but increased the concentrations of sex steroid hormone binding globulin (SHBG) by 10% average [349], indicating its SHBG-associated anti-tumor potential. However, negative results have also been observed. A phase I pilot clinical trial enrolling 11 colon cancer patients demonstrated that oral intake of resveratrol at 80 mg per day did not inhibit Wnt pathway in colon cancers (NCT00256334) [350]. Currently, the data from more completed or ongoing trials have not been posted, and they are expected to provide a robust evaluation of resveratrol's real therapeutic effects on cancers in the future. Flavonoids harbor a C6-C3-C6 skeleton. Different substituents on the carbon skeleton exhibit distinct antioxidative properties. The hydroxyl groups on the phenyl ring react with free radicals to generate relatively stable flavonoid radicals [351]. Flavonoids can bind to the amino acid residues of xanthine oxidase via hydrogen bonds and affect NOX enzyme activity via hydroxyl group and double bond, thereby inhibiting ROS-producing enzymes [351]. Besides, flavonoids could chelate metal ions to prevent the Fenton reaction and disrupt the binding of KEAP1 and NRF2 to promote antioxidant gene transcription [351]. Notably, whether polyphenols exhibit anti-oxidant or pro-oxidant activity depends on factors including chemical properties, cell type, and oxidative stress level; in some cases, polyphenols exert pro-oxidative effects. They can react with metal cations to form labile peroxy

radicals, a type of radical with an oxygen atom attached to an aromatic ring [295]. Aroxil radicals can react with oxygen to form $O_2\bullet^-$ [295]. Compounds, such as ferulic acid and apigenin, can also activate NOXs to generate ROS inside the cells [295]. These pro-oxidant effects may have anti-cancer properties. In a study by Suganuma et al., (–)-epicatechin administration with 100 μ M EGCG ([3H](–)-epigallocatechin gallate) incorporated significantly induced apoptosis of human lung adenocarcinoma cell PC-9, suggesting that EGCG may serve as a potential anti-lung cancer therapeutic agent [281]. Previous studies have indicated that polyphenols can potentially exert protective effects against cancer, while further clinical research is warranted to confirm their pharmacokinetics and efficacy [280, 351–354].

Pyrazolinone-based synthetic small molecules also contribute to ROS scavenging as their antioxidant potential was comprehensively assessed [355]. The pyrazolinones reported in cancer research include antipyrine and edaravone. Antipyrine derivatives have shown antioxidant and anti-tumor effects on Ehrlich ascites carcinoma cells [356]. Edaravone has been approved for the treatment of amyotrophic lateral sclerosis and acute ischemic stroke. The equilibrium between the neutral and anionic forms of edaravone underlies its antioxidant activity in vivo. The edaravone anion transfers an electron to $\bullet OH$, converting them into corresponding anions and terminating free radical chain reactions [357]. Additionally, edaravone significantly prevents mitochondrial oxidative damage [358] and activates the NRF2-ARE pathway to upregulate the expression of multiple antioxidant enzymes [359]. While some early in vitro and in vivo assays suggested potential anticancer activity, recent studies demonstrate no significant cytotoxicity of edaravone against MCF-7 and HT-29 cancer cell lines [360]. Although exhibiting limited anti-cancer efficacy, edaravone's antioxidant and anti-inflammatory properties make it suitable for protecting normal cells from the adverse effects of chemotherapy, radiotherapy, or immunotherapy [361]. Notably, edaravone reacts with pterin derivatives to form a substance that undergoes rapid reaction with NADH, generating ROS and inducing cell death [362].

GSH is an effective antioxidant that plays a bidirectional role in cancer development. It rapidly detoxifies oxidative stress. The clinical applications of GSH are limited due to the difficulty in crossing cell membranes [363]. Cys is a substrate for GSH synthesis, but its toxicity prevents its use in humans [363, 364]. NAC, a precursor of Cys, was synthesized with low toxicity. NAC's cellular protective effects have been observed in vitro, where NAC serves as a source of Cys for GSH synthesis, thereby increasing intracellular GSH generation [364]. Some studies do suggest that NAC can inhibit the proliferation

of tumor cells [310–312]. However, frustrating results of NAC have also been reported. In Conaway et al. 's study, NAC was incorporated into the diet of A/J mice at concentrations of 160 and 80 mmol/kg to evaluate its preventive potential against 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK)-induced lung tumors [311]. The results showed that at the higher dose (0.8 MTD, 160 mmol/kg diet), NAC significantly delayed the malignant progression of lung tumors from adenoma to adenocarcinoma in NNK-treated mice, as evidenced by the reduced incidence of adenocarcinomas and corresponding increase in adenomas at 52 weeks. However, NAC did not significantly inhibit the overall incidence and multiplicity of lung tumors [311]. Moreover, Volkan et al. reported that diet supplementation with NAC increases tumor progression and reduces survival in mice with lung cancer induced by B-RAF and K-RAS. Elevated GSH expression in cancer tissues alleviates tumor oxidative stress and sustains tumor growth; therefore, its anti-cancer effects have not been confirmed [270].

Benzoquinone is a natural compound with special carbonyl structures that make it easily reduced, and its derivatives exert antioxidant activities in human disease [365]. Distinct benzoquinone derivatives have been applied in cancer intervention, including CoQ10, MitoQ, and SKQs. CoQ10, also known as ubiquinone, is a benzoquinone-containing antioxidant. Though CoQ10 decrease has been found in cancers, the efficacy of CoQ10 supplementation alone in human cancer control via antioxidation has not been widely reported. The MitoQ is a decyl-triphenylphosphonium-cation (TPP)-linked CoQ10 with enhanced mitochondrial targeting capabilities. Notably, MitoQ is the first mitochondria-targeting agent entering clinical trials, and the safety of MitoQ administration has been verified [366], suggesting its potential in cancer treatment. Oral administration of MitoQ could decrease mitochondrial ROS and inhibit the growth and metastasis of human breast [367] and pancreatic cancer cells [314]. However, intraperitoneal injection of MitoQ did not affect BRAF-driven melanoma and KRAS-driven lung cancer development [315]. Plastoquinone derivatives (SkQs) were reported to harbor a larger "window" between anti- and pro-oxidant concentration (higher concentration) than MitoQ, meaning that SkQs may exert stronger antioxidant effects [368]. SkQ1 is one of the active SkQs, and the nanomolar concentrations of SkQ1 treatment suppressed fibrosarcoma and rhabdomyosarcoma tumor cell growth via antioxidant action [316]. However, the insufficient improvement of oncological parameters and survival of PDAC-bearing mice after SkQ1 treatment has also been reported [317].

Although some research suggests that the non-enzymatic antioxidants may have a therapeutic effect on

certain cancer types, such as lycopene for prostate cancer. However, more exciting results from clinical trials are still lacking, indicating that the current understanding of their roles in the human body is limited. The development of novel antioxidants in cancer control and detailed evaluation of their efficacy and safety are expected. In addition, more clinical trials are needed to validate the pharmacokinetic properties of current antioxidants, the optimal route of administration, and their potential synergies with existing therapies to better understand their role and potential in cancer treatment.

Combating cancers by targeting ROS-generating enzymes

Given the pivotal role that ROS plays in cancer progression, attempts to target ROS generation to repress tumor growth have been initiated. NADPH oxidases are comprised of seven members, including NOX1–5 and dual oxidases 1 and 2. These ROS-generating enzymes have been employed as the main targets for tumor control. Diphenyleneiodonium was the first non-selective NOX inhibitor discovered. It forms a relatively stable covalent adduct by interacting with FAD, inhibiting electron transfer from NADPH to molecular oxygen [369], thus reducing ROS generation and exhibiting anti-cancer effects in colon and epithelial ovarian cancer cells [318, 319]. Pyrazolopyridine dione derivatives, including GKT136901 and GKT137831, function as dual inhibitors targeting the NOX1/4 isoforms, while exhibiting reduced efficacy against NOX2 and NOX5, as indicated by IC₅₀ values of approximately 100–200 nM for NOX1/4 and greater than 1 μ M for NOX2/5. Notably, GKT136901 demonstrates a tenfold selectivity for NOX1/4 over NOX2/5. In contrast, GKT137831 is characterized by enhanced pharmacokinetic properties while maintaining effective NOX1/4 inhibition [370]. Preclinical investigations have highlighted their therapeutic potential in attenuating tumor growth, particularly in models of KRAS-driven pancreatic and colorectal cancers, by disrupting ROS-mediated pro-survival signaling pathways [371]. However, these NOX inhibitors lack target specificity, and their precise pharmacological effects remain to be elucidated [372].

Employment of NRF2-AREs-antioxidant axis and enzymic antioxidation for cancer control

As previously discussed, the transcription factor NRF2 triggers antioxidant gene expression and combats oxidative stress. The main mechanism of NRF2 activators is to block the binding of NRF2 and KEAP1 or reduce the level of KEAP1, weakening KEAP1's pro-degradation effect on NRF2, thereby promoting the expression of various antioxidant genes. Several inhibitors blocking NRF2-KEAP1 binding have been discovered, but some have not yet been confirmed to exert their antitumor effects through

