Review Article

Dual Roles of Reactive Oxygen Species in Tumorigenesis and Therapeutic Targeting

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Abstract

Reactive oxygen species (ROS) are integral to both the promotion and suppression of cancer. Acting as signaling molecules at physiological levels and as cytotoxic agents at high concentrations, ROS orchestrate complex interactions that define cancer initiation, progression, and therapeutic response. Understanding this duality is essential for developing precise redox-based cancer therapies. This review synthesizes current evidence on the multifaceted roles of ROS in carcinogenesis, tumor progression, and treatment, emphasizing redox-targeted therapeutic strategies that exploit oxidative vulnerabilities in cancer cells. A comprehensive literature search was conducted across several databases using the keywords "reactive oxygen species," "oxidative stress," "redox signaling," "cancer therapy," and "antioxidants." Recent experimental and clinical studies were analyzed to integrate mechanistic insights and translational advances. ROS contribute to all phases of carcinogenesis through oxidative DNA damage, activation of oncogenic pathways (MAPK, PI3K/Akt/mTOR), and suppression of tumor suppressors such as p53. They promote epithelial–mesenchymal transition (EMT), angiogenesis, and immune evasion via redox-sensitive transcription factors (NF-κB, HIF-1α). Conversely, excessive ROS generation beyond the cellular antioxidant threshold induces apoptosis, providing a therapeutic avenue. Pro-oxidant approaches—including radiotherapy, photodynamic therapy, and chemodynamic nanotherapy—exploit this vulnerability, while antioxidant therapies protect normal tissues but risk diminishing treatment efficacy. Emerging combinatorial strategies integrating ROS modulation with immunotherapy and nanocarrier delivery offer enhanced selectivity and reduced toxicity. ROS stand at the crossroads of cancer pathogenesis and treatment. The future of redox oncology lies in precision modulation—achieving a therapeutic balance that selectively disrupts tumor homeostasis while preserving normal cell integrity. Personalized, biomarker-guided strategies targeting ROS dynamics hold the potential to revolutionize cancer therapy.

Keyword: Reactive oxygen species, oxidative stress, cancer therapy, antioxidants.

Introduction

Reactive oxygen species (ROS) represent a broad class of oxygen-derived molecules that encompass both free radicals and non-radical oxidants. These include the superoxide anion (O_2^-), hydroxyl radical (OH), peroxyl radicals (ROO), hydrogen peroxide (H_2O_2), singlet oxygen ($^1O_2$), and hypochlorous acid (HOCl) [1,2]. Under normal physiological conditions, ROS are continuously produced as inevitable byproducts of aerobic metabolism, particularly within the mitochondrial electron transport chain at complexes I and III, as well as through enzymatic reactions involving NADPH oxidases (NOX), xanthine oxidase, cytochrome P450 enzymes, and peroxisomal oxidases [3,4]. These reactive species, though potentially harmful, also play essential roles as secondary messengers in intracellular signaling cascades that regulate a wide array of biological functions, including gene transcription, cell proliferation, differentiation, apoptosis, and immune responses [5-7]. To counterbalance the potentially deleterious effects of ROS, cells possess a sophisticated

