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Review article

Oxidative Stress and Malignancy: The Central Role of Reactive Oxygen Species (ROS) in Cancer

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Abstract:

Reactive oxygen species (ROS) are unavoidable byproducts of aerobic metabolism that play a dual and paradoxical role in cancer biology. At physiological levels, ROS function as essential second messengers regulating proliferation, differentiation, and survival signaling. However, excessive ROS accumulation beyond cellular antioxidant capacity induces oxidative stress, leading to DNA damage, genomic instability, and malignant transformation. This review provides a comprehensive synthesis of the molecular mechanisms linking ROS to cancer initiation, progression, and therapeutic vulnerability. We examine the major sources and types of ROS, with particular emphasis on mitochondrial and enzymatic generation, and detail the adaptive antioxidant systems exploited by cancer cells, including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidases (GPX), total antioxidant capacity (TAC), and lipid peroxidation biomarkers such as malondialdehyde (MDA). The review further elucidates how ROS regulates key oncogenic processes, including DNA mutagenesis, redox-sensitive signaling pathways, epithelial–mesenchymal transition, angiogenesis, and immune evasion. Importantly, we discuss ROS-induced cell death pathways—apoptosis and ferroptosis—and highlight emerging ROS-based therapeutic strategies, including photodynamic therapy, chemodynamic therapy, ferroptosis inducers, and ROS-responsive drug delivery systems. Finally, we explore future directions in personalized ROS-targeted cancer therapy, integrating redox profiling, nanotechnology, and immunotherapy. Collectively, this review underscores ROS not merely as byproducts of cancer metabolism but as central determinants of tumor behavior and promising targets for precision oncology.

Keywords: Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidases (GPX), total antioxidant capacity (TAC), malondialdehyde (MDA).

1. Introduction:

Cancer represents one of the most significant threats to human health, claiming approximately 10 million lives annually. While our understanding of cancer etiology has evolved substantially, reactive oxygen species (ROS)—highly reactive oxygen-containing molecules produced during cellular metabolism—have emerged as critical mediators in both the initiation and progression of cancer [1-3]. The relationship between ROS and cancer is paradoxical: at physiological levels, ROS serve as essential second messengers regulating cell growth; however, when ROS accumulation exceeds cellular antioxidant capacity, oxidative stress results,

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promoting genomic instability and malignant transformation. This review synthesizes current knowledge on the ROS-cancer correlation, examining antioxidant enzyme systems including glutathione peroxidase (GPX), catalase (CAT), superoxide dismutase (SOD), malondialdehyde (MDA), and total antioxidant capacity (TAC), along with emerging ROS-based therapeutic interventions.

2. Definition and causes of cancer:

Cancer is clinically defined as a malignant neoplasm characterized by uncontrolled proliferation of abnormal cells with the capacity for invasiveness and metastasis to distant organs [4,5]. Unlike benign tumors, which remain localized, malignant cancers possess fundamental hallmarks: unrestricted cellular proliferation, impaired differentiation, resistance to apoptosis, and the capacity to evade immune surveillance. Cancer develops through progressive accumulation of genetic alterations involving activation of oncogenes (KRAS, MYC) and inactivation of tumor suppressor genes (p53, BRCA1) [6,7].

The etiology of cancer is multifactorial, involving interactions between genetic predisposition, environmental exposures, chronic inflammation, and oxidative stress. Major causative factors include: [8-10].

- Genetic factors: Inherited mutations in tumor suppressors and oncogenes
- Environmental exposures: Tobacco smoke, ultraviolet/ionizing radiation, asbestos, air pollutants, heavy metals
- Chronic inflammation: From persistent infections (hepatitis B/C, Helicobacter pylori) and inflammatory diseases
- Oxidative stress: ROS-induced DNA damage from mitochondrial dysfunction and upregulated NADPH oxidases

3. Definition and types of reactive oxygen species:

Reactive oxygen species are atoms or molecules with unpaired electrons in their outer shell, making them highly reactive and capable of rapid oxidation-reduction reactions with biological macromolecules [2,11,12]. ROS are continuously generated as byproducts of aerobic cellular metabolism, particularly during oxidative phosphorylation in mitochondria. Under physiological conditions, cells maintain ROS at low steady-state levels through antioxidant defense systems. However, when ROS accumulation exceeds cellular antioxidant capacity, oxidative stress ensues, causing irreversible damage [2,12].