the NRF2 pathway [73, 373, 374]. Several NRF2 activators activate NRF2 via various pathways, including nordihydroguaiaretic acid, enzastaurin, omaveloxolone, and dimethyl fumarate. NGAD (Nordihydroguaiaretic acid) inhibits GSK-3 phosphorylation at Ser9 and Thr390, and this prevents NRF2 degradation in a KEAP1-independent way [375]. NGAD demonstrated chemopreventive capability against skin cancer, as indicated by its mitigatory effects on TPA-induced mouse cutaneous oxidative stress [325]. The treatment of NGAD also reduced the quantity of ROS-damaged phenylalanine in GBM cells, showing a ROS scavenging potential [324]. A phase I dose-escalation trial (NCT00404248) on 35 patients with recurrent high-grade glioma has investigated the role of the NGAD derivative tetra-O-methyl nordihydroguaiaretic acid (TMNDGA) intravenous infusion. The results showed that a 1700 mg/day MTD, a 28% stable disease rate, and a 13% continuing treatment rate were obtained, suggesting its future study value [376]. However, a recent trial on 20 recurrent high-grade glioma patients with oral administration of TMNDGA demonstrated that increased dosage (up to 6000 mg/day) did not increase systemic exposure with a maximal AUC < 5 $\mu\text{g} \cdot \text{h}/\text{mL}$ and was terminated prematurely (NCT02575794) [377], indicating the limited bioavailability of oral TMNDGA administration. Another inhibitor, enzastaurin, also exhibits inhibitory effects on GSK-3. Enzastaurin is a direct PKC-selective inhibitor and could target the Ser9 of GSK-3 β as well and might prevent NRF2 degradation [326, 378]. Enzastaurin exhibits therapeutic effects against lymphoma (NCT03263026 and NCT01432951). A randomized, double-blind, phase III trial (NCT00332202) comparing enzastaurin with vehicle in patients with high-risk diffuse large B-cell lymphoma (DLBCL) who achieved remission after first-line treatment revealed that enzastaurin did not significantly improve disease-free survival in these patients after they attained a complete response to R-CHOP (C/EBP homologous protein) therapy [379]. As an approved agent for the treatment of Friedreich's ataxia, omaveloxolone (RTA 408) is a semi-synthetic triterpenoid NRF2 activator whose anticancer activity has been demonstrated in multiple studies [328, 380]. At low concentrations, this triterpenoid binds to KEAP1 and reduces NRF2 degradation, which potentially reverses tumor immune evasion by decreasing ROS in the MDSC-related TME, thereby inhibiting tumor growth [381, 382]. At high concentrations, they suppress tumor growth by modulating signaling pathways such as NF- κ B and JNK [381]. Dimethyl fumarate (DMF) and its metabolites activate NRF2 through alkylation of KEAP1 cysteine residues and nuclear export of BACH1, demonstrating efficacy across diverse cell types. Substantial evidence indicates DMF's capacity to suppress proliferation and invasion in

multiple cancer cell lines [329, 330, 383], while concurrently attenuating the pro-invasive function of TAMs within the TME [384]. Currently, DMF is approved for the treatment of psoriasis and multiple sclerosis, but its role in tumor therapy is subject to further clinical trial validation. Moreover, NRF2 activation enhances the anti-tumor activity of immune cells while enduring oxidative stress [385].

Abnormally downregulated antioxidant enzymes could promote cancer progression. In addition to activating the cellular antioxidant enzyme expression, endogenous or exogenous supplementation of antioxidant enzymes or enzymatic analogs is also considered a feasible strategy to inhibit tumor progression. Several synthetic SOD mimics have been developed, with metalloporphyrins gaining extensive research attention. For instance, Mn (manganese) porphyrin has been demonstrated to exert anti-tumor effects [322, 323] due to its ability to promote cancer cell apoptosis. But this was achieved by its ability to enhance intracellular H_2O_2 accumulation [386]. Messerli et al. used a macromolecular extracellular SOD3 mimic, poly(nitroxide)-albumin, to treat breast cancer and found that the intervention could reduce tumor ROS levels, inhibiting the proliferation and colony formation of highly metastatic 4T1 breast cancer cells. It also increases blood flow in the core region of breast cancer tumors and suppresses their lung metastasis [327]. Meanwhile, the development of SOD3-derived strategies can be used to mitigate treatment-associated complications following standard-of-care oncological interventions. Jang et al. found that increased SOD3 levels in cerebrospinal fluid by choroid plexus adeno-associated virus vector can combat lifelong neurological chemotherapy-related cognitive impairment, offering hope for alleviating chemotherapy complications and sequelae in cancer patients [387]. Greenberger et al. conducted a phase I-II clinical study and discovered that the oral administration of SOD3 plasmid/liposomes could control esophagitis during radiotherapy and chemotherapy for non-small cell lung cancer (NCT00618917). This suggests that SOD3, as a tumor treatment strategy, can simultaneously possess anti-tumor effects and control the complications following tumor treatment, thereby benefiting cancer patients.

In addition, there are other enzymatic antioxidants, such as GPx2 [388], that also show potential for tumor therapy. Although GPx2 expression is upregulated in a variety of cancers, it exhibits cancer-suppressing effects at different stages of cancer [389]. In the early stage of cancer, GPx2 can inhibit the expression of COX2 by removing the hydroperoxide required for COX2 activity and thus suppress the initiation of gastrointestinal tumors [390]. Banning et al. found that GPx2-knockdown cells have a higher ability to migrate and invade than

GPx2-expressing controls [391], suggesting GPx2 has an anti-metastatic effect in advanced cancer. Ebselen is a GPx mimic developed for ROS reduction. It shows an inhibitory effect on lung cancer cells via GSH depletion. Notably, ebselen also targets the cys292 and cys361 of the autophagy protein ATG4B to suppress colorectal cancer progression [392]. Meanwhile, it eliminates dormant cancer stem cells and promotes CD8+ T-cell infiltration when combined with anti-PD-L1 therapy in esophageal cancers via Quiescent fibroblast-derived QSOX1 (quiescin sulphydryl oxidase 1) inhibition [393]. Also, ebselen's anti-tumor effects *in vivo* have been observed in pancreatic and renal cancer by binding to the c165 and c237 of QSOX1 [394]. These findings reveal ebselen as an efficient anti-cancer agent with pleiotropic capabilities. However, no clinical trial has been completed to validate its efficacy and safety on humans.

Blocking transmembrane transport of ROS for cancer control

H₂O₂ exhibits complex crosstalk with oncological signals, and its transmembrane transport was facilitated by AQPs, which play a critical role in tumorigenesis. Therefore, AQP inhibitors have been developed for tumor control. The Auphen-derived organogold compounds, a class of AQP3 inhibitors, can markedly reduce H₂O₂ influx and intracellular ROS accumulation in melanoma cells, and this correlates with their impaired adhesion, proliferation, and migration [331]. Polymer-based nanoplateforms constructed from these compounds inhibit H₂O₂ transport in breast cancer cells, significantly suppressing tumor metastasis [395]. Notably, Auphen monotherapy increases lung metastasis, potentially through off-target AQP suppression in healthy tissues that systemically compromises metabolic coordination [396]. Z433927330 is a potent and selective AQP7 inhibitor [397]. It binds to the endofacial side of AQP7 to form hydrogen bonds with loop B backbone and Gln183 in transmembrane segment 4, thereby reducing leukemic cell (NB4 cell) proliferation [332]. AqB011 can selectively inhibit AQP1 and does not affect H₂O transport at up to 200 μM [398]. Docking models reveal that AqB011 interacts with intracellular loop D of AQP1, which is a critical site for AQP1 ion channel blockade, significantly impairing migration of AQP1-positive human colon cancer cells, while the cell viability was not affected [333]. The clinically approved AQP1 inhibitor bacopaside II inhibits colon cancer growth via cell cycle arrest and apoptosis induction [334]. The combined therapy of AqB011 and bacopaside II demonstrates enhanced anti-migratory effects compared to monotherapy [399].

As mentioned above, ROS-targeted antioxidant therapy demonstrates complex and multifaceted potential in

cancer prevention and treatment [346]. Non-enzymatic antioxidants, including vitamins, polyphenols, carotenoids, pyrazolinone, and GSH-related agents (e.g., NAC), have shown tumor growth inhibition capabilities *in vitro* and in animal models [250, 251, 256]. For instance, vitamin C significantly reduces tumor growth in ovarian, pancreatic, and glioma xenograft models, with its favorable safety profiles and synergistic effects with chemotherapy demonstrated in some clinical trials [250, 251, 256]. However, clinical studies on vitamin A and E have yielded less optimistic results, with some cases even showing increased cancer risk [266, 269]. Polyphenols display antioxidant and anti-cancer properties in laboratory studies, in which resveratrol inhibits malignant biomarkers in cancers such as colorectal and breast cancers, as clinically validated [348, 349]. Besides, the carotenoid lycopene has exhibited significant clinical effects in patients with both non-metastatic and metastatic prostate cancer as it reduced PSA, IGF-1 signals, and angiogenesis levels [277, 344]. However, limited promising results have been obtained for other antioxidant drugs.

Collectively, while numerous antioxidant agents show promising antitumor or preventive effects in preclinical studies, clinical trial outcomes remain inconsistent, suggesting deeper mechanistic insights await discovery. Notably, antioxidants can protect normal cells from oxidative stress-induced damage and mitigate treatment-related side effects, potentially representing a key future application direction [400, 401]. Although antioxidant therapy in cancer management currently lacks consensus, its clinical prospects remain considerable, particularly given its successful application in other diseases [402–404]. Significant interindividual variations in responses to oxidative stress and antioxidants necessitate the development of personalized assessment approaches for targeted therapies. Future research should focus on optimizing drug dosages, administration routes, and combination strategies with other therapies. There is an urgent need to develop antioxidants with enhanced targeting specificity, lower toxicity, and improved pharmacological profiles, coupled with well-designed clinical trials to validate their safety and efficacy in cancer treatment, ultimately providing more effective therapeutic options for cancer patients.

Overloading ROS induces tumor cell damage and death

Although cancerous ROS levels may exhibit pro-tumoral effects, a high ROS level that exceeds a compensatory threshold could induce tumor cell death, thereby achieving an anti-tumor effect. One strategy to elevate intracellular ROS levels is to induce a burst in intracellular ROS load. Meanwhile, destroying tumor cell antioxidant

