Archives of Advances in Biosciences

Review Article

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# Comprehensive Mechanistic Mapping of ROS Driven Oncolysis for Precision Therapeutics

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**Received:** 02 Jan 2026; **Accepted:** 16 Feb 2026; **Published:** 28 Apr 2026

**Cite this article as:** Prusty, A. K., & Sahoo, S. K. . Comprehensive Mechanistic Mapping of ROS Driven Oncolysis for Precision Therapeutics. Archives of Advances in Biosciences. 2026 17(1):1-19. https://doi.org/10.22037/aab.v17i1.51392

## Abstract

**Contex:** Reactive oxygen species (ROS) have a contradictory function in cancer biology because they promote both oncogenic signaling and mediate cell death. At the molecular level, ROS consist of free radicals like O2•⁻, •OH and ONOO-, as well as non-radical oxidants like H2O2 and 1O2. Cytochrome P450 uncoupling, xanthine oxidase, ER oxidative protein folding (Ero1–PDI), peroxisomal β-oxidation, mitochondrial leakage (Complexes I/III), and NADPH oxidases (NOX1–5, DUOX1–2) are mechanisms that naturally produce these species. Exogenous stimuli such as photodynamic treatment, radiation, and nanoparticle-induced redox cycling further increase oxidative flux. In order to adapt, cancer cells reorganize redox homeostasis by upregulating SOD2, while glutathione peroxidases (GPX4), catalase, peroxiredoxins, and thiol buffers (GSH, thioredoxin) detoxify peroxides and maintain cysteine residues in a reduced form. Since Nrf2 hyperactivation encourages the long-term transcription of cytoprotective enzymes, the Nrf2-Keap1 axis is crucial to this network. Such hypertrophied antioxidant defenses establish a "redox setpoint" by keeping ROS levels below fatal thresholds but high enough to sustain oncogenic signaling via MAPK/ERK, JAK/STAT, NF-κB, and stability of HIF-1α.

**Evidence Acquisition:** A systematic search of major electronic databases was conducted through 2025 using redox-related keywords. Relevant peer-reviewed articles were selected and synthesized to evaluate ROS mechanisms and their therapeutic potential in oncology. The search integrated databases such as PubMed and Scopus, utilizing specific terms like Redox Homeostasis and Ferroptosis to ensure a comprehensive evaluation of current therapeutic vulnerabilities.

**Results:** The analysis highlights broad clinical applications in early cancer detection (skin, gastrointestinal, respiratory, cervical, and other organs), non-cancerous diseases (inflammation, infection, wound monitoring), and intraoperative guidance. Despite advantages like non-invasiveness and real-time diagnosis, limitations such as limited light penetration depth, complexity of data interpretation, and the inability to fully replace histopathology remain significant challenges.

**Conclusion:** Additional ROS amplification overwhelms defenses when GPX4 and GSH are reduced, leading to ferroptosis via lipid peroxidation, cytochrome c release, caspase activation, or mitochondrial permeability transition. A "redox vulnerability" is created as a result, which may be used therapeutically In parallel, ROS-induced DNA damages (such as 8-oxoG) activate ATM/ATR pathways, and ER stress initiates CHOP-mediated apoptosis. Crucially, immunogenic cell death brought on by oxidative damage can also release DAMPs including ATP, HMGB1, and calreticulin to boost antitumor immunity. Through the combination of redox buffering systems, antioxidant adaptations, and molecular-level ROS formation, this review reframes ROS as a biochemical language and therapeutic lever in oncology.