antioxidant defense network composed of both enzymatic and non-enzymatic components. Enzymatic antioxidants such as superoxide dismutases (SOD), catalase, glutathione peroxidases (GPx), and peroxiredoxins (Prx) catalytically decompose ROS into less reactive species [8]. Non-enzymatic antioxidants, including reduced glutathione (GSH), ascorbic acid (vitamin C), α-tocopherol (vitamin E), carotenoids, and flavonoids, further scavenge free radicals and maintain cellular equilibrium [9]. This delicate balance between oxidant generation and antioxidant activity is fundamental to the maintenance of cellular homeostasis. When disrupted, it results in oxidative stress—a condition defined as an imbalance between pro-oxidant and antioxidant systems in favor of the former, leading to potential oxidative damage to lipids, proteins, and nucleic acids [10]. Under physiological conditions, ROS serve a dual purpose. At low to moderate concentrations, they act as signaling molecules that regulate various processes, a concept referred to as oxidative eustress [11]. In this context, ROS modulate signaling pathways, including those mediated by mitogen-activated protein kinases (MAPK), phosphoinositide 3-kinase (PI3K)/Akt, and apoptosis signal-regulating kinase 1 (ASK1) [12,13]. They also influence transcriptional responses through the activation of transcription factors such as nuclear factor erythroid 2-related factor 2 (Nrf2), activator protein 1 (AP-1), hypoxia-inducible factor 1α (HIF-1α), and nuclear factor-kappa B (NF-κB) [14,15]. Through these mechanisms, ROS orchestrate cellular responses to external stimuli, facilitate adaptation to stress, and regulate immune and inflammatory signaling [16]. Conversely, excessive accumulation of ROS, a state known as oxidative distress, can overwhelm antioxidant defenses and result in non-specific oxidative damage to cellular macromolecules [5]. Elevated ROS levels can attack polyunsaturated fatty acids in membranes, initiating lipid peroxidation; oxidize proteins, leading to enzyme inactivation and structural modification; and inflict direct damage on DNA by causing strand breaks and base modifications [17]. These oxidative lesions contribute to genomic instability, one of the hallmarks of cancer [18]. Carcinogenesis is a multistep process encompassing initiation, promotion, and progression, during which normal cells acquire a malignant phenotype through cumulative genetic and epigenetic alterations [19]. Oxidative stress has been implicated in all these stages. Persistent ROS exposure can induce mutations in oncogenes and tumor suppressor genes, disrupt DNA repair pathways, and promote chromosomal rearrangements [20]. For instance, oxidative DNA lesions such as 8-hydroxy-2'-deoxyguanosine (8-OHdG) serve as biomarkers of oxidative stress and are elevated in various malignancies, including breast, lung, liver, and prostate cancers [21]. Furthermore, ROS-mediated activation of signaling cascades such as PI3K/Akt/mTOR and MAPK promotes cellular proliferation, inhibits apoptosis, and supports angiogenesis and metastasis [22]. Interestingly, while ROS contribute to tumorigenesis, they can also be exploited therapeutically. Cancer cells typically exhibit higher basal ROS levels than normal cells due to oncogene activation, increased metabolic activity, and mitochondrial dysfunction [23]. This heightened oxidative state renders tumor cells more susceptible to further oxidative insults. Therefore, pharmacological strategies that selectively elevate ROS in cancer cells—surpassing their antioxidant threshold—can trigger oxidative stress-induced apoptosis [15]. Conversely, antioxidant-based therapies aim to restore cellular balance and protect

normal tissues from oxidative damage during chemotherapy or radiotherapy [24]. This dual therapeutic perspective underscores the importance of understanding the biology of ROS in cancer to design more precise.

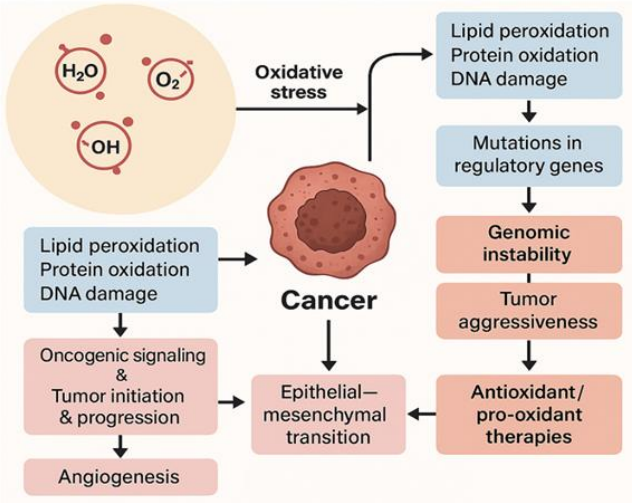

Figure 1: Oxidative Stress, ROS, and Cancer Development

This schematic illustrates the dual role of reactive oxygen species (ROS) in cancer development. Under normal conditions, ROS such as hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), and hydroxyl radical (OH) are generated as natural byproducts of cellular metabolism and contribute to physiological signaling. When ROS production exceeds the cellular antioxidant capacity, oxidative stress occurs, leading to the oxidation of lipids, proteins, and DNA. The resulting oxidative damage induces mutations in key regulatory and tumor suppressor genes, promoting genomic instability, oncogenic signaling, and malignant transformation.

Literature Search Strategy

A comprehensive literature search was performed to identify studies addressing the roles of reactive oxygen species (ROS) in cancer biology, signaling, and therapy. Electronic databases including PubMed, Scopus, Web of Science, and Google Scholar were searched from January 2000 to September 2025. The search combined Medical Subject Headings (MeSH) and free-text terms such as reactive oxygen species, oxidative stress, and cancer, signaling pathways, antioxidants, pro-oxidant therapy, nanomedicine, Ferro ptosis and redox regulation. Boolean operators (AND/OR) were used to refine results. Reference lists of relevant articles and recent reviews were manually screened to ensure completeness and to identify additional studies [25–27].