Table 2 The ROS-overloading strategies in cancer control

Categories	Drug names	Mechanism	ROS	Effects	Tumors	References
ATF-6 inhibitors	Melatonin	RET induction	Increase	Anti-tumor	Head and neck squamous cell carcinoma	[405]
Complex I inhibitors	SMIP003	Complex I Q site inhibition	Increase	Anti-tumor	Triple-negative breast cancer	[406]
	Metformin	Complex I FMN site inhibition	Decrease	Anti-tumor	Colon cancer	[407]
	Phenformin	Complex I inhibition	Increase	Anti-tumor	Brain tumors	[408]
					Melanoma, breast, colon, lung, and prostate cancer	[409]
DNA cross-linking agent	Carboxyamidotriazole	Complex I inhibition	Increase	Anti-tumor	Colon cancer	[410]
	Cisplatin	MtDNA damage	Increase	Anti-tumor	Prostate cancer	[411]
		Mitochondrial content elevation	Increase	Anti-tumor	Ovarian cancer	[412]
PML-RAR α inhibitors	Arsenic trioxide	GSH depletion	Increase	Anti-tumor	Leukemia	[413]
		Complex IV inhibition	Increase	Anti-tumor	Leukemia	[414]
		TrxR and Prx inhibition	Increase	Anti-tumor	Breast cancer	[415]
Topoisomerase inhibitors	DOX	NADPH-to-DOX electron transfer	Increase	Anti-tumor	Breast cancer	[416]
		NOX indirect activation			Human osteosarcoma	[417]
					Leukemia	[418]
Nanoparticles	PTX@TPGS-PBTE NPs	ROS-targeted PTX delivery	Utilize ROS	Anti-tumor	Head and neck cancer	[419]
	Nanoparticles (CPT-Pt (IV) combined with P1 and mPEG2K-DSPE)	ROS-mediated cisplatin/camptothecin release	Utilize ROS	Anti-tumor	Colon cancer	[420]
	MOFs	GSH depletion	Increase	Anti-tumor	Liver cancer and breast cancer	[421]
Radiation therapy		Free electron-H ₂ O interaction	Increase	Anti-tumor		[422]
PDT		Photosensitizer irradiation-induced ROS generation	Increase	Anti-tumor		[423]
RDT		Photosensitizer irradiation-induced ROS generation via high-energy X-ray	Increase	Anti-tumor		[424]
SDT		Sonoexcitation and ultrasonic cavitation	Increase	Anti-tumor		[425, 426]
CDT		Fenton reactions	Increase	Anti-tumor		[427]
Xc- System inhibitors	Erastin	Xc- System blockade	Increase	Anti-tumor	Osteosarcoma, fibrosarcoma, and lung cancer	[428]
		Induction of VDAC opening	Increase	Anti-tumor	Lung cancer	[429]
					Fibrosarcoma, Ewing's sarcoma, neuroblastoma, adult acute monocytic leukemia	[430]
	IKE	Xc- system blockade	Increase	Anti-tumor	Diffuse large B-cell lymphoma	[431]
	Sorafenib	Xc- system blockade	Increase	Anti-tumor	Hepatocellular carcinoma and renal cell carcinoma	[432]
Cyst(e)inases		Blood cystine depletion	Increase	Anti-tumor	Prostate carcinoma and breast cancer	[433]
GCL inhibitors	BSO	GCL inhibition	Increase Increase	Anti-tumor	Renal cancer and ovarian cancer	[434]

Table 2 (continued)

Categories	Drug names	Mechanism	ROS	Effects	Tumors	References
CYP450 inhibitors	PEITC	GSH depletion	Increase	Anti-tumor	Breast cancer	[435]
					Leukemia	[436]
					Lung, colon, and ovarian cancer	[437]
NRF2 inhibitors	BITC				Non-small cell lung cancer cells	[438]
	Brusatol	NRF2 protein expression suppression	Increase	Anti-tumor	Pancreatic cancer	[439]
	Halofuginone	Global protein translation inhibition	Increase	Anti-tumor	Lung adenocarcinoma, Oesophageal cancer	[440]
	ML385	Neh1 domain of the NRF2 protein binding	Increase	Anti-tumor	Head and neck squamous cell carcinoma cancer cell	[441]
Trx/TrxR inhibitors					Breast cancer	[442]
	PX-12	Trx inhibition	Increase	Anti-tumor	Acute myeloid leukemia	[443]
	Ethaselen	Trx inhibition	Increase	Anti-tumor	NSCLC and gastric cancer cell	[444, 445]
	Piperine	TrxR Sec residue binding	Increase	Anti-tumor	Cervical cancer, Non-small cell lung cancer, hepato-cellular liver carcinoma	[446]
	MGd	TrxR-targeting capability	Increase	Anti-tumor	Metastatic renal cell carcinoma	[447]
					Multiple myeloma	[448]
					Lymphoma	[449]
	Auranofin	TrxR-targeting capability	Increase	Anti-tumor	Human thyroid cancer cell	[450]
					Epithelial ovarian cancer cell	[451]
					Glioblastoma and NSCLC	[452]
					NSCLC	[453]
					Pancreatic cancer	[454]
Prx inhibitors	Celastrol	Prx-2 Cys172 residue binding	Increase	Anti-tumor	Chronic lymphocytic leukemia	[455]
					Gastric cancer	[456]
NQO1/GSTP1 inhibitors	5-Methyl-N-(5-nitro-thiazol-2-yl)-3-phenylisoxazole-4-carboxamide (MNPC)	NQO1 and GSTP1 active sites binding	Increase	Anti-tumor	Glioblastoma	[457]
Phenothiazinium redox cyclers	3,7-diaminophenothiazinium-based redox cyclers	Electron transfer and NQO1 substrate	Increase	Anti-tumor	Melanoma	[458]
HIF-1α inhibitors	2-methoxyestradiol	Mitochondrial membrane potential disruption	Increase	Anti-tumor	Neuroblastoma	[459]

ATF-6 activating transcription factor 6, *ERT* reverse electron transfer, *FMN* flavin mononucleotide, *NADPH* nicotinamide adenine dinucleotide phosphate, *DOX* doxorubicin, *NOX* nicotinamide adenine dinucleotide phosphate oxidase, *PTX* paclitaxel, *MOFs* metal–organic frameworks, *PDT* photodynamic therapy, *RDT* radiodynamic therapy, *SDT* sonodynamic therapy, *CDT* chemodynamic therapy, *VDAC* voltage-dependent anion channel, *IKE* imidazole ketone erastin, *BSO* buthionine sulfoximine, *GCL* glutamate cysteine ligase, *PEITC* phenethyl isothiocyanate, *BITC* benzyl isothiocyanate, *NSCLC* non-small cell lung cancer, *TrxR* thioredoxin reductase, *MGd* Motexafin Gadolinium, *Prx* peroxiredoxin, *Cys* cystatin, *NQO1* NAD(P)H dehydrogenase quinone 1, *GSTP1* glutathione S-transferase P1

capability through antioxidant enzymes or substrates targeting is also feasible to mediate ROS-related anti-cancer effects (Table 2).

Burdening cancer cells with elevated ROS load

The mitochondrial respiratory chain generates ROS, and targeting mitochondrial complexes or DNA can lead to electron leakage for excessive ROS generation. Selective inhibitors targeting the Q site of complex I can achieve a rapid superoxide generation via forward electron transport,

enhancing NADH-based ROS accumulation [35, 460]. Conversely, inhibiting the upstream FMN site in Complex I reduced ROS generation [407]. In complex III, partial reduction of Q or inhibition of downstream complexes amplifies ROS production [39]. Compound SMIP003 competitively inhibits the Q site of mitochondrial complex I, resulting in high $O_2^{\bullet-}$ levels that trigger the unfolded protein response and lead to 4T1 tumor cell death [406]. The commonly used biguanide-type diabetes drug, phenformin, also inhibits mitochondrial complex I Q site to induce ROS generation [408]. Metformin was found to selectively inhibit the mitochondrial complex I FMN, increasing ROS generation and playing a role in cancer prevention [461, 462]. Furthermore, melatonin can induce RET in complex I. The induced RET increased ROS generation via modification of CoQ redox and mitochondrial membrane potential in head and neck cancer cells to facilitate their apoptosis [405].

Many cancer chemotherapies exert cytotoxic effects by inducing ROS generation. Cisplatin has been widely used in treating human cancers via various mechanisms. Cisplatin induces apoptosis, probably by activating p53's pro-oxidative function, triggering ROS generation [463]. Additionally, cisplatin can directly damage mtDNA [411, 412] and increase the mitochondrial content in ovarian cancer cells [412], ultimately promoting ROS accumulation. Arsenic trioxide inhibits mitochondrial complex IV, impairing mitochondrial respiratory function and reducing the efficiency of the electron transport chain. This leads to increased electron leakage and superoxide generation. Concurrently, it slightly decreases cellular GSH content, weakening the cell's antioxidant capacity. The reduced antioxidant capacity allows superoxide levels to rise further, exacerbating cellular oxidative stress and ultimately causing cell damage and apoptosis [414]. Carboxyamidotriazole targets mitochondrial complex I, thus producing ROS to suppress glucose and lipid metabolism utilization to inhibit cancer development [410]. The anthracycline drug DOX (doxorubicin) also contains quinone and hydroquinone residues, which receive electrons from NADPH and generate H_2O_2 via a non-enzymatic reaction [464]. It may also induce excessive activation of poly(ADP-ribose) polymerase and depletion of NAD⁺ and NADP⁺ [418], indirectly activating NOXs and H_2O_2 production [417], thereby inducing tumor cell apoptosis. However, DOX-derived ROS also causes cardiotoxic side effects [465–467], limiting its application in widespread cancer therapy. Nanomedicine, a novel anti-cancer strategy, has been developed rapidly and contributes to inducing ROS-mediated cytotoxicity. PTX@TPGS-PBTE NPs can kill tumor cells via targeted delivery of PTX (paclitaxel) and induce an intracellular ROS burden [419]. Besides, the chemotherapeutic drugs cisplatin and camptothecin can be released inside tumor

cells under high ROS levels, activating the cGAS (cyclic GMP–AMP synthase)–STING pathway and immune response [420], the selective drug release enhances the targeting specificity of chemotherapy drugs, which improves their efficacy while mitigating their side effects.

RT (radiation therapy) generates free radicals that damage cellular DNA. When tumor tissue is exposed to X-ray radiation, the absorption of high-energy radiation by H_2O leads to excitation and ionization [468]. This process produces numerous free electrons and initiates cascade reactions with the surrounding H_2O molecules, resulting in substantial ROS generation [422, 469]. However, RT dosage is limited due to the impact of ionizing radiation on healthy tissues. Radiosensitizers can accelerate ROS production and DNA damage to selectively strengthen the therapeutic effect on cancerous tissues [470].