**Keywords:** ROS, Oncoferroptosis, Redox Vulnerability, Oncooxidation, Apoptosis, Fentonization

## 1. Contex

Cancer is a complex biological problem in which each tumor comprises a self-organizing population of malignant cells that constantly interact with their microenvironment. In order to maintain life and growth, cells must take in, integrate, and respond to biochemical cues under the circumstances that would normally result in senescence or largely because of altered information processing in signaling networks. It is now recognized that redox biology plays a crucial role in controlling the proportion of oxidants to antioxidants in cancer, even though chromosomal instability and epigenetic reprogramming are attributed to this adaptive flexibility. Reactive oxygen species (ROS) are a chemically varied set of molecules made from oxygen. They include free radicals like the superoxide anion ($O_2^{\bullet-}$) and hydroxyl radicals ($^{\bullet}OH$) as well as non-radical oxidants like hydrogen peroxide ($H_2O_2$) and singlet oxygen ($^1O_2$). In healthy physiology, ROS are generated by metabolic signaling and mitochondrial respiration, which support immune defense and wound repair.(1) By oxidizing particular cysteine, methionine, or tyrosine residues, these short-lived, local messengers might alter the position, interaction potential, or activity of signaling proteins. The complex antioxidant system that regulates the generation of ROS in a healthy condition is made up of glutathione peroxidases (GPXs), peroxiredoxins, catalase, superoxide dismutase ($SOD_S$), and non-enzymatic compounds such as reduced glutathione (GSH), thioredoxin, ascorbate, and tocopherols.(2) However, compared to normal cells, tumor cells operate at higher ROS levels as a functional adaptation rather than as an inadvertent result of metabolic dysregulation. Inactivation of tumor suppressors, especially p53 (Tumor Protein p53) loss, and oncogenic activation by KRAS (Kirsten Rat Sarcoma Virus Oncogene Homolog), MYC (Myelocytomatosis Viral Oncogene Homolog), BRAF (v-Raf Murine Sarcoma Viral Oncogene Homolog B1), or PI3K (Phosphoinositide 3-Kinase) alter cellular metabolism in favor of glutaminolysis, aerobic glycolysis, and changed mitochondrial oxidative phosphorylation.(3) It is certain that these metabolic rewiring events, aberrant growth factor signaling, and hypoxic stress will enhance the production of ROS in mitochondria, Nicotinamide Adenine Dinucleotide Phosphate Hydrogen (NADPH) oxidases (NOX), and peroxisomes. Rather than being detrimental in these situations, ROS are essential co-factors in the cancer signaling network, boosting mitogenic cascades such as mitogen-Activated Protein Kinase/Extracellular Signal-Regulated Kinase (MAPK/ERK) and Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT), promoting the nuclear translocation of transcription factors Activator Protein-1 (AP-1) and Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB), and stabilizing Hypoxia-Inducible Factor-1 alpha (HIF-1α) to promote angiogenesis.(4) Nevertheless, ROS and cancer share a dualistic molecular conundrum that makes it both a potential weakness and a factor in the growth of tumors. On the one hand ROS are second messengers that combine metabolic and mitogenic signals, enabling cancer cells to infiltrate, proliferate, and avoid destruction. On the other hand, elevated ROS levels result in oxidative stress alterations to proteins, lipids, and DNA that overwhelm repair systems, obstruct energy generation, and initiate processes that ultimately lead to programmed cell death. ROS is kept at a level below the lethal threshold (sweet spot), when oxidative damage is irreversible, but high enough in cancer cells to preserve signaling advantages. Redox rheostats can be used to explain this conundrum.(5) This redox setpoint is maintained by hypertrophied antioxidant mechanisms. Because of the Superoxide Dismutase 2 (SOD2) is upregulated in mitochondria, superoxide is rapidly transformed into $H_2O_2$, which is less reactive and simpler to manage.(6) Lipid peroxidation is inhibited by increased expression of Glutathione Peroxidase 4 (GPX4) and peroxiredoxins, but glutathione overproduction supplies a large thiol buffer to neutralize electrophiles and maintain the reduced state of protein cysteines. This antioxidant phenotype is frequently regulated by the transcription factor Nuclear Factor Erythroid 2–Related Factor 2 (Nrf2). Kelch-like ECH-associated protein 1 (Keap1) sequesters Nrf2 in the cytoplasm of healthy cells, where the ubiquitin-proteasome system degrades it. KEAP1 mutations or hyperactivation of Phosphoinositide 3-Kinase/Protein Kinase B (PI3K/AKT) signaling cause constitutive antioxidant gene expression in cancer by stabilizing Nrf2. Consequently, the system's resistance to long-term oxidative stress is only slightly increased.(7) A "redox vulnerability" results from this delicate balance: cancer's antioxidant defenses are operating at nearly maximum efficiency, leaving little margin for unexpected increases in ROS. Therapeutically, targeted amplification of ROS in tumors can result in catastrophic oxidative collapse without putting normal cells at risk because they have a bigger reserve buffering capacity and function at lower basal ROS. The concept is in line with the theory of non-oncogene addiction, which maintains that stress-response pathways are not the cause of the transformation but rather become essential for cancer cells to survive in their altered state. (8)