Criteria

The selection process followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to enhance methodological transparency, though this review adopts a narrative synthesis approach due to heterogeneity among study designs [28,29].

Data Extraction and Synthesis

Two reviewers independently screened titles, abstracts, and full texts, extracting data on study design, cancer type, ROS quantification methods, signaling pathways, and therapeutic mechanisms. A narrative synthesis method was employed, as described by Popay et al. (2006), to identify convergent evidence, controversies, and gaps in the literature [30]. Quantitative pooling was avoided due to the mechanistic heterog-eneity of included studies [31].

Quality Assessment

The methodological quality of included studies was appraised using validated instruments based on study type. Preclinical models were assessed via SYRCLE's risk-of-bias tool [32], randomized controlled trials using the Cochrane Risk of Bias 2.0 framework [33], and observant-

ional or cohort studies using the Newcastle–Ottawa Scale [34]. Only moderate- to high-quality studies were retained for analysis to ensure reliability of synthesized evidence.

Ethical Considerations

This review used secondary data extracted from published literature; therefore, no ethical approval or informed consent was required. All included studies were assumed to comply with institutional and international ethical standards as reported by their authors.

Oxidative Stress, ROS, and Cancer Development

Reactive oxygen species (ROS)—including hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), and hydroxyl radical (OH)—are oxygen-derived molecules produced as metabolic byproducts within cells. Under physiological conditions, they participate in cellular signaling and homeostasis. However, when ROS generation surpasses the antioxidant defense threshold, oxidative stress occurs, leading to the oxidation of lipids, proteins, and nucleic acids [9]. Persistent oxidative injury induces mutations in regulatory genes, particularly tumor suppressor genes, which normally prevent abnormal proliferation. Dysfunction of these genes, together with ROS-driven activation of oncogenic signaling cascades, establishes a pro-carcinogenic microenvironment [6,35]. ROS-mediated activation of oncogenes enhances cell proliferation, survival, and metabolic reprogramming, promoting tumor initiation and progression [36]. Chronic oxidative imbalance also impairs DNA repair processes and fosters genomic instability—hallmarks of malignant transformation [37]. While moderate ROS levels regulate physiological signaling, persistent elevation shifts cellular control toward pro-tumorigenic outcomes [38]. Consequently, targeting oxidative stress and ROS modulation has become an emerging strategy in cancer therapy either through antioxidant interventions to protect normal tissues or through pro-oxidant therapies that selectively elevate ROS beyond the cancer cell tolerance threshold to induce apoptosis [39,40]. Excessive oxidative stress also drives critical processes in tumor aggressiveness, notably epithelial–mesenchymal transition (EMT) and angiogenesis. EMT involves the transformation of epithelial cells into mesenchymal phenotypes with enhanced motility and invasiveness. Under oxidative stress, epithelial cells lose polarity and adhesion, reorganize cytoskeletal components, and acquire migratory characteristics [41]. This process is regulated by multiple signaling pathways, including transforming growth factor-β (TGF-β), Wnt/β-catenin, Notch, and Hedgehog, along with transcription factors such as Snail, Slug, Twist, Zeb1/2, and FOXC2 [42,43]. During EMT, epithelial markers (E-cadherin, cytokeratin) are downregulated, whereas mesenchymal markers (vimentin, N-cadherin, MMP-2, MMP-9) are upregulated, enhancing invasion and metastatic potential [44]. Similarly, ROS modulate angiogenesis, the process of new blood vessel formation essential for tumor growth and metastasis. Elevated ROS activate PI3K/Akt/mTOR and MAPK pathways, promoting the expression of hypoxia-inducible factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF) [45,46]. These mediators stimulate endothelial cell proliferation, migration, and capillary sprouting, sustaining tumor vascularization and expansion [47]. Thus, ROS-induced EMT and angiogenesis synergistically contribute to cancer progression and metastasis.

In summary, excessive ROS production fosters a tumor-promoting milieu by inducing DNA

damage, activating oncogenic signaling, and stimulating EMT and angiogenesis. A clearer understanding of these mechanisms offers opportunities for targeted antioxidant or redox-modulating therapies to mitigate carcinogenesis [48].