Given the low tumor specificity of conventional cancer therapies, locally activated dynamic therapies, including PDT (photodynamic therapy), RDT (radiodynamic therapy), SDT (sonodynamic therapy), and CDT (chemodynamic therapy), have been widely employed for tumor control [427, 471, 472]. PDT delivers a designed photosensitizer to tumor sites, absorbing light of a specific wavelength and entering an excited state. Excited photosensitizers can undergo Type I and Type II reactions. Type I generates ROS by interactions with water and oxygen, while Type II produces cytotoxic singlet oxygen by activating oxygen [423]. Both reactions cause oxidative stress damage, enabling selective tumor-killing effects [423]. For instance, a bimetallic ion-modified metal–organic framework nanozyme (Zr^{4+} -MOF- Ru^{3+} / Pt^{4+} -Ce6@HA, ZMRPC@HA) possesses catalase and glutathione oxidase activities, enhancing the oxidative stress pressure in deep-tissue tumors and successfully inhibiting their growth and differentiation [473]. Recent advances have focused on engineering photosensitizers that can be activated more effectively by different penetrating light sources [474]. While preclinical studies have extensively demonstrated the anti-tumor immunity elicited by PDT in various mouse tumor models, there is limited clinical evidence supporting this property. RDT is an emerging paradigm extending conventional PDT, which substitutes visible/infrared light with high-energy X-rays to enable photosensitizer activation in deep-seated malignancies. This overcomes the limitations of dispersed energy and the limited treatment depth of PDT [475]. For instance, the RDT system based on gold nanoclusters can directly absorb low-dose X-rays to generate ROS, efficiently killing cancer cells even under hypoxic conditions and enhancing the antitumor immune response [476]. Additionally, RDT using CsI(Na)@MgO nanoparticles and 5-aminolevulinic acid, which activates photosensitizers via X-ray irradiation, has shown

significant potential for the effective treatment of deep tumors [477]. These modified nanomaterial-based RDT not only promote ROS generation but also improve targeting and deep-tissue treatment capabilities. Compared to traditional PDT, they can utilize the high penetration of X-rays more effectively to activate photosensitizers, generating a higher level of ROS in deep tumors for better therapeutic effects, thus offering new insights and methods for the clinical translation of RDT [476–479].

The SDT utilizes sonosensitizers to generate ROS under acoustic wave stimulation and exhibits superior tissue penetration with high-frequency mechanical vibration. Sonosensitizers demonstrate tumor-selective accumulation analogous to photosensitizers, enabling ultrasound-triggered ROS production for localized tumor ablation [53, 425]. Recently, alginate-coated AuNRs^{ALG} (alginate-coated gold nanorods) generated a high level of singlet oxygen after exposure to ultrasound irradiation, which induces apoptosis via the mitochondrial pathway in breast cancer cells [480]. An antibacterial nanoplatfrom Au@BSA-CuPpIX was designed for colorectal cancer therapy. This nanosonosensitizer was found to effectively eliminate *E. nucleatum* in colorectal cancer via ROS generation under ultrasound, thereby enhancing the therapeutic efficacy of SDT against orthotopic colorectal cancer and suppressing pulmonary metastasis. Furthermore, the incorporated gold nanoparticles reduced the phototoxicity of metal porphyrins accumulated in the skin, preventing severe inflammation and cutaneous damage [481]. Various sonosensitizers are being developed [482], and inorganic sonosensitizers are considered more advantageous regarding stability, compatibility, and photothermal conversion efficiency [483]. For instance, copper-cysteamine (Cu-Cy) nanoparticles, which serve as an inorganic sonosensitizer, have been employed in the treatment of breast cancer cells. Upon activation by FUS (focused ultrasound), these nanoparticles produce ROS that facilitate apoptosis and necrosis in tumor cells. Experimental results demonstrated that the combination of Cu-Cy and FUS treatment reduced cell viability to 45% and decreased tumor volume by 74% in 4T1 breast tumor models [484], while the Cu-Cy group showed no significant cytotoxicity when ultrasound was absent.

CDT introduces iron-based nano-drugs into the body, releasing ferrous ions under acidic conditions of the tumor and initiating Fenton reactions to convert high concentrations of H₂O₂ into •OH [427]. This process overcomes the limitations of the tissue penetration capacity of PDT, SDT, and RT because it does not require external energy input [485]. The TME features, including acidity and excess H₂O₂ [9], enable CDT's targeted release. Excessive •OH is generated from H₂O₂ via Fenton reaction and can induce tumor cell death [427].

Apart from iron, various metals can act as CDT reagents in Fenton-like reactions. However, further research is necessary to develop novel metal-based/non-metal CDT formulations to improve efficacy and reduce toxicity [486]. For instance, in one study, researchers developed a new nanoplatfrom that can specifically release ROS in the TME through nanoparticle-triggered intratumoral catalytic chemical reactions, achieving selective killing of tumor cells [427]. This nanoplatfrom enhances treatment precision and reduces side effects on normal tissues. Additionally, some studies have explored the use of different metal ions in CDT and found that certain metal ions can more efficiently catalyse the Fenton reaction under specific conditions, producing more ROS and thus enhancing the killing effect on tumor cells [485, 486]. These studies offer new insights and approaches for the development of CDT, potentially further improving its applicability in tumor therapy.

Blocking the cellular antioxidative system to inhibit cancer development

Tumor cells' antioxidative network greatly contributes to their survival and growth, in which the GSH and Trx systems have been widely reported as critical components for tumor redox homeostasis [487]. The GSH and Trx systems consist of GSH, GSR, glutaredoxin, Trx, TrxR, and NADPH, respectively, forming the two primary independent antioxidant systems in eukaryotes [488]. Within these two systems, GSR and TrxR transfer electrons from NADPH to GSSG or Trx-S₂ (oxidized Trx), converting them to their reduced states and participating in the subsequent antioxidant reactions. Meanwhile, transcription factor NRF2 governs the expression of multiple antioxidant enzymes. Various strategies have been designed to target the GSH and Trx system as well as NRF2 activities to destroy the tumor cell redox balance, thereby inhibiting tumor progression.

GSH, a critical antioxidant in cancer, is a promising target for cancer control, triggering strategies to inhibit GSH synthesis and deplete GSH reserves. GSH substrates elimination, transmembrane transport blockage, and synthesis inhibition have been investigated for cancer control. Cys is essential for GSH synthesis [489]. The system x_c⁻ (cystine/glutamate antiporter) is a specific cystine transporter that imports cystine from the extracellular amino acid pool [490] and is upregulated in many cancers [491]. Targeting the system x_c⁻ to inhibit Cys intake and GSH depletion can lead to tumor cell ferroptosis [492]. Erastin inhibits cystine uptake by blocking the system x_c⁻ [428, 493]. However, their poor solubility and renal toxicity limit their application. Exosome-loaded erastin enhanced therapeutic effects in cancers

compared to free erastin [494]. Additionally, more water-soluble erastin analogs, including piperazine-erastin and imidazole ketone erastin, have been developed and present improved anti-cancer effects [431, 495]. The combined treatment with celastrol and erastin significantly increased ROS generation, disrupted mitochondrial membrane potential, and promoted mitochondrial fission [496]. But this finding warrants further clinical evaluation. Sorafenib, an approved anti-cancer drug for hepatocellular and renal cell carcinoma [432], also inhibits the system χ_c^- [428]. Additionally, depleting blood cysteine using cyst(e)inase simultaneously facilitates system χ_c^- inhibition and GSH depletion [433].

GSH depletion and synthesis inhibition also lead to tumor cell oxidative damage. GCL is the rate-limiting enzyme for GSH synthesis, and its irreversible inhibitor, BSO (buthionine sulfoximine), is commonly used as an adjuvant agent, which is demonstrated to suppress glutathione levels and induce lipid peroxidation, thereby inhibiting cell viability [434]. A nano-reaction platform based on iron-based metal-organic frameworks (MOFs), BSO&OXA@MOF-LR, loaded with OXA (oxaliplatin) and BSO, effectively inhibits GSH generation and mitigates cancer cell resistance to chemotherapy drugs [497]. The BSO-based compound, Nap-DFDFY-CS-DEVD-BSO, contains a BSO segment that inhibits intracellular GSH synthesis. This compound is reduced by GSH and transformed into Nap-DFDFY-thiol. It exhibits the dual functions of GSH depletion and inhibition, displaying high cytotoxicity [498]. Other drugs have focused on depleting existing GSH levels over a short period. Isothiocyanates, including phenethyl isothiocyanate, benzyl isothiocyanate, and sulforaphane, contain a carbon atom in the $-N=C=S$ group that can react with the cysteine thiol group on GSH catalyzed by GST to form conjugates [499]. They effectively deplete GSH in various cancers [438, 500, 501]. Moreover, compounds containing α , β -unsaturated carbonyls, such as cinnamaldehyde, can attack GSH via Michael addition and have anti-cancer potential [502, 503]. Certain redox-active MOFs exhibit catalase-like activity that persistently catalyzes H_2O_2 to generate O_2 . In addition to supplementing O_2 , these MOFs can also effectively reduce GSH concentration by absorbing and oxidizing GSH [421, 504], further amplifying ROS damage.

Emerging evidence highlights the widespread overexpression of NRF2 across multiple tumor types, with its hyperactivation serving as a compensatory mechanism under oxidative stress [505], exhibiting complex roles in tumorigenesis and progression [373, 506]. Therefore, NRF2 inhibitors have garnered significant attention for cancer control. Certain natural dietary NRF2 inhibitors directly bind to NRF2 to block its activity, while others

modulate upstream or downstream pathways, demonstrating antitumor potential. For example, luteolin suppresses NRF2 expression, wogonin inhibits NRF2 mRNA transcription, brusatol and halofuginone block NRF2 translation by suppressing global protein synthesis, and trigonelline prevents NRF2 nuclear translocation [507, 508]. Brusatol suppresses NRF2 protein expression, elevates ROS levels in pancreatic cancer cells to overcome chemoresistance [439], indicating therapeutic promise in cancer treatment [509]. Similar to the mechanism of brusatol, halofuginone is a febrifugine derivative, and it reduces NRF2 synthesis by inducing cellular amino acid starvation response and inhibiting global protein translation, thereby attenuating tumor cell chemoresistance [440, 510]. Certain polyphenols, such as procyanidins, can also act as NRF2 inhibitors, offering preventive and therapeutic benefits against cancer [511]. Currently, a novel and validated NRF2-targeting inhibitor ML385 has exhibited great potential in cancer inhibition. ML385's anti-cancer effects have been widely observed in preclinical studies. ML385 directly binds to the Neh1 domain of the NRF2 protein and decreases its DNA binding capability [512]. ML385 exerted highly selective cytotoxicity to cancer cells with KEAP1 mutations and showed significant anti-cancer efficacy when combined with carboplatin treatment in NSCLC. It also inhibits the NRF2/HO-1 pathway and suppresses head and neck squamous cell carcinoma cancer cell growth and breast cancer cell stemness [441, 442]. Meanwhile, ML385 could inhibit NRF2 nuclear translocation in cancer cells treated with ionising radiation, and this increased ROS level and ferroptosis, thus sensitizing esophageal squamous cell carcinoma to radiotherapy [513]. In leukemia, ML385 treatment enhanced the efficacy of doxorubicin. Interestingly, ML385 treatment decreased KEAP1 protein levels. However, whether it directly regulates KEAP1 stability or functions via other pathways remains unclear [514]. ML385 has exhibited great potential in multiple cancer control, while no clinical trial has been launched so far.