ROS excess starts a multi-pronged cascade of deadly events at the molecular execution level. The integrity of respiratory chain complexes I and III is compromised in mitochondria when ROS oxidize

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cardiolipin in the inner membrane. In addition to lowering Adenosine Triphosphate (ATP) synthesis, this also increases electron leakage and superoxide production, creating a vicious cycle that ends with the opening of the mitochondrial permeability transition pore (mPTP). Oxidative phosphorylation is stopped by the subsequent loss of membrane potential, and the intrinsic apoptotic program is carried out by the activation of Caspase-9 and downstream Caspase-3 brought on by the release of cytochrome c into the cytosol. ROS cause oxidative base lesions in the nucleus, the most prevalent of which is 8-oxo-7,8-dihydroguanine (8-oxoG).(9) Replication fork stalling and double-strand breaks result from these lesions, if they are not fixed by base excision repair (BER) equipment that activates Ataxia Telangiectasia Mutated (ATM)/Ataxia Telangiectasia and Rad3-related (ATR) kinase signaling. This can lead to mitotic catastrophe, senescence, or apoptosis, depending on the tumor suppressor protein p53 status. Furthermore, ROS target lipids in cellular membranes, particularly polyunsaturated fatty acids, which initiates cascades of lipid peroxidation that result in the production of deadly aldehydes such as 4-hydroxynonenal (4-HNE) and malondialdehyde (MDA).(10) These electrophiles combine with proteins and DNA to produce adducts, which worsen molecular damage. This lipid peroxidation goes into overdrive when glutathione is depleted or GPX4 is suppressed, leading to ferroptosis, an iron-dependent, non-apoptotic form of cell death that is becoming recognized as an essential tumor-suppressive mechanism.(11)

At the same time, ROS induced protein misfolding in the endoplasmic reticulum that triggers the Unfolded Protein Response (UPR) via the Protein Kinase RNA-like Endoplasmic Reticulum Kinase (PERK), Inositol-Requiring Enzyme 1 alpha (IRE1α), and Activating Transcription Factor 6 (ATF6) pathways; if the Endoplasmic Reticulum (ER) stress persists, pro-apoptotic transcription factors such as C/EBP Homologous Protein (CHOP) are activated, ultimately leading to cell death. Importantly, ROS induced mortality is not necessarily immune-silent. Oxidative stress can cause Immunogenic Cell Death (ICD), which is characterized by calreticulin exposure on the cell surface, ATP release into the extracellular space, and High Mobility Group Box 1 (HMGB1) release from the nucleus.(12) As Damage-Associated Molecular Patterns (DAMPs), these molecules bridge the gap between innate and adaptive immunity by attaching to Pattern Recognition Receptors (PRRs) on dendritic cells and macrophages. In preclinical models, ROS inducers have been shown to cooperate with immune checkpoint inhibitors, suggesting a dual benefit of direct tumor death and immune activation. ROS based strategies exploit a biophysical inevitability, unlike kinase inhibitors or monoclonal antibodies, which target a single molecular node and can be avoided by mutational escape, oxidative damage cannot be reversed once it exceeds the capacity for repair, regardless of the mutational landscape.(13) This universality suggests that redox-modulating therapies should work well against a range of tumor genotypes. ROS generation will be counteracted by adaptive antioxidant responses, too much systemic ROS will damage healthy tissues such as hematopoietic progenitors, intestinal epithelium, and cardiomyocytes, therefore accuracy is essential.(14)