Signaling Pathways in Oxidative Stress and Cancer

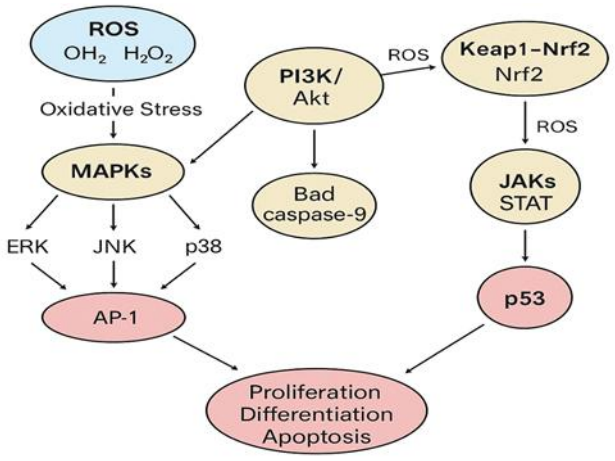

Figure 2: Signaling Pathways in Oxidative Stress

Oxidative stress influences several intracellular signaling cascades that determine cell fate, including survival, proliferation, and apoptosis. Among the most affected systems are those responsive to oxidative cues, linking reactive oxygen species (ROS) generation to the initiation and progression of cancer. ROS activate mitogen-activated protein kinases (MAPKs), such as ERK, JNK, and p38, which subsequently phosphorylate transcription factors like activator protein-1 (AP-1) and nuclear factor kappa B (NF-κB). These transcription factors regulate genes that control proliferation, differentiation, and apoptosis. Depending on the cellular context, this activation may result in adaptive survival responses or trigger programmed cell death [49]. The phosphatidylinositol 3-kinase (PI3K)/Akt signaling axis is similarly affected by ROS. Oxidative stress can stimulate PI3K activity, leading to Akt phosphorylation, which suppresses pro-apoptotic proteins such as Bad and caspase-9. Consequently, cells gain resistance to apoptosis, a process often associated with oncogenic transformation and treatment resistance [50]. Another important system responding to oxidative stress is the Keap1–Nrf2 pathway. Under basal conditions, Keap1 binds to Nrf2 and promotes its degradation via the ubiquitin–proteasome pathway. In the presence of ROS, Nrf2 dissociates from Keap1, translocates into the nucleus, and forms a complex with sMaf proteins that binds antioxidant response elements (ARE). This triggers the transcription of detoxifying and cytoprotective genes essential for maintaining cellular stability [51]. Reactive oxygen species also modulate the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway. Oxidative stress activates JAKs, leading to STAT phosphorylation and nuclear migration, where STATs upregulate genes associated with inflammation, proliferation, and survival—thus linking oxidative signals to tumor-promoting inflammatory responses [52,53]. Furthermore, ROS-induced DNA damage activates the tumor suppressor protein p53, a key regulator of cell cycle and apoptosis. Mild oxidative stress triggers p53-dependent DNA repair and cell cycle arrest, while severe or irreparable damage induces apoptosis to eliminate compromised cells. Failure of this control mechanism allows the survival of genetically unstable cells, facilitating carcinogenesis [54]. Together, these interconnected pathways illustrate how oxidative stress governs cell behavior, tipping the balance between survival and death. Chronic dysregulation of these signaling networks contributes significantly to tumor initiation, progression, and resistance to therapy [55].

Reactive Oxygen Species (ROS)-Based Therapeutic Strategies in Cancer

Reactive oxygen species (ROS) have emerged as both key mediators of tumorigenesis and exploitable vulnerabilities in cancer therapy. While malignant cells maintain elevated basal ROS levels due to oncogene activation, metabolic reprogramming, and mitochondrial dysfunction, this heightened oxidative state renders them susceptible to further oxidative insults that can surpass their antioxidant buffering capacity and trigger cell death [23,56]. Consequently, modern redox-modulating therapies aim to selectively increase ROS within tumors, inhibit antioxidant defenses, or combine both strategies while preserving normal tissue integrity [55].

Strategies to Increase ROS Generation

Conventional Pro-oxidant Therapies

Radiotherapy, chemotherapy, and photodynamic therapy (PDT) remain the primary sources of therapeutic ROS. Ionizing radiation induces hydroxyl radicals (•OH) and superoxide ($O_2^{\bullet -}$) through water radiolysis [57]. PDT and sonodynamic therapy (SDT) generate singlet oxygen ($^1O_2$) via photo-activated or ultrasound-activated sensitizers in the presence of molecular oxygen [58]. Chemotherapeutics such as anthracyclines, β-lapachone, and arsenic trioxide produce ROS through redox cycling or metabolic activation [59,60].