The TrxR/Trx system is critical for eliminating ROS, such as H_2O_2 , and has been implicated in cancer. PX-12 is the first inhibitor of Trx with clinical development, and it causes irreversible thioalkylation of Cys73 of Trx1 [515, 516]. It has exhibited inhibitory effects alone or synergistic effects with other anti-tumor drugs on distinct cancer cells [443, 517–519]. However, the evidence from clinical data has demonstrated the limited efficacy of PX-12. A previous phase I trial was launched to evaluate the effects of PX-12 on patients with advanced solid tumors. In this study, the patients were administered with PX-12 infusion at 9–300 mg/m² in 1 h or 3 h, and no objective responses were observed. Only seven patients achieved stable disease, and one patient with appendiceal

adenocarcinoma had a minor response of 18.3% [520]. Another phase II study of PX-12 on previously treated advanced pancreatic cancer also reported no consistent decrease in SUV, Trx-1 levels, or CA 199 levels and was terminated early due to limited antitumor activity as well as low baseline Trx-1 levels [521] (NCT00177242). Further, a prolonged infusion trial was initiated and reported no observed response either after PX-12 72-h infusion (300 mg/m²/24 h) by efficacy evaluation, with only one patient with rectal cancer having stable disease [522]. Similarly, a phase IB trial has demonstrated that the infusion of PX-12 with the maximally tolerated dose (300 mg/m²/24 h) on patients with malignant gastrointestinal cancers did not show significant clinical activity and trends in plasma Trx-1, VEGF, or FGF-2 changes [515]. In addition to PX-12, more Trx/TrxR targeting agents are being investigated recently.

Compared to Trx inhibition, TrxR-targeting strategies have gained more attention in recent years. The TrxR1 inhibitor, Motexafin Gadolinium (MGd), is a pentadentate aromatic metalloporphyrin with non-competitive TrxR1-inhibitory capability [523] to promote ROS accumulation under radiation therapy [524]. Therefore, MGd has been used as a radiosensitizer in cancers [524]. Early clinical trials have demonstrated good tolerance, selective biolocalization in tumors, and detectability at MRI imaging [525, 526] in patients with cancers. Renschler et al. conducted a series of clinical trials to investigate the performance of MGd in patients with brain metastases. In their studies, MGd administration (5 mg/kg/d) obtained a high radiologic response rate as well as high rates of freedom from neurologic progression at 1 year when combined with 30 Gy in 10 fractions of whole-brain radiation therapy in patients with brain metastases [527, 528]. This also improved time to neurologic and neurocognitive progression [529, 530]. Moreover, MGd did not cross the intact blood–brain barrier in normal brain tissue while maintaining measurable uptake and improving the median survival time (16.1 months compared to 11.8 months in the control group) in patients with GBM [531, 532]. However, opposite results were also observed that the combination of standard radiotherapy with temozolomide and MGd achieved no significant survival improvement in GBM patients [533]. In pediatric patients with newly diagnosed intrinsic pontine gliomas, the addition of MGd did not improve the survival either, compared to a standard 6-week course of radiation [534]. In non-CNS tumors, some preclinical studies have indicated the anti-tumor efficacy of MGd in blood tumors [448, 449], while the clinical results of solid tumors showed that the therapeutic effects of MGd are limited, currently. MGd infusion alone did not result in significant clinical responses in metastatic renal cell

carcinoma [447]. Meanwhile, no significant therapeutic response differences were obtained for patients with different non-brain malignancies administered with a combination of MGd and doxorubicin [535]. No significant improvement in response rate, PFS, or OS was observed for NSCLC patients administered pemetrexed 500 mg/m² plus MGd 15 mg/kg every 21 days, either [536].

Auranofin is a class of gold-containing compound that targets TrxR through substitution by cysteine or selenocysteine amino acid residues in the active site of TrxR [537]. It is first proved for rheumatoid arthritis but recently demonstrated potent antitumor activity both in vitro and in vivo [538, 539]. Multiple investigations focusing on auranofin alone or in combination with other anticancer agents support its repurposing as an adjuvant to overcome chemotherapy resistance or enhance conventional treatment efficacy [524, 540, 541]. Combination of Auranofin with everolimus (mTOR inhibitor) triggers synergistic cell death induction in an oxidative-stress-dependent manner, which activates autophagy, ERS, and JNKs signaling pathways in breast and colon cancer cells [542]. A recent study also involved a nanopatform for auranofin and doxorubicin co-delivery, and this strategy significantly sensitized ferroptotic and apoptotic effects on breast cancer cells [543]. In GBM, auranofin also exhibited promising anti-cancer capabilities when combined with GSH system inhibitors L-BSO or PPL [544]. Meanwhile, auranofin alone also exerts ROS-induced apoptosis and growth inhibition in anaplastic thyroid cancer [450]. Notably, increased ROS mediated by auranofin induces PD-L1 expression, resulting in immunosuppression, while its combination with anti-PD-1 antibody enhances anticancer activity in murine B-cell lymphoma [545]. Currently, clinical trials covering phase I, II studies are being carried out to investigate auranofin's roles in chronic lymphocytic leukemia (NCT01419491), ovarian cancer (NCT03456700), recurrent epithelial ovarian, primary peritoneal, and fallopian tube cancer (NCT01747798), lung cancer (NCT01737502), and recurrent GBM (NCT02770378), while their results have not been posted.

Etheselen is an organoselenium-containing TrxR1 inhibitor designed by Zeng et al. [546]. Its dose-dependent inhibitory effects on NSCLC and gastric cancer cell growth have been identified [444, 445], and it also exhibits synergistic efficacy with sunitinib and sodium selenite for colon cancer and NSCLC cancer cells, respectively [547, 548]. One clinical trial investigating etheselen's roles in disease control rate, survival improvement, and safety on NSCLC patients has been completed, but no data have been reported (NCT02166242). Butaselen is another organoselenium-containing compound for TrxR-targeting designed by Zeng et al. [549]. This

novel TrxR inhibitor has presented therapeutic efficacy in hepatocellular carcinoma cells [549–551]. Butaselen administration decreased the incidence of DEN/CCL4/ethanol-induced hepatocellular carcinoma in mice and protected them from developing fibrosis and cirrhosis. Meanwhile, it inhibited hepatocarcinoma growth in the syngeneic mouse model and this is facilitated via cell cycle arrest and apoptosis induced by TrxR-inhibition [549]. Interestingly, butaselen also decreased the expression of total and phosphorylated STAT3 and downregulated PD-L1 expression in hepatocellular carcinoma cells [550]. Moreover, butaselen promoted NK and T-cell infiltration and activities in TME in vivo via upregulated CXCR3, NKG2D, and their ligands. Butaselen administration exerts synergistic effects when combined with PD-1 blockade [551]. These preclinical studies indicate butaselen's potential for hepatocellular carcinoma control and immunotherapeutic efficacy improvement.

In addition to NRF2, GSH, and Trx/TrxR systems, other antioxidant components are present in cells, such as Prx, NQO, and SODs. The Prx system is also critical in maintaining tumor cell redox homeostasis as previously discussed, and Prx inhibition could enhance intracellular ROS accumulation, thus suitable for cancer cell elimination. Celastrol is a bioactive constituent extracted from a Chinese herb, binding to the Cys172 residue of Prx-2 to inhibit its antioxidant activity for H_2O_2 reduction. Celastrol can effectively inhibit the

growth of gastric cancer in vivo and in vitro, suggesting its potential therapeutic effects [456]. Celastrol has been frequently developed as a candidate for nanoplateform-based co-delivery, nanohybrids, and PTORAC-based strategies in treating cancers including NSCLC, pancreatic cancer, and hepatocellular carcinoma, etc. [552–555]. Besides, celastrol exhibits immunotherapeutic potential due to its capability to induce ICD or PD-L1 expression in tumor cells [556, 557]. PHB binds to Prx-3 in the mitochondria, reducing mitochondrial ROS. Knocking out *PHB* or pharmacologically inhibiting PHB via rocaglamide A can effectively inhibit GBM growth and enhance radiotherapy activity [187]. NQO1 is elevated in gliomas, and it prevents oxidative-stress-mediated glioma cell death [457]. 5-methyl-N-(5-nitrothiazol-2-yl)-3-phenylisoxazole-4-carboxamide has been discovered to target the active sites of NQO1 and glutathione S-transferase Pi 1 via High-throughput screening, and it exhibits significant potential as an anti-cancer drug [457]. The PRCs (3,7-diaminophenothiazinium-based redox cyclers), such as thionine, toluidine blue, and methylene blue, can function as substrates for NQO1. NQO1-mediated electron transfer from NADPH reduces these compounds to their leuco-forms, which can spontaneously transfer electrons to oxygen, generating ROS [458]. Previous studies have indicated that 2-methoxyestradiol can inhibit SOD activity, accumulating $O_2^{\bullet-}$ in the mitochondria,

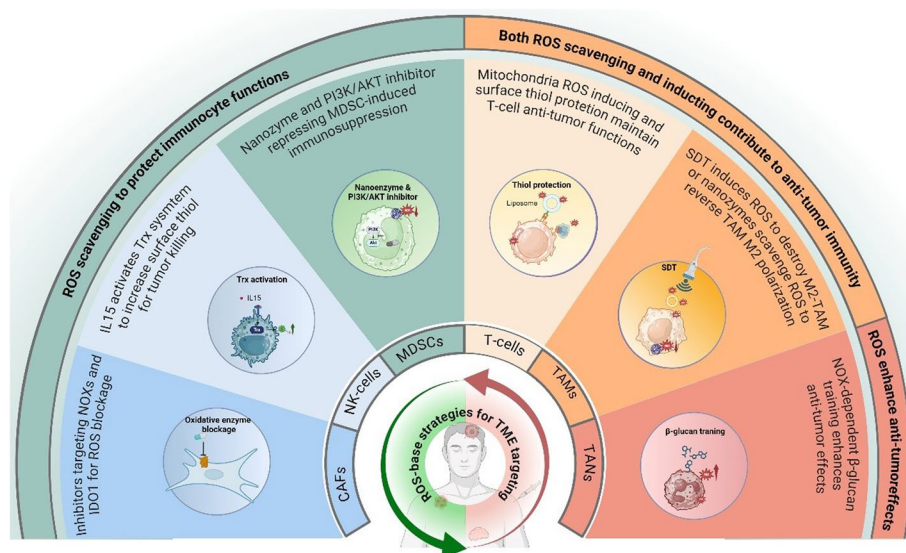


Fig. 6 Comprehensive summary of the role of oxidative stress in TME targeting. Antioxidative strategies, including T-cell thiol protection, NK cell Trx system activation, CAF oxidative enzyme inhibition, MDSC PI3K/Akt blockade, and macrophage ROS scavenging, have been adopted to facilitate immunological cytotoxicity and immunosuppression reversal. Meanwhile, ROS-inducing β -glucan training of neutrophils and SDT treatment of M2 macrophages inhibited cancer progression. TME, tumor microenvironment. NK cells, natural killer cells. Trx, thioredoxin. CAFs, cancer-associated fibroblasts. MDSCs, myeloid-derived suppressor cells. ROS, reactive oxygen species. SDT, Sonodynamic Therapy. The figure was created using BioRender.com

causing mitochondrial membrane damage and cell death [558]. However, the SOD-based mechanism of 2-methoxyestradiol is suspected, and its capability to induce ROS generation [559] and inhibit cancer development has been confirmed [459].