This review focuses on the molecular mapping of ROS dynamics in cancer, aiming to provide a comprehensive analysis of how ROS determine cancer cell fate. The review will examine ROS as a network of chemically distinct species, each with defined reactivity, half-life, and compartmentalization, interacting with antioxidant systems in a context-dependent manner. The review aims to serve as a reference for molecular oncology researchers and a conceptual framework for developing next-generation ROS-based cancer therapeutics. It will explore how mitochondrial superoxide, cytosolic $H_2O_2$, peroxisomal ROS, and NOX-derived oxidants differ in their signaling outputs, how oxidative post-translational modifications modulate the activity of kinases, phosphatases, and transcription factors, and how redox fluctuations integrate with metabolic checkpoints, DNA damage signaling, and immune engagement. It will also address how tumor heterogeneity influences ROS biology and why certain cancer subtypes are more susceptible to ROS-based interventions. The review will attempt to uncover the evolutionary and systems-level logic behind cancer's redox wiring, integrating insights from structural biology, redox chemistry, metabolic flux analysis, and immuno-oncology. A systematic literature search was conducted using databases like PubMed, Scopus, and Google Scholar, resulting in roughly 100 articles. After screening for duplicates and relevance, only the most pertinent studies were included based on the manuscript's scientific objectives.The goal is not just to summarize current knowledge but to reframe ROS as a language and lever of cancer biology, allowing therapeutic interventions to manipulate the fate of malignant cells.(10)

## 2. Evidence Acquisition

This narrative review was conducted through a comprehensive search of electronic databases, including PubMed, Web of Science, Scopus, and Google Scholar, covering literature published up to 2025. The search strategy utilized keywords such as

"Reactive Oxygen Species," "Redox Homeostasis," "Antioxidant Defense Systems," "Ferroptosis," and "Oncogenic Signaling." Studies were selected based on their relevance to ROS production mechanisms, antioxidant adaptations in cancer cells (e.g., Nrf2-Keap1 axis), and therapeutic interventions like photodynamic therapy. Inclusion criteria focused on peer-reviewed original research and high-impact review articles. To ensure quality and depth, reference lists of retrieved articles were manually screened to identify additional relevant studies, providing a holistic overview of the "redox setpoint" and "redox vulnerability" in oncology.

## 3. Results

### 1. ROS Fundamentals in Cellular Systems

ROS are characterized by heightened reactivity as compared to the triplet ground state of molecular oxygen. Their behavior is influenced by their electrical configuration, redox potential, and the microenvironment in which they are formed. In cancer biology, ROS play a paradoxical role: at low-to-moderate concentrations, they serve as second messengers in proliferative and survival pathways. However their intracellular accumulation surpasses the buffering capacity of antioxidant systems, they induce oxidative damage severe enough to result in cell death. Understanding ROS at the molecular level, including their chemical identities, routes of formation, and segregated destiny, provides the mechanistic basis for using them in targeted anticancer therapies discuss below.(15)

### 1.1. Biochemical Nature of ROS

The term ROS encompasses both the non-radical yet highly oxidizing compounds that can readily generate radicals by redox cycling or electron transfer, as well as free radicals, which are species with one or more unpaired electrons.

**Radical ROS:**

The $O_2^{\bullet-}$ is created when molecular oxygen undergoes monoelectronic reduction, which adds a single unpaired electron to its antibonding π* orbital. This radical's kinetics are limited by its negative charge, which also inhibits membrane diffusion, despite the fact that it is somewhat reactive with biomolecules. Its reactivity is increased by secondary reactions, including spontaneous or enzymatic dismutation to hydrogen peroxide or conjunction with nitric oxide to create peroxynitrite ($ONOO^-$) that is a nitrating and oxidizing agent.(16) Peroxynitrite ($ONOO^-$) forms when $O_2^{\bullet-}$ reacts rapidly with nitric oxide (•NO). It protonates to ONOOH, which decomposes into highly reactive (˙OH) and nitrogen dioxide radical ($\bullet NO_2$), causing oxidative and nitrative damage to biomolecules.(17)