ROS are classified into two categories:

Free Oxygen Radicals:

Superoxide anion (O_2^-): The primary ROS generated at mitochondrial electron transport chain complexes I and III. Rapidly converted to hydrogen peroxide by superoxide dismutase (SOD), superoxide participates in cellular signaling and serves as a precursor for more reactive ROS species [2,12,13].

Hydroxyl radical (OH): The most reactive and shortest-lived ROS species (nanosecond lifespan), primarily generated through the Fenton reaction with ferrous iron. Due to extreme reactivity, hydroxyl radicals cause indiscriminate damage to DNA, proteins, and lipids [11,12,14,15].

Nitric oxide (NO) and other radicals: Nitric oxide generated by nitric oxide synthase can react with superoxide to form peroxynitrite ($ONOO^-$), a potent oxidant involved in cancer-related signaling [13].

Non-Radical Reactive Oxygen Species:

Hydrogen peroxide (H_2O_2): A stable, membrane-permeable non-radical ROS serving as a critical second messenger. Unlike superoxide, H_2O_2 is highly diffusible and can cross cellular membranes via aquaporin channels, enabling redox signal transmission between subcellular compartments [11,12].

Singlet oxygen ($^1O_2$): An electronically excited oxygen form with high reactivity toward organic

molecules, particularly involved in photodynamic cancer therapy [11,16].

Peroxynitrite ($ONOO^-$) and other species: Additional non-radical ROS, including organic hydroperoxides, hypochlorite (HOCl), and ozone (O_3) [17,18].

4. ENZYMATIC ANTIOXIDANT SYSTEMS

Cancer cells require elevated baseline ROS for growth signaling, yet must avoid ROS levels that trigger lethal cell death. To navigate this redox tightrope, cancer cells upregulate multiple antioxidant enzyme systems:

4.1. GLUTATHIONE PEROXIDASE (GPX)

Glutathione peroxidase comprises a family of at least eight selenoprotein isoforms (GPX1-GPX8) that catalyze the reduction of hydrogen peroxide and lipid hydroperoxides using reduced glutathione (GSH) as the reducing substrate [19-22]. The catalytic cycle involves:

$2\ GSH + H_2O_2 \rightarrow GSSG + 2\ H_2O$

Oxidized GSSG is recycled back to GSH by glutathione reductase using NADPH, maintaining a high intracellular GSH/GSSG ratio (approximately 100:1) [21].

Key isoforms include:

GPX1 (cytosolic): The most abundant isoform; allelic loss of the GPX1 gene is common in cancer, suggesting tumor-suppressive function. However, when present, GPX1 is often upregulated in advanced cancers for ROS scavenging [21,23].

GPX4 (membrane-associated): Specialized for the reduction of complex lipid hydroperoxides in cell membranes; the critical enzyme protecting against ferroptosis. GPX4 inhibition is the primary mechanism of ferroptosis-induced cancer cell death [24].

Cancer cells exhibit elevated GPX expression to detoxify ROS, maintain growth signaling, and resist chemotherapy. This dependence creates vulnerability: ferroptosis inducers specifically target GPX4 by depleting cellular cystine pools and preventing glutathione synthesis, exploiting cancer cells' ROS-saturated state [22,24].

4.2. CATALASE (CAT)

Catalase is a ubiquitous, heme-containing iron enzyme that catalyzes H_2O_2 decomposition into water and oxygen without requiring cofactors, making it an independent defense line against H_2O_2: [25-27].