The involvement of ROS in cancer immunotherapy

Cancer immunotherapy has seen notable success in treating cancers that are resistant to standard therapies; it enhances the immune system's anti-cancer response by boosting host immunocytes and reversing the immunosuppressive microenvironment to promote cancer elimination (Fig. 6). Improving the antioxidant capacity or ROS-based immunocyte cytotoxicity against tumor cells may enhance the effectiveness of cancer immunotherapy.

ROS-associated strategies for anti-tumor immunity enhancement

T-Fulips is a liposome composed of anti-CD3 F(ab')₂ fragments and TEMP (2,2,6,6-tetramethylpiperidine), targeting T-cells by anti-CD3 F(ab')₂ fragments and protecting the -SH on the T-cell surface with TEMP, thereby preserving T-cell anti-tumor function [224]. Moreover, TEMP is converted to the paramagnetic compound TEMPO during redox reactions, allowing MRI (magnetic resonance imaging) assessment [224]. Studies have also indicated that pre-treatment with antioxidants such as N-acetyl cysteine or rapamycin can upregulate thiol levels and antioxidant gene expression in CD8⁺ T-cells, enhancing their antioxidant and anti-cancer capacity [560]. Venetoclax disrupts the respiratory chain supercomplex and accelerates ROS generation in CD3⁺CD4⁻CD8⁻ double-negative T-cells and CD8⁺ T-cells, enhancing CD8⁺ T-cell cytotoxicity [561]. In HCC, high PGAM1 (phosphoglycerate mutase 1) expression reduces the infiltration and activation of CD8⁺ T-cells [562]. Inhibition of PGAM1 promotes CD8⁺ T-cells infiltration and promotes ferroptosis in HCC cells by inducing energy stress and ROS-dependent AKT inhibition to downregulate LCN2 (lipocalin-2) [562]. In the TME, IL-15 can activate the Trx system through mTOR, increasing thiol levels on the NK cell surface to stabilize its tumor-killing capability and reverse microenvironment immunosuppression [563]. Inversely, some immune training can enhance the anti-tumor activity of innate immune cells. For instance, training TANs with β -glucan generates excessive ROS in a NOX-dependent manner to exert anti-tumor effects [564].

ROS-associated strategies for immunosuppression elimination

The tumor immune-suppressive microenvironment is vitally important in immunotherapy blockade. Targeting and depressing immunosuppressive cells by ROS is

another effective way to reshape the immunosuppressive TME. CAFs rely on continuous NOX4-mediated ROS production to maintain their immunosuppressive phenotypes. Therefore, the selective NOX1/4 inhibitor GKT137831 can specifically target CAFs, attenuating TGF- β 1-induced CAF activation and reshaping the tumor immune-suppressive microenvironment [565, 566]. Inhibiting indoleamine-2,3-dioxygenase 1 and NOX2 also impedes ROS generation, disrupting the interaction between CAFs and monocytes and reducing MDSC generation [207]. The Zr-CeO nanozyme converts $O_2^{\bullet -}$ to H_2O_2 and H_2O_2 to O_2 to eliminate ROS via SOD-like and CAT-like activities, respectively [25]. Reduction of ROS levels inhibits MDSC proliferation and immunosuppression [25]. The PI3K/AKT pathway inhibitor, IPI-549, can also effectively reduce ROS levels in MDSCs, promoting MDSC apoptosis and reducing its immunosuppressive activity against CD8⁺ T-cells [567]. Additionally, ROS nanozyme could scavenge ROS to modulate macrophages by blocking ERK and JAK/STAT pathway activation, inhibiting their M2-related gene expression, such as *Arg1*, *Chil3*, and *Retnla*, and stimulating their M1 marker expression [24, 25, 568]. The SDT-based M2-targeting nanoparticles M-H@lip-ZA could target M2 macrophages in TME and induce their depletion. This also decreases tumor hypoxia and immunosuppressive cytokines releases, while strengthening vasculature normalization, intertumoral perfusion, and anti-cancer cytokines secretion [569].

A promising strategy to convert TME from 'cold' to 'hot' and overcome immunosuppression is to trigger ICD (immunogenic cell death) in cancer cells with long-term anti-cancer immunity [570]. ICD immunogenicity is primarily mediated by DAMPs (damage-associated molecular patterns) exposed to dying cells, including calreticulin, HSPs (heat shock proteins), secreted ATP, and high mobility group protein B1 [571]. Most of these DAMPs can be recognized by PRRs (pattern recognition receptors) on the DC surface, improving antigen presentation and CD8⁺ T-cell cytotoxicity [572–574]. Research has demonstrated that ERS is a prerequisite to induce ICD, and ROS critically influences ERS [571]. ICG/AuNR@BCNP was designed as an ERS nano-orchestrator targeting PERK (protein kinase R-like endoplasmic reticulum kinase)/CHOP pathway to optimize ERS control, thereby promoting ICD [575]. Elevated lactate levels due to severe hypoxia in TME and metabolic reprogramming of tumor cells (the Warburg effect) may limit ROS production [576]. PLNP^{Cu} can degrade lactate into H_2O_2 , which is then converted into anti-tumor ROS via a Fenton-like reaction [577]. PP^{IR780-ZMS} can control the release of ZMS (manganese zinc sulfide nanoparticles) under near-infrared light, triggering Mn^{2+} -mediated CDT to

Table 3 The role of oxidative stress-based strategies in immunotherapies

Drugs	Mechanism	ROS	Effects	Tumors	References
T-Fulips	Improve the antioxidant capacity of T cells	NA	Anti-tumor	Breast cancer, colon cancer, and melanoma Melanoma	[224] [560]
Venetoclax	Damage the respiratory chain	Increase	Anti-tumor	Acute myeloid leukemia	[561]
IL-15	Activate the Trx system of NK cells	NA	Anti-tumor	Chronic myelogenous leukemia and non-small cell lung cancer	[563]
Zr-CeO Nanozyme	SOD-like and CAT-like enzyme activation	Decrease	Anti-tumor	Renal cancer and breast cancer	[25]
IPI-549	Inhibit PI3K/AKT pathway	Decrease	Anti-tumor	Colon cancer	[567]
β-Glucan	Train TAN to generate ROS	Increase	Anti-tumor	Lung cancer and melanoma	[564]
M-H@Lip-ZA	Kill M2-TAM utilizing ROS	Increase	Anti-tumor	Breast cancer	[569]
ICG/AuNR@BCNP	Induce ICD by tumor cell ERS	Increase	Anti-tumor	Glioblastoma and melanoma	[575]
NP-I-CA-TPP	Induce ICD by consuming GSH	Increase	Anti-tumor	Osteosarcoma	[581]
PPIR780-ZMS	Induce ICD by CDT	Increase	Anti-tumor	Melanoma	[578]
Cardiac Glycosides	Induce ICD by inhibiting sodium–potassium ATPase	Increase	Anti-tumor	Breast, colorectal, head and neck, and hepatocellular carcinoma	[579]
Micheliolide	Induce ICD by inhibiting TrxR	Increase	Anti-tumor	Hepatocellular carcinoma	[580]
PLNPCu	Induce ICD by Fenton-like reaction	Increase	Anti-tumor	Breast cancer	[577]

IL-15 interleukin-15, CAT catalase, PI3Kγ phosphoinositide 3-kinase gamma, TAN tumor-associated neutrophil, M2-TAM M2-like tumor-associated macrophage, ICD immunogenic cell death

induce ERS [578]. Menger et al. found that cardiac glycosides (CGs) are also an ICD inducer. CGs activate ERS by inhibiting sodium–potassium ATPase on the cell membrane, increasing intracellular calcium ion concentration [579]. Micheliolide, a TrxR inhibitor, can induce ROS generation and ERS in hepatocellular carcinoma cells [580]. These effects induce robust ROS-based ERS and lead to tumor cell ICD, remodeling TME immunity. Therefore, combining immunotherapy with ROS intervention has been widely recognized as a promising strategy to overcome tumor therapeutic resistance (Table 3).

ROS-based strategies in combinatorial therapies

Given tumor heterogeneity, single therapies can quickly induce resistance and attenuate treatment effects [582, 583], while combination therapy can reduce or delay the occurrence of drug resistance through the synergistic effect of different mechanisms.

Combining therapies with ROS-associated strategies increases tumor-killing efficacy

Given the higher resistance to oxidative damage in tumor cells, integrating ROS-based therapies with additional treatment could increase the tumor-killing efficacy. Hui, K et al. studied the synergistic effect of bortezomib, a proteasome inhibitor, and romidepsin, a histone deacetylase inhibitor, in the treatment of gastric cancer, and found that this combined therapy could induce autophagy and apoptosis in MAPK- and ROS-dependent way, exhibiting enhanced killing effect on gastric cancer cells [584]. In GBM, cells have a high demand for iron to promote tumor growth and

progression, so these cells are susceptible to ferroptosis, of which SLC7A11 (solute carrier family 7 member 11) is a key antagonist [585]. SIRT3 (Sirtuin-3) inhibition leads to the accumulation of ferrous and ROS in mitochondria, and the mitochondrial autophagy pathway is upregulated after SIRT3 knockdown in GBM cells [585]. Above, this provides an idea for a combination therapy that targets SIRT3 and inhibits SLC7A11 to induce iron death in GBM.