(˙OH) exhibits no selectivity in its targets, reacting with rate constants approaching $10^9$–$10^{10}$ $M^{-1}\cdot s^{-1}$. It is formed via Fenton chemistry, where $Fe^{2+}$ donates an electron to hydrogen peroxide, or by the Haber–Weiss cycle, in which superoxide and hydrogen peroxide react via metal catalysis. The hydroxyl radical's lack of diffusion beyond a few nanometers ensures damage remains localized to its site of formation having a property that both limits and focuses its cytotoxic potential.(18) This is the Fenton reaction, where ferrous iron ($Fe^{2+}$) reacts with hydrogen peroxide to generate highly reactive (˙OH). It amplifies oxidative stress by causing DNA strand breaks, protein oxidation, and lipid peroxidation in cells.(19)

**Non-radical ROS:**

$H2O_2$ can oxidize using two electrons even though it doesn't have any unpaired electrons. It can flow through aquaporin channels in membranes due to its relative stability. When redox-active metals are not present, it is comparatively harmless; but, in situations that are high in iron or copper, it becomes the precursor to hydroxyl radicals. In ($^1O_2$), an electronically excited form of oxygen that reduces the spin constraint for reactions with organic substrates, one of the π* antibonding orbitals is doubly filled with paired electrons. By oxidizing heteroatom centers, aromatic rings, and electron-rich double bonds, it produces hydroperoxide in lipids and irreversibly oxidizes amino acid side chains like histidine and tryptophan. Rather of existing separately, these species are interconverted through a network of redox changes. Radical species frequently serve as the kinetic entry points for ROS chemistry, and their subsequent transformation into diffusible oxidants enables the spatial spread of oxidative stress throughout cellular compartments.(20)

### 1.2. Endogenous Sources of ROS

The intracellular ROS landscape is shaped by multiple generation sites, each with distinct chemical signatures and kinetic profiles.

#### 1.2.1. Mitochondrial Electron Transport Chain (ETC) (Complex I & III leakage)

When electrons prematurely reduce oxygen in the mitochondria instead of passing through the respiratory complexes sequentially, ROS are created. By releasing electrons from iron-sulfur clusters or Flavin Mononucleotide (FMN) clusters to oxygen, Complex I [ NADH: Ubiquinone Oxidoreductase] exclusively generates superoxide within the mitochondrial matrix. In tumor cells with changed metabolic flux, this is preferable when the Nicotinamide Adenine Dinucleotide reduced form to oxidized form ratio ($NADH/NAD^+$ ratio) and proton

motive force are both high. (21)On the matrix and intermembrane sides, Complex III (Cytochrome $bc_1$ complex, also called ubiquinol–cytochrome c oxidoreductase) produces superoxide via semiquinone intermediates in the Q-cycle. Antimycin A-induced semiquinone stabilization is an illustration of how inhibitors can raise ROS generation. Superoxide is more easily transformed into ($^{\bullet}OH$) by the physicochemical environment of the mitochondrial matrix, which is rich in Manganese ions ($Mn^{2+}$) and ($Fe^{2+}$). This creates localized oxidative pressure, which can permeabilize the mitochondrial membrane by lipid peroxidation.(22)