$2\ H_2O_2 \rightarrow 2\ H_2O + O_2$

Catalase exhibits biphasic kinetics: at high H_2O_2 concentrations (>1 mM), it decomposes H_2O_2 rapidly to water and oxygen; at low concentrations (<1 mM), it exhibits peroxidatic activity, oxidizing non-NADPH hydrogen donors (alcohols, phenols) while being reduced to water. This dual functionality enables efficient function across physiological H_2O_2 concentrations [26,27].

Catalase is frequently upregulated in cancer cells as part of antioxidant defense adaptation, enabling cancer cells to tolerate high ROS while maintaining proliferation. Elevated catalase activity correlates with enhanced antioxidant capacity in colorectal, prostate, and pancreatic cancers [28,29].

4.3. SUPEROXIDE DISMUTASE (SOD)

Superoxide dismutases are metalloenzymes catalyzing the dismutation of superoxide anion radical ($O_2^{\bullet -}$) to hydrogen peroxide (H_2O_2) and molecular oxygen at extraordinarily rapid rates: [30,31].

$2\ O_2^- + 2\ H^+ \rightarrow H_2O_2 + O_2$

Three mammalian SOD isoforms exist with distinct roles:

SOD1 (Cu/ZnSOD): The most abundant intracellular SOD isoform (~80% of total), located in cytosol, nucleus, and mitochondrial intermembrane space. SOD1 is frequently overexpressed in cancers, particularly lung adenocarcinomas and leukemias, driving

proliferation and survival. SOD1 inhibitors (ATN-224, LCS-1) show anticancer promise [9,32].

SOD2 (MnSOD): Exclusively localized in mitochondrial matrix; exhibits dichotomous role depending on tumor stage. During tumor initiation, low SOD2 allows superoxide accumulation, promoting mutagenic DNA damage; during metastatic progression, SOD2 is upregulated, scavenging superoxide while elevating H_2O_2 levels, driving redox signaling that promotes migration and invasion [32,33].

SOD3 (EcSOD): The secreted, extracellular form; generally reduced in human cancers, with loss correlating with poor prognosis and enhanced invasiveness [31,32].

4.4. MALONDIALDEHYDE (MDA) AS OXIDATIVE STRESS BIOMARKER

Malondialdehyde is the principal end-product of lipid peroxidation, generated when ROS oxidize polyunsaturated fatty acids in cellular membranes and lipoproteins [34-36]. MDA is a highly toxic aldehyde that reacts with lysine and arginine residues on proteins, forming protein-DNA and protein-protein cross-links that impair function and cause mutations [37,38].

Serum and tissue MDA levels are significantly elevated in cancer patients compared to healthy controls, typically 2-10 fold higher in malignant tumors [39,40]. MDA serves as an efficient biomarker for cancer diagnosis, stage assessment, and monitoring antioxidant therapy response. Notably, elevated MDA correlates inversely with antioxidant enzyme activity (SOD, CAT, GPX), revealing the oxidative stress signature in cancer [40,41].

4.5. TOTAL ANTIOXIDANT CAPACITY (TAC)

Total antioxidant capacity is a comprehensive measure of the cumulative antioxidant potential of all enzymatic and non-enzymatic antioxidants in biological samples, reflecting combined activities of:

- **Enzymatic antioxidants:** SOD, CAT, GPX
- **Non-enzymatic antioxidants:** Reduced glutathione (GSH), vitamins C and E, uric acid, albumin, bilirubin, carotenoids [42,43].

In cancer, TAC is typically significantly decreased, reflecting impaired enzymatic defense and depletion of non-enzymatic antioxidants through excessive consumption by elevated ROS [16,43]. Reduced TAC in cancer patients correlates with increased cancer risk, advanced disease stage, poorer survival, and increased metastatic potential. TAC measurements guide antioxidant therapy optimization and assess treatment response [10,42].