Recently, the advent of nanomedicine-based ROS therapy has provided a platform for combinatorial therapies. A synergistic approach can be formed by combining open-source and throttling strategies to achieve high ROS concentrations with the ability to induce tumor cell damage. PGC-DOX, an intelligent nano-catalytic theranostic, uses poly (ethylene glycol)-modified GOx (glucose oxidase) loaded with DOX to catalyze intracellular glucose to produce H₂O₂, facilitating an in situ Fenton reaction in conjunction with CDT to generate a high •OH level. This synergistic approach enhances the anti-tumor effect with minimal side effects [586]. Liposome-based nano-drugs co-loaded with doxycycline hydrochloride and Ce6 (chlorin e6) simultaneously disrupt mitochondrial function and enhance PDT [587]. Fe²⁺@UCM-BBD loaded with DOX, Ce6, and Fenton reagent (Fe²⁺) achieved a controlled release of DOX in the acidic TME, enabling the combined treatment of PDT, CDT, and chemotherapy [588]. GSH deprivation is critical in nanomedicine-based combinatorial therapy [589]. MCPP is a nanomedicine combining PTX and the photosensitizer P18 (purpurin 18). PTX-SS-PTX is a GSH-responsive dimeric form of PTX connected by a disulfide bond, designed to release PTX and deplete GSH in the TME. P18

generates ROS upon laser irradiation, inducing cytotoxicity and ICD, while PTX-SS-PTX enhances this effect by reducing GSH levels, creating a synergistic anti-tumor response [590].

Integrating nano-technology with ROS-based strategies promotes immunotherapy efficacy

TME-targeting nanomaterials have been applied to integrate ROS-generating therapy with immunotherapy. A nano-drug containing a photosensitizer and PI3K γ inhibitor uses PDT to induce ICD and inhibit immune suppression induced by the PI3K γ /Akt pathway in MDSCs [567]. CCA-M1EVs (M1-like macrophage-derived extracellular vesicles) use surface CPPO to facilitate CDT. The drug-loaded M1EVs can penetrate the blood–brain barrier, specifically target and accumulate in gliomas enriched with M2 macrophages, and induce the polarization of M2 macrophages towards the M1 phenotype, thereby achieving immunomodulation of the TME [591]. The PIH-NO system can accumulate in the mitochondria and alleviate intracellular hypoxia to enhance SDT, leading to mitochondrial dysfunction and amplify ICD effects [592]. Meanwhile, the PIH-NO-derived NO could convert M2-TAM into M1-TAM and simultaneously deplete MDSCs in TME [592].

Moreover, nanotechnology can integrate ROS-based cytotoxicity with ICB (immune checkpoint blockade) therapy. S- α PDL1/ICG@NP-mediated PDT generates ROS and induces ICD, sensitizing the tumor to immunotherapy via subsequent anti-PD-L1 antibody release [593]. The UCNPs@Cu-Cys-GOx nano-system also generates ROS to reverse immunosuppression and strengthen PD-1/PD-L1 therapeutic effects to inhibit primary tumors [594]. Additionally, the nano-drug-mediated ROS therapies exhibit good compatibility with other immune checkpoint inhibitors, including Gal-9, Tim-3, and CD47 [595, 596]. He et al. summarized that PDT-induced ROS can also be combined with tumor vaccines, immune adjuvants, and other agents [597]. Also, the PDT-induced pyroptosis has been summarized as “photo-pyroptosis” to demonstrate PDT’s synergistic immunotherapy [598].

Nanomedicine, a promising application in cancer therapy, has demonstrated its ability to integrate multiple therapeutic effects, potentially overcoming therapeutic resistance in cancers. ROS-mediated cytotoxicity and TME remodeling have been widely considered in nanomaterial design due to their strong anti-tumor effects and compatibility with other therapies, exhibiting great potential for developing future therapeutic strategies.

The clinical prospects of artificial intelligence, biomaterials, and imaging techniques in oxidative stress

Artificial intelligence in oxidative damage detection and antioxidative prediction

The short lifespan of ROS in the TME and different subcellular locations makes direct measurement of ROS challenging. Machine-learning-based approaches have been applied to the experimental measurement of ROS. Some supervised learning models, such as neural networks, logistic regression, and decision trees, can quantify oxidative stress damage in biological samples [599]. In addition, Weighted Gene Expression Network Analysis with GO term enrichment could be combined with clinical analysis to identify genes with diagnostic value related to local immune and oxidative stress [600]. As previously mentioned, various substances can exert antioxidant effects. A recent study combined artificial intelligence with oxidative stress to develop a new machine-learning model to identify proteins with antioxidant properties, achieving relatively high accuracy [601, 602]. Machine-learning algorithms can predict the nanoparticle-based antioxidant efficiency [603].

Bioengineering in ROS-based cancer therapies improvement

Various engineered biomaterials exhibit tumor-specific ROS modulation capabilities, or with nanocarrier systems, enhancing pharmaceutical ROS-regulation efficiency. Meanwhile, the ROS-responsive mechanisms enable precise microenvironmental targeting. Several nanomaterials, such as PTX@TPGS-PBTE NPs, ZMRPC@HA, Zr-CeO, PGC-DOX, and Fe²⁺@UCM-BBD, have demonstrated good anti-tumor effects and exhibit great potential when combined with immunotherapy. The development of energy-converting biomaterials, including noble metals, metal semiconductors, and MOFs, has enhanced the efficacy of energy-driven cancer therapies, including RT, PDT, and SDT, with minimal side effects [604]. A novel radiosensitizer, Met-CuS@DSH, which encapsulates metformin and copper sulfide nanoparticles in an injectable DNA supramolecular hydrogel, has been developed [605]. With targeted delivery to tumor tissues, it can effectively reverse tumor hypoxia and promote the generation of ROS [605]. In addition, some nanomaterials have antioxidant properties that can neutralize ROS. Ultra-small ruthenium nanoparticles can mimic SOD activity to scavenge O₂•⁻, and this TME-responsive ROS scavenger can be used as an adjuvant therapeutic agent to minimize side effects and improve drug efficacy [606]. To control ROS toxicity, attempts can also be made to selectively eliminate cytotoxic ROS while

retaining physiological ROS balance. Modulating the surface state of herbal CDs (carbon dots) can rationally construct dynamic ROS nanomodulators. For example, phenolic OH-containing CDs derived from honeysuckle (*Lonicera flos*) and dandelion showed appropriate redox potentials, and they were able to scavenge cytotoxic ROS such as $\bullet\text{OH}$ and ONOO^- [607]. However, it was ineffective against essential ROS such as $\text{O}_2\bullet^-$, H_2O_2 , and NO [607].

PTK-UR (poly(thioketal)-urethane) is a porous scaffold that can deliver macrophages to tumor tissues and rapidly degrade in response to local ROS in the tumor [608]. Injectable smart hydrogels with a three-dimensional network structure can serve as carriers for anti-tumor drugs or even cells, achieving localized storage and controlled release, and can exert systemic anti-tumor effects [609]. The PAA-MnO₂ mineralized hydrogel, with its ability to selectively mineralize in response to the high ROS levels found in tumor tissues, not only facilitates cancer detection through a visible sol–gel transformation but also effectively scavenges ROS, which in turn enhances the accuracy and reliability of cancer monitoring, thus demonstrating great potential for cancer monitoring [610]. Numerous emerging therapeutic strategies use hydrogels for anti-inflammatory purposes [611]. Chitosan and its derivatives produce minimal side effects and have redox regulatory potential when implanted into mammals [612]. However, their degradability, biocompatibility, and toxicity issues have yet to be fully resolved.

Oxidative stress in imaging-based tumor monitoring

The combination of redox-sensitive agents or probes and imaging techniques has been applied to detect tumor oxidative stress status. Several MRI contrast agents, such as stable nitroxide free radicals, activatable paramagnetic complexes, and hyperpolarized [1-¹³C] dehydroascorbic acid, can detect redox conditions in tumor cells and tissues. Stable nitroxide free radicals are cell-permeable and provide T1 contrast through 1-electron transfer reactions, with their reduction rate dependent on ROS- and ROS-scavenging systems [613]. The redox-specific probes developed for tumor oxidative stress detection contain several types, including fluorescent, self-luminous, nano-engineered, photoacoustic, and quantum dot probes. Several fluorescent probes have been developed for the real-time monitoring of tumor oxidative stress. These probes consist mainly of a fluorophore, linker, and recognition group [614]. The fluorophore is oxidizable and produces fluorescent products upon oxidation [613]. Research has also found that some self-luminous nano-probes can image high-ROS inflammation sites [615], with some possessing strong anti-tumor properties [616]. A nano-probe based on peroxalate ester derived from

vitamin E emits a chemiluminescent signal to precisely locate disease sites under high H_2O_2 conditions in the TME [617]. A photoacoustic probe, based on a BODIPY scaffold, can cross the blood–brain barrier and perform dynamic imaging of oxidative stress in the mouse brain using PA imaging. This probe responds reversibly and ratiometrically to oxidative stress, changing its optical properties in the presence of ROS [618]. Small quantum dot-based sensors, which can be detected using electron paramagnetic resonance, MRI, and optical imaging, are capable of tracking and monitoring the overall redox state and oxidative stress in cells and tissues. Recently, quantum dots were found to have size and surface properties that can be tailored to respond to specific redox changes, making them effective for detecting the altered redox environments often found in tumors [619]. Currently, these probes confront multifaceted challenges, including controllable synthesis, toxicity, metabolic clearance, and more convenient imaging technologies [620]. However, future development in nanomanufacturing and bioinspired surface engineering is promising to enable more advanced probe synthesis and precise control over probe biodistribution. Meanwhile, the biodegradable scaffold platforms will enable *in vivo* clearance to reduce metabolic risk, accelerating their translation.