### 1.2.2. NADPH Oxidases (NOX1–NOX5, DUOX1–2)

NADPH oxidases function as specialized ROS producers by transferring two electrons from NADPH to molecular oxygen via heme prosthetic groups and Flavin Adenine Dinucleotide (FAD). The regulatory subunits and activation triggers of NADPH Oxidase 1 (NOX1)–NADPH Oxidase 5 (NOX5) differ; NADPH Oxidase 4 (NOX4) is constitutively active and mainly generates $H_2O_2$ through the immediate dismutation of superoxide at its active site, while NADPH Oxidase 2 (NOX2) requires cytosolic subunit assembly upon phosphorylation events. (23)Dual Oxidase 1 (DUOX1) and Dual Oxidase 2 (DUOX2) peroxidase-like domains can use $H_2O_2$ to directly oxidize halides and pseudohalides. When activated pharmacologically, NADPH oxidase enzymes can drive oxidative thresholds past the survival limit, yet their constant activity in cancer cells sustains oxidative signaling cascades like ERK1/2 or (Akt) activation. These enzymes are purpose-built for ROS production, often used in signaling but also implicated in cancer cell proliferation.(24)

### 1.2.3. Endoplasmic Reticulum Protein Folding (Ero1, PDI)

Redox chemistry and ROS generation are linked by oxidative protein folding in the ER lumen. Protein disulfide isomerase (PDI), which catalyzes thiol–disulfide exchange, oxidizes cysteine residues in developing polypeptides. By directing electrons to molecular oxygen through its FAD cofactor, endoplasmic reticulum oxidoreduction 1 (Ero1) reoxidizes PDI and produces $H_2O_2$. Misfolded protein accumulation, such as that which occurs in tumor hypoxia or nutritional stress, hyperactivates Ero1, leading to spikes in ER-localized ROS that play a role in the Ca2+ signaling and mitochondrial death pathways.(25)

This oxidative folding pathway is a major source of $H_2O_2$ during high protein synthesis or ER stress.

### 1.2.4. Peroxisomal β-Oxidation of Fatty Acids

Peroxisomes initiate the β-oxidation of very long-chain fatty acids by Acyl–Coenzyme A oxidases (ACOXs), which transfer electrons directly to $O_2$ instead of through electron transport chains. This results in the production of $H_2O_2$ in a 1:1 stoichiometric connection with substrate turnover. Peroxisomal catalase rapidly breaks down $H2O_2$, but in excess, like in lipid-rich tumor settings, any leftover $H2O_2$ may seep into the cytosol and cause damage or redox signaling.

In peroxisomes, acyl-CoA oxidase catalyzes β-oxidation, with each fatty acid molecule producing one molecule of hydrogen peroxide. (26)

### 1.2.5. Cytochrome P450 Enzymatic Activity

Cytochrome P450 monooxygenases activate molecular oxygen ($O_2$) through a heme iron core by introducing one oxygen atom into the substrate and reducing the other to water. When electron transport from NADPH that cytochrome P450 reductase is isolated from substrate oxidation, "leakage" to oxygen occurs, producing superoxide or Hydrogen Peroxide ($H_2O_2$). Overexpressed Cytochrome P450 (CYP) isoforms in tumor cells, particularly those involved in xenobiotic metabolism, increase the basal ROS load and can cooperate with pro-oxidant treatment.

In cancer, overactive P450 enzymes can add to ROS burden.(27)

### 1.2.6. Xanthine Oxidase Reaction

Xanthine oxidase, which is created by post-translational modification of xanthine dehydrogenase, converts hypoxanthine and xanthine to uric acid. Its molybdenum cofactor and iron-sulfur clusters give FAD electrons, which transform $O_2$ into superoxide. By being more active in ischemia or inflammatory conditions that both of which are common in tumor microenvironments, by enzyme connects oxidative damage and metabolic stress.

In some cases, superoxide is produced instead of hydrogen peroxide.(28)

## 1.3. Exogenous Sources of ROS

Cancer medicines intentionally exploit pathways that produce ROS to particularly damage tumor cells. Ionizing radiation cleaves water molecules via Compton scattering or photoelectric absorption, producing hydroxyl radicals and solvated electrons in femtoseconds. The nucleotides and backbone of DNA are the targets of these radicals, which concentrate damage that is too severe for repair mechanisms to manage.(29)