Nanomedicine-Driven ROS Amplification

Chemodynamic therapy (CDT) employs transition metal nanoparticles (Fe^{2+}, Cu^{+}, Mn^{2+}) that catalyze Fenton or Fenton-like reactions to convert endogenous hydrogen peroxide (H_2O_2) into highly reactive •OH radicals [61]. Nanozymes and catalytic nanomaterials have been designed to either increase ROS or relieve hypoxia by decomposing H_2O_2 into O_2, thereby augmenting PDT or radiotherapy efficacy [62,63].

Reduction of ROS Levels as a Therapeutic Strategy

Since moderate levels of reactive oxygen species (ROS) are known to promote the molecular and biochemical changes driving tumor initiation, progression, and survival, reducing intracellular ROS has been explored as a potential preventive and therapeutic approach in cancer. Antioxidant-based treatments aim to neutralize free radicals, enhance ROS-detoxifying enzymes, or inhibit ROS-generating systems such as NOX. Experimental studies have shown that compounds like N-acetylcysteine (NAC) and vitamin C can suppress carcinogenesis in animal models by downregulating hypoxia-inducible factor-1α (HIF-1α), thereby impairing angiogenesis. Similarly, mitochondrial-targeted antioxidants have been reported to attenuate tumor formation in mice [64]. Chemotherapy often depletes endogenous antioxidant reserves through lipid peroxidation, worsening oxidative stress; thus, supplementing antioxidants has been proposed to mitigate treatment-related toxicity. For instance, vitamin E was found to reduce chemotherapeutic side effects and, when combined with omega-3 fatty acids, extend survival in terminal cancer patients [64]. However, clinical evidence remains inconsistent and frequently contradictory. Large-scale trials in head and neck, lung, and prostate cancers showed that dietary supplementation with β-carotene, vitamins A or E, or NAC failed to prevent tumor development and, in some cases, increased cancer incidence and mortality. Experimental data also revealed that NAC accelerated the growth of lung cancers and melanoma. These paradoxical outcomes may

stem from antioxidants' ability to block ROS-dependent apoptosis, which is essential for eliminating precancerous or damaged cells. Moreover, exogenous antioxidants might counteract ROS-based mechanisms underlying radiotherapy and chemotherapy, thereby reducing their therapeutic efficacy [64]. ROS-centered therapies harness the intrinsic oxidative fragility of cancer cells. The most promising future directions combine targeted ROS amplification with precision inhibition of antioxidant systems, integrated with immunotherapy or nanocarrier delivery [65].

Discussion

Reactive oxygen species (ROS) are now recognized as central regulators of cancer biology, functioning as both molecular drivers of carcinogenesis and potential therapeutic targets. Their dual nature—capable of inducing either cell survival or cell death—creates a complex redox landscape that underpins the paradoxical role of oxidative stress in tumor development and therapy. The evidence synthesized in this review underscores that the biological outcome of ROS exposure depends primarily on concentration, cellular localization, and the efficiency of antioxidant defense mechanisms [55]. ROS-mediated oxidative stress is intimately linked to all stages of cancer progression—from initiation and promotion to metastasis. Persistent oxidative damage to DNA, proteins, and lipids contributes to genomic instability, a fundamental hallmark of malignancy [56]. Oxidative DNA lesions such as 8-hydroxy-2′-deoxyguanosine (8-OHdG) are widely reported in breast, liver, and prostate cancers, correlating with disease aggressiveness and poor prognosis [6]. Moreover, ROS-driven activation of oncogenic pathways (MAPK, PI3K/Akt/mTOR) and inhibition of tumor suppressors (p53) further sustain the malignant phenotype [22]. These mechanisms also facilitate epithelial mesenchymal transition (EMT) and angiogenesis through redox-sensitive transcription factors such as HIF-1α and NF-κB, supporting invasion, vascular remodeling, and metastasis [66,67]. Collectively, oxidative stress acts not only as a mutagenic factor but also as a signaling modulator that shapes the tumor microenvironment toward a pro-survival, pro-metastatic state [68]. While excessive ROS levels promote cancer progression, they also expose a therapeutic vulnerability. Cancer cells, due to metabolic reprogramming and mitochondrial dysfunction, operate under a high basal ROS state near the threshold of cytotoxicity [69]. This fragile redox balance provides an opportunity for selective targeting—by further increasing oxidative stress to lethal levels or by attenuating ROS to prevent mutagenic signaling. Consequently, both pro-oxidant and antioxidant strategies have been pursued, each with distinct biological rationales and limitations. Pro-oxidant therapies including radiotherapy, photodynamic therapy (PDT), and chemotherapeutics such as anthracyclines and arsenic trioxide intentionally elevate ROS to induce apoptosis through oxidative DNA and mitochondrial damage [23]. Recent advances in nanomedicine, such as chemodynamic therapy (CDT), further exploit endogenous tumor H_2O_2 to generate hydroxyl radicals via Fenton reactions [61]. By leveraging tumor-specific conditions like acidity and hypoxia, these nanoplatforms enhance ROS production while minimizing systemic toxicity [62]. Moreover, the integration of ROS-based modalities with immunotherapy (e.g., immune checkpoint blockade) has demonstrated synergistic effects through the induction of immunogenic cell death (ICD), which enhances T-cell activation and antitumor immunity [70].