5. ROS-CANCER INTERACTIONS

5.1. ROS-Mediated DNA damage and Mutagenesis

Elevated ROS causes extensive oxidative modifications to DNA nucleobases, particularly guanine, generating 7,8-dihydro-8-oxoguanine (8-oxo-dG)—a mutagenic lesion that mispairs with adenine, causing G→A transversion mutations activating oncogenes or inactivating tumor suppressors [2,17,42]. Beyond direct damage, ROS impair DNA repair machinery itself: ROS oxidize 8-oxoguanine DNA N-glycosylase 1 (hOGG1), impairing base excision repair; ROS degrade BRCA2, blocking homologous recombination repair. This dual impairment creates a permissive environment for genomic instability [2,44].

5.2. ROS-DRIVEN PROLIFERATION AND SURVIVAL SIGNALING

Low to moderate ROS levels activate pro-survival and pro-proliferative signaling cascades essential for cancer growth through multiple mechanisms [45-47].

ROS directly oxidize cysteine residues in protein tyrosine phosphatases (PTPs), particularly PTEN and PTP1B, creating modifications that inhibit

phosphatase activity. Loss of PTP activity allows unopposed activation of the PI3K/Akt/mTOR axis—a hallmark of malignant proliferation. Similarly, ROS oxidize JNK-inactivating phosphatases, sustaining MAPK/Erk pathway activity and driving proliferation [48,49].

ROS activate transcription factors NF-κB and HIF-1α through multiple pathways, promoting expression of anti-apoptotic proteins (Bcl-2, Bcl-xL, MCL-1), proliferation signals (cyclins, CDKs), and immune evasion molecules [2,46].

5.3. ROS-MEDIATED EPITHELIAL-MESENCHYMAL TRANSITION (EMT) AND METASTASIS

ROS drives EMT through activation of transcription factors (Snail, Slug, Twist, ZEB1) that suppress epithelial markers (E-cadherin) while promoting mesenchymal markers (N-cadherin, vimentin) [2,50]. ROS activate matrix metalloproteinases and serine proteases (urokinase plasminogen activator), enabling extracellular matrix degradation and cancer cell invasion [44,45].

5.4. ROS-DRIVEN ANGIOGENESIS

ROS promote angiogenesis by stabilizing HIF-1α under normoxic and hypoxic conditions through direct inhibition of prolyl hydroxylases (PHDs), allowing HIF-1α to activate transcription of vascular endothelial growth factor (VEGF) and other pro-angiogenic factors [46,47]. ROS enhances endothelial cell migration, tube formation, and matrix degradation via MMP activation, amplifying angiogenic signaling [2,44].

6. ROS-INDUCED CELL DEATH PATHWAYS

When ROS accumulation exceeds cellular antioxidant capacity, ROS shift from growth-promoting signals to lethal stress stimuli, triggering multiple programmed cell death pathways: [51-53].

6.1. ROS-INDUCED APOPTOSIS

ROS oxidize cardiolipin in mitochondrial membranes, causing cytochrome c release into the cytosol. ROS activate mitochondrial permeability transition pore (MPTP) opening and regulate Bcl-2 family proteins: ROS oxidize anti-apoptotic Bcl-2 and Bcl-xL, reducing anti-apoptotic function, while promoting pro-apoptotic BAX and BAK conformational changes [51,52]. Cytosolic cytochrome c binds APAF-1 and procaspase-9, forming the apoptosome, which activates caspase-3, executing apoptosis [52].

6.2. ROS-INDUCED FERROPTOSIS

Ferroptosis is an iron-dependent, non-apoptotic programmed cell death characterized by lipid peroxide accumulation and loss of mitochondrial membrane potential. Ferroptosis inducers deplete intracellular cystine pools (via system xc^- inhibition), preventing glutathione synthesis, while simultaneously inhibiting glutathione peroxidase 4 (GPX4) [54,55]. With both GSH synthesis impaired and GPX4 inhibited, cells cannot neutralize lipid hydroperoxides, leading to catastrophic lipid ROS accumulation and ferroptotic death. Ferroptosis offers a mechanistically distinct pathway to cancer cell death, bypassing apoptosis resistance mechanisms [12,52,55].