Chemotherapeutic drugs such as doxorubicin undergo redox cycling between quinone and semiquinone states, which transfers electrons to oxygen and generates superoxide. Indirectly causing

mitochondrial ROS, cisplatin damages respiratory complexes. Arsenic trioxide alters the redox balance to favor oxidative stress by targeting antioxidant proteins that are rich in thiols. Photodynamic treatment (PDT) introduces a photosensitizer that, upon absorption of photons, transforms into an excited triplet state. By transferring energy to triplet oxygen, this state produces singlet oxygen with high local reactivity and millisecond lifetimes. In lipid-rich membranes, $O_2$ triggers peroxidation cascades that destabilize organelles and plasma membranes.(30)

Exogenous sources initiate Some oxidative stress via direct photophysical, radiolytic, or catalytic processes. Exogenous ROS sources generate oxidative stress through physical, chemical, and catalytic mechanisms acting outside the cell. Ultraviolet (UV) radiation excites photosensitizers or cellular chromophores, promoting electron transfer to oxygen and producing superoxide anions or singlet oxygen. Ionizing radiation induces radiolysis of water, forming hydroxyl radicals, solvated electrons, and hydrogen radicals; the electrons rapidly react with oxygen to yield superoxide. PDT uses light-activated photosensitizers to form singlet oxygen via Type II energy transfer or hydroxyl radicals via Type I electron transfer. (31)

Silver nanoparticles (AgNPs) undergo oxidative dissolution, releasing $Ag^+$ ions and electrons; electrons reduce oxygen to superoxide, while $Ag^+$ catalyzes hydrogen peroxide and hydroxyl radical formation. Gold nanoparticles (AuNPs), when excited by light, release hot electrons that generate superoxide. Cold atmospheric plasma (CAP) produces diverse ROS and reactive nitrogen species by ionizing gases and water vapor, forming superoxide, ozone, and hydroxyl radicals. Heavy metals such as $Fe^{2+}$ or $Cu^+$ catalyze Fenton reactions, converting hydrogen peroxide into hydroxyl radicals. Photothermal agents, when heated by near-infrared light, accelerate radical-producing chain reactions in lipids and proteins.(32) Together, these exogenous mechanisms overwhelm antioxidant defenses, creating a lethal oxidative environment for cancer cells. For molecular reactions (Table 1)

Endogenous: mitochondria (ETC leakage), NADPH oxidase, xanthine oxidase, peroxisomes → $O_2^{\bullet-}$ → $H_2O_2$ → $^{\bullet}OH$ (via Fenton reaction) → oxidative damage to DNA, lipids, proteins; Exogenous: UV, ionizing radiation, chemicals, pollutants, toxins → → ROS ($O_2^{\bullet-}$ , $H_2O_2$, $^{\bullet}OH$, $1O2$) → lipid peroxidation, DNA strand breaks, protein oxidation → signaling dysregulation / cytotoxicity