Conversely, antioxidant-based therapies have been explored to protect normal tissues or prevent tumor initiation by neutralizing ROS or enhancing endogenous detoxification systems. Agents such as N-acetylcysteine (NAC), vitamins C and E, and mitochondrial-targeted antioxidants have shown protective effects in preclinical models by downregulating HIF-1α and suppressing angiogenesis [71]. However, clinical trials have yielded inconsistent—and sometimes paradoxical results. While some studies reported improved patient tolerance during chemotherapy, others revealed increased cancer incidence and reduced survival in patients receiving antioxidant supplements such as β-carotene and NAC [72]. These conflicting findings suggest that antioxidants may inadvertently protect tumor cells by inhibiting ROS-induced apoptosis or interfering with redox-based cancer therapies [73]. Therefore, antioxidant therapy requires careful context-dependent application, guided by tumor type, stage, and concurrent treatment modality. A major challenge in redox oncology lies in discriminating between physiological and pathological ROS signaling. Low-to-moderate ROS concentrations are indispensable for cellular communication and adaptive stress responses (oxidative eustress), whereas high levels lead to oxidative distress and cell death [74]. The therapeutic goal should not be indiscriminate ROS suppression or augmentation, but rather selective redox modulation precisely tuning ROS flux to exploit tumor vulnerabilities without compromising normal cell integrity. Emerging research supports a two-hit redox strategy: (1) transiently inhibit antioxidant defenses (e.g., glutathione or thioredoxin systems, Nrf2 signaling) to lower the tumor's oxidative threshold, followed by (2) a pro-oxidant assault (e.g., PDT, CDT, or radiotherapy) to push cancer cells beyond their tolerance limit [75]. This combined approach maximizes tumor cytotoxicity while minimizing resistance and toxicity. Furthermore, integrating nanocarrier systems can improve site-specific delivery and reduce systemic side effects [63]. Parallel to these efforts, the use of mesenchymal stem cell (MSC)-derived exosomes has emerged as a promising adjunct for protecting normal tissues from therapy-induced oxidative damage, thereby widening the therapeutic window [76]. Despite substantial progress, translating redox-based therapies into clinical success remains challenging. The primary obstacles include tumor heterogeneity, adaptive antioxidant upregulation, and difficulties in accurately quantifying intracellular ROS dynamics [65]. The inconsistent outcomes of antioxidant supplementation underscore the necessity for biomarker-guided and personalized strategies. Future research should focus on real-time redox imaging, molecular profiling of Nrf2/Keap1 and SLC7A11/GPX4 pathways, and identifying predictive markers for ROS sensitivity [76]. Additionally, combinatorial approaches integrating ROS modulation with immune or metabolic therapies hold significant potential to overcome resistance and achieve durable responses [77].

Conclusion

ROS are central to the fine balance between cancer promotion and suppression. Their manipulation offers powerful yet delicate opportunities for therapeutic intervention. A deeper understanding of ROS-dependent signaling networks and tumor-specific redox vulnerabilities will enable the rational design of personalized redox-modulating therapies. Ultimately, achieving therapeutic precision in oxidative modulation—neither too much nor too

little—represents the key to unlocking the full potential of redox-targeted cancer treatment.

Conflict of interest

None

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