7. ROS-BASED THERAPEUTIC INTERVENTIONS

7.1. PHOTODYNAMIC THERAPY (PDT)

Photodynamic therapy is a light-based cancer treatment in which photosensitizers, excited by light, generate ROS for tumor cell killing. When photosensitizers absorb light, they transition to excited states and transfer energy to oxygen molecules, generating ROS through [56,57]:

Type I reactions: Direct hydrogen/electron transfer with biological substrates, forming free radicals that react with oxygen to generate superoxide and hydroxyl radicals.

Type II reactions: Direct energy transfer to oxygen, generating singlet oxygen ($^1O_2$)—a highly toxic ROS that damages tumor membranes, proteins, and organelles. Type II reactions typically dominate, accounting for 70-90% of ROS.

Enhancement strategies include: [58,59]

NIR light-excited PDT: Near-infrared light (700-1000 nm) penetrates tissues to 10-15 mm, enabling deeper tumor treatment. Strategies include direct NIR-absorbing photosensitizers, upconversion nanoparticles that absorb 980 nm NIR and emit visible light, activating conventional photosensitizers, and two-photon excitation.

X-ray-excited PDT: Nanoscintillators convert high-energy X-rays to UV/visible light, activating photosensitizers in deep tumors with excellent X-ray penetration [16,57].

Nanoparticle-based PDT: Organic and inorganic nanocarriers improve photosensitizer solubility, tumor targeting, and accumulation, enhancing PDT efficacy [55,57].

7.2. CHEMODYNAMIC THERAPY (CDT)

Chemodynamic therapy leverages Fenton and Fenton-like reactions between metal ions and tumor H_2O_2 to generate cytotoxic hydroxyl radicals:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + {\bullet}OH + OH^-$$

Metal ions (Fe^{2+}, Cu^+, Mn^{2+}) catalyze the conversion of endogenous tumor H_2O_2 to hydroxyl radicals. CDT advantages include: no light or ultrasound required, direct utilization of tumor microenvironment chemistry, and minimal off-target effects. Enhancements involve engineered nanoparticles that increase H_2O_2 levels and improved metal catalysts with better valence cycling [16,54].

7.3. FERROPTOSIS INDUCERS

Ferroptosis inducers represent a novel class of anticancer agents, particularly effective against apoptosis-resistant cancers. Mechanisms include: [54,60]

System xc^- inhibitors (erastin, sulfasalazine): Block the cystine/glutamate antiporter, depleting cystine and preventing glutathione synthesis.

GPX4 inhibitors (RSL3, artesunate): Directly inhibit glutathione peroxidase 4, preventing lipid peroxide reduction.

Ferroptosis inducers show particular promise in p53-mutant cancers lacking apoptotic capacity and drug-resistant tumors with Bcl-2 family upregulation [60].

7.4. ROS-RESPONSIVE DRUG DELIVERY

Modern nanoparticle-based drug delivery exploits elevated tumor ROS to trigger drug release at tumor sites while sparing normal tissues with physiological ROS levels. ROS-responsive nanoparticles contain linkers (thioketal, thioester, disulfide bonds) cleaved by ROS, releasing encapsulated drugs when nanoparticles encounter the high-ROS tumor environment. This improves therapeutic specificity and reduces systemic toxicity [57,58,61].

7.5 IMMUNOTHERAPY AND IMMUNOGENIC CELL DEATH

ROS and cell death pathways are intimately linked to immunogenic cell death (ICD)—cell death triggering anti-tumor immune responses. During ICD, dying tumor cells release danger-associated molecular patterns (DAMPs), including calreticulin (CRT), high-mobility group box 1 (HMGB1), and adenosine triphosphate (ATP). These DAMPs stimulate antigen presentation by dendritic cells and proliferation of cytotoxic T lymphocytes, generating anti-tumor adaptive immune responses [54][55].