Combining fluorescent probes with various imaging techniques allows non-invasive, real-time, highly sensitive, and high-resolution monitoring of cellular physiological and pathological states. Meanwhile, the abnormal oxidative stress features in TME provide precise tracking of tumor lesions *in vivo* for better tumor monitoring. PET imaging is being used to visualize the interior of tumors, providing better insights into the TME and aiding in the development of appropriate diagnostic and treatment plans [613]. (18)F-FASu is a PET tracer that targets the system x_c^- transporter, which is upregulated in tumor cells under oxidative stress to increase cystine uptake for glutathione synthesis; it allows for high-specificity tumor imaging with lower background noise than 18F-FDG [621]. Some fluorescent probes can perform *in vivo* imaging of specific endogenous ROS, GSH, and other endogenous antioxidant components [614], as well as oxidative damage products (lipids, proteins, and DNA) [622], and can differentiate between tumor and normal tissues [623]. Luminescent fluorescent probes can specifically and sensitively detect gamma-glutamyl transferase (GGT), which is overexpressed in many tumors and associated with their growth, invasion, and resistance to chemotherapy, thus enabling real-time imaging of tumor biology. These probes contain a GGT-cleavable peptide substrate linked to a fluorescent dye, and upon specific recognition and hydrolysis by GGT, the dye is released and fluoresces, allowing for precise localization

and monitoring of tumor development and treatment response [624].

The limitation of ROS-based therapy in clinical practice

The spatiotemporal dynamics of ROS limit ROS-based therapies

While ROS-based therapeutic strategies demonstrate promising potential, they are constrained by several limitations. ROS encompasses a group of molecules such as $O_2^{\bullet-}$ and H_2O_2 , exhibiting divergent biological roles. Significant differences exist in their chemical reactivity, half-lives, and subcellular localization. In both clinical and preclinical studies, the specific ROS species involved are often generalized as “ROS” without further differentiation, largely due to the rapid interconversion rates among ROS and technical challenges in their detection. Therefore, additional studies are warranted to delineate their individual properties and tumor-specific mechanisms in cancer biology. ROS may exert distinct roles in different stages of cancer development [625]. This dynamic nature necessitates precise spatiotemporal regulation of ROS during therapeutic interventions. However, current technologies face challenges in achieving real-time monitoring and dynamically adjustable treatment strategies, potentially leading to uncontrollable therapeutic outcomes.

The off-target effects of ROS-based strategies increased their toxicity to healthy tissues

The complexity of ROS regulation remains incompletely elucidated. On the one hand, physiological levels of ROS function as critical signaling molecules and are essential for cellular physiology, including immunocytes, with their levels precisely regulated. However, elevated ROS levels also trigger oncogenic signaling pathways to promote tumor initiation and progression. On the other hand, elevated ROS levels could be utilized to induce tumor cell death, but they can concurrently damage immunocytes' function. This narrow therapeutic window poses challenges in achieving sufficient cancer cell eradication without harming non-malignant cells. For instance, the liver, as the principal metabolic organ for metabolizing most chemotherapeutic agents, generates excessive ROS during drug detoxification, and the resultant oxidative stress has been linked to hepatic pathologies [626]. Arsenic trioxide induces oxidative stress through multiple pathways, leading to hepatotoxicity [627]. Additionally, doxorubicin triggers oxidative stress via Fenton reactions, generating $O_2^{\bullet-}$ and $\bullet OH$, which damage enzymes, lipids, and nucleic acids in cardiomyocytes [628]. Similar to cardiomyocytes, neurons are highly vulnerable to irreversible oxidative damage due to their non-renewable

nature, significantly compromising patients' quality of life. Certain chemotherapeutics, such as cisplatin, paclitaxel, and oxaliplatin, have been shown to induce oxidative stress in the central or peripheral nervous systems, contributing to neurotoxicity [629]. Therefore, when clinically intervening to modulate redox balance, it is critical to determine the proper concentration of ROS to be precisely regulated in the target region. One feasible strategy is to integrate antioxidant supplementation to protect healthy tissues from drug-induced oxidative damage. A recently initiated clinical trial (NCT05539053) is evaluating the preventive and therapeutic efficacy of NAC against PIPN (paclitaxel-induced peripheral neuropathy) in patients diagnosed with ovarian, tubal, and peritoneal malignancies. This trial stratifies participants into three arms: a short-course NAC regimen (2,400 mg/day orally administered for one week per paclitaxel cycle), a long-course NAC regimen (2,400 mg/day daily over nine weeks), and a control group receiving paclitaxel monotherapy. The PIPN incidence rates and severity were compared among these patients during chemotherapy administration. Similarly, the protective effects of MitoQ supplementation on doxorubicin-induced cardiovascular toxicity via oxidative stress were prospectively evaluated in breast cancer patients (NCT05146843). The oxidative stress markers, endothelium-dependent dysfunction of peripheral vascular beds, arterial stiffness, central blood pressure, and physical capability were compared in patients receiving MitoQ and placebo 20 mg per day during chemotherapy. Currently, the results of these trials have not been posted. Furthermore, while certain agents exhibit antitumor efficacy by modulating ROS levels, the underlying mechanisms remain incompletely elucidated, with non-ROS-related pathways being increasingly identified. These off-target effects may not be detrimental; instead, combination therapies integrating ROS modulation could demonstrate synergistic antitumor activity superior to ROS-targeted monotherapies.

The low bioavailability and therapeutic resistance decreased the efficacy of ROS-based treatments

Many ROS-targeting therapies require an adequate oxygen supply to generate cytotoxic ROS. However, hypoxia is a hallmark of many solid tumors [630], which restricts ROS production and consequently diminishes therapeutic efficacy. Meanwhile, ROS inducers or scavengers frequently face bioavailability challenges due to biological barriers. Nanotechnology has great potential to improve pharmaceutical bioavailability, as nanoscale formulations have demonstrated that local or systemic delivery of these compounds to the target site improves pharmacokinetics and enhances the delivery kinetics [631, 632]. Some of the nanomedicines, such as PGX-DOX,

CCA-M1EV, PTX@TPGS-PBTE NPs, and MET-CuS@DSH mentioned earlier, demonstrate the ability to target tumor cells. In addition, Fe^{2+} @UCM-BBD enables controlled drug release within tumor tissues, while carbon dots enable the selective scavenging of cytotoxic ROS, thereby mitigating ROS-induced damage to normal tissues. Moreover, tumors activate adaptive antioxidant defense to counteract damage induced by oxidative stress. Whereas, it remains unclear whether the tumor cell subpopulation surviving from the attack of ROS overload intervention could exhibit enhanced antioxidant capacity. This may raise a challenge that the drug dosage required for ROS-inducing tumor cell killing might increase over time, leading to therapeutic resistance.

Conclusion

Oxidative stress is involved in various cancer hallmarks and has been a hotspot in investigating cancerous targets. However, oxidative stress regulation is highly dynamic and complex due to various ROS sources and abundant oxidative stress modulators inside tumor cells and TME. Therefore, we introduced endogenous ROS generation and the oxidative regulatory network. The main source of ROS is the mitochondrial electron transport chain [33]. The electron released from complex I and III generates $\text{O}_2\bullet^-$ when reacting with oxygen, the $\text{O}_2\bullet^-$ are subsequently converted into ONOO^- with NO or H_2O_2 by SODs. The ER, peroxisomes, and NOXs in the cytoplasm also generate abundant ROS. Multiple ROS generators provide various targets for ROS-based therapies. Although the roles of oxidative stress and ROS in cancer have been widely revealed, the complexity of ROS regulation severely limited the development of interventions that employ a single supplement or single target blockage in tumor cells due to their poor tumor absorbability [363], specificity [372], and unsatisfactory anti-cancer effects [270], probably leading to unsatisfying outcomes of clinical administration of single antioxidant or ROS inhibitor. Nevertheless, targeting ROS to remodel TME has exhibited exciting discoveries. Altering ROS levels in the TME has presented enhanced cytotoxicity of CD8⁺ T-cells [560] and NK cells [563] and alleviated TME immunosuppression by depleting MDSCs [567] and M2 macrophages [24, 25, 568]. However, one issue should be noted that the tumor cells and non-tumor cells in the TME exhibited diverse sensitivities to certain ROS levels, and altering the tumor ROS level might cause unpredictable effects on tumor progression. Given the importance of TME in cancer development, TME-targeting ROS strategies warrant further investigation to control cancer, and

TME-targeting ROS treatment should be robustly verified using credible animal model experiments.

Moreover, biomaterials and nanotechnology combined with ROS-based therapies can precisely deliver drugs to tumor tissues, overcoming the limitations of poor drug selectivity, extending the duration of drug action, and penetrating biological barriers. This can increase the local concentration of drugs in tumor tissues, thereby enhancing therapeutic efficacy while reducing cytotoxicity to healthy tissues. Some drugs can release oxygen at their site of action, significantly increasing ROS generation. Nanomedicine can maximize ROS cytotoxicity inside tumors via selective local activation and strong dynamic effects [587], induce ICD [580], or remodel the TME for extended tumor control [567]. Besides, it provides a platform for synergistic combinatorial treatment to facilitate multiple targeting, including GSH depletion [590] and lactate degradation [577]. Nano-based ROS strategies are compatible with ICB therapeutic reagents [595, 596] and can enhance anti-PD-L1 treatment [594]. The integration of ROS-based strategies and ICB therapy on nano- and biomaterial platforms holds promise for further development because ICB therapy garners significant attention for its ability to control advanced cancers. Imaging techniques allow for in vivo imaging of oxidative stress, enabling non-invasive, real-time, high-sensitivity, and high-resolution monitoring of the physiological and pathological states of cells. A novel practice related to oxidative stress is that various artificial intelligence learning models can be used to quantify ROS levels and efficiently screen for potential antioxidants.

Although numerous strategies have been developed with increasing understanding of the role of oxidative stress in cancer pathology, the regulatory network of oxidative stress in cancer remains highly interconnected and complex. More laboratory and clinical attempts are required to gradually obtain precise evaluation of distinct oxidative-stress-targeting strategies in cancer control.

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Authors' contributions

JD.W and X.L wrote the first draft of the paper (Writing original draft). X.L, JD.W, Z.Y, Y.W, and J.W critically revised the paper. Z.X, S.H, P.L, and Q.C developed the idea and concept, supervised and revised the paper (Writing-review-editing). All authors reviewed the manuscript and agreed to publication.

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Data availability

No datasets were generated or analysed during the current study.

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Consent for publication

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Competing interests

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