ROS promotes ICD through ER stress-induced DAMP release and NLRP3 inflammasome activation. Combining ROS-elevating therapies (PDT, chemotherapy) with checkpoint inhibitor immunotherapy amplifies anti-tumor immune responses and improves long-term disease control [16,55].

8. FUTURE APPLICATIONS

8.1 PERSONALIZED ROS-TARGETED THERAPY

Future cancer medicine will increasingly rely on ROS-centered therapeutic strategies tailored to individual tumor biology. Comprehensive assessment of tumors will **include:** [43,53-55]

- ROS generation capacity measurement via fluorescent probes

- Antioxidant enzyme expression profiling (SOD, CAT, GPX transcriptomics)
- Oxidative damage markers (MDA, protein carbonyls, 8-oxo-dG)
- Genetic alterations in ROS metabolism (SOD mutations, Keap1/Nrf2 status)

Tumors with high baseline ROS and impaired antioxidant capacity would be candidates for ROS-escalating therapies (PDT, CDT, ferroptosis inducers). Tumors with robust antioxidant defenses benefit from combination approaches targeting multiple pathways simultaneously [43,53,54].

8.2 NANOTECHNOLOGY INTEGRATION

Next-generation nanoparticles will integrate: [58,59]

- Photosensitizers or sonosensitizers for ROS generation
- Chemotherapy payloads for direct cell killing
- Tumor-targeting moieties (antibodies, peptides)
- Imaging agents (fluorophores, radionuclides) for visualization
- Immunomodulatory molecules for immune activation

Multi-stimuli responsive nanoparticles (ROS + pH + enzyme-responsive) will enable enhanced selectivity and real-time monitoring of drug release [16,58].

8.3 COMBINATION THERAPEUTIC STRATEGIES

Future paradigms will combine ROS-modulating therapies: [53-55,58]

ROS escalation + antioxidant inhibition: PDT + SOD inhibitors, chemotherapy + GPX4 inhibitors + ferroptosis inducers, CDT + catalase inhibitors.

ROS escalation + immunotherapy: PDT + PD-1/PD-L1 checkpoint inhibitors, chemodynamic therapy + CTLA-4 inhibitors, ferroptosis inducers + cancer vaccines.

Strategic sequencing of ROS therapies may enhance efficacy through antioxidant priming of normal tissues before therapy, pulsed ROS escalation to prevent adaptive antioxidant upregulation, and recovery phases enabling normal tissue repair [55,58].

9. Conclusion:

The relationship between reactive oxygen species and cancer is multifaceted and therapeutically exploitable. ROS initiate malignant transformation through genotoxic damage and genomic instability, yet simultaneously promote cancer progression through redox signaling, driving proliferation, metastasis, and immune evasion. Cancer cells have evolved elaborate antioxidant defenses enabling navigation of the redox tightrope, maintaining ROS at optimal growth levels while avoiding lethal cell death.

This sophisticated antioxidant adaptation creates critical vulnerabilities. Ferroptosis inducers exploiting GPX4 dependence, SOD inhibitors targeting ROS-addicted tumors, and ROS-escalating therapies (PDT, CDT) all leverage cancer cells' antioxidant dependence for therapeutic benefit. Comprehensive assessment of tumor ROS metabolism through biomarkers (MDA, TAC, antioxidant enzyme profiling) will enable personalized therapy selection, optimizing efficacy while minimizing toxicity.

Future cancer medicine will employ ROS-centered therapeutic strategies integrating nanotechnology-enabled drug delivery, combination therapies targeting multiple antioxidant pathways, and immunotherapy synergy through immunogenic cell death. As mechanistic understanding deepens and clinical translation accelerates, ROS-targeted cancer therapy promises substantially improved outcomes for patients with aggressive, chemotherapy-resistant, and metastatic malignancies.

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