$H_2O_2$

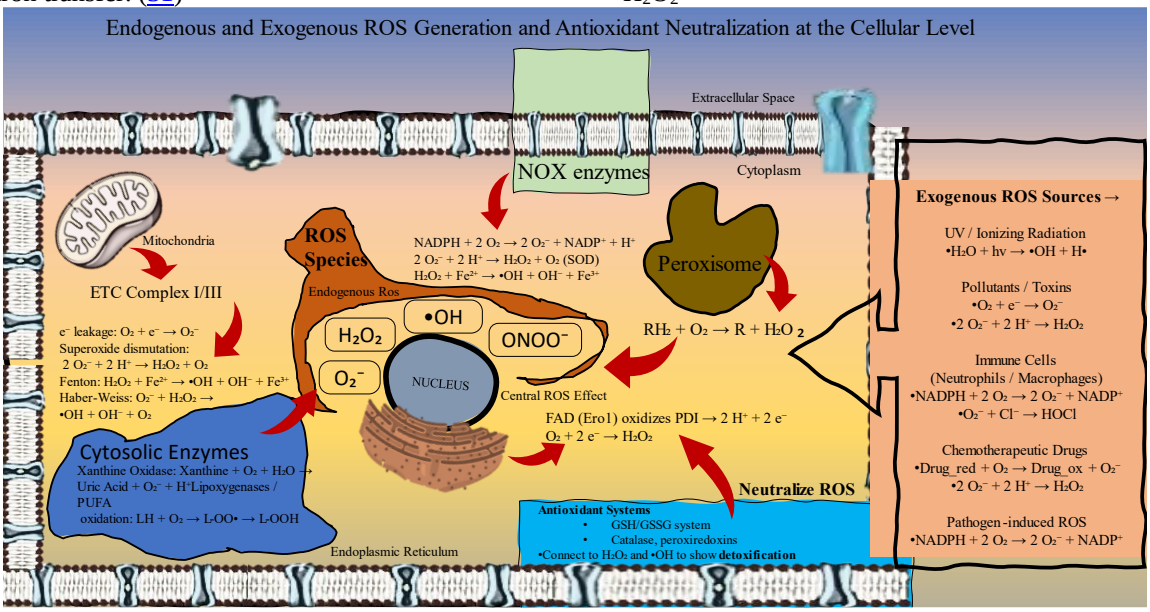


**Figure1.** This figure illustrates the major endogenous and exogenous sources of reactive oxygen species (ROS) in and around the cell, their primary molecular reactions, and the cellular antioxidant defense systems. Endogenous sources include mitochondria (ETC: electron transport chain), endoplasmic reticulum (ER), peroxisomes, cytosolic enzymes, and NADPH oxidases (NOX1–5). Exogenous sources comprise ultraviolet (UV) and ionizing radiation, environmental pollutants, inflammatory immune cells (neutrophils, macrophages), chemotherapeutic drugs, and pathogen-induced ROS. Antioxidant defense mechanisms include enzymatic systems such as superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx), and non-enzymatic antioxidants like reduced glutathione (GSH), vitamins C and E. ROS are neutralized through reactions such as $O_2^{-}$ → $H_2O_2$ → $H_2O$, lipid peroxide detoxification, and peroxynitrite ($ONOO^-$) scavenging, thereby preventing oxidative damage to DNA, proteins, and lipids.

### 1.4. ROS Homeostasis and Compartmentalization: The Fine Line Between Signaling and Cytotoxicity

ROS homeostasis refers to the delicate balance between their generation and removal within cells. Low to moderate ROS levels are essential for physiological signaling, regulating processes such as cell growth, immune defense, and differentiation. However, excessive ROS can oxidize lipids, proteins, and nucleic acids, leading to oxidative stress and potential cell death. Homeostasis is maintained by a network of antioxidant defenses, including enzymatic systems like superoxide dismutase, catalase, and glutathione peroxidase, as well as non-enzymatic molecules such as glutathione, vitamin C, and vitamin E.(32) This compartmentalization means that ROS are not uniformly distributed but are produced, regulated, and act within specific cellular locations. Mitochondria generate superoxide through electron leakage in the respiratory chain, peroxisomes produce hydrogen peroxide during fatty acid oxidation, and the endoplasmic reticulum releases ROS during oxidative protein folding. NADPH oxidases at the plasma membrane release ROS into extracellular or localized intracellular domains, while lysosomes generate hydroxyl radicals through Fenton chemistry. This spatial regulation ensures that ROS signaling occurs precisely where needed, preventing uncontrolled damage to other cellular structures. Together, homeostasis and compartmentalization maintain redox balance, enabling ROS to function as controlled messengers while minimizing harmful oxidative stress, a principle vital in redox-based cancer therapy.

The cytotoxicity of ROS signaling is intimately linked to its geographical origin and diffusion restrictions. The high levels of Manganese Superoxide Dismutase (MnSOD), glutathione, and peroxiredoxins in the mitochondrial matrix under stress produce a buffered but responsive ROS pool that can swiftly shift toward the onset of apoptosis. The cytosolic enzymes catalase and Copper/Zinc Superoxide Dismutase (Cu/ZnSOD) prevent the accumulation of $H_2O_2$ while allowing for transient oxidative signaling through cysteine sulfenylation of kinases and phosphatases.(33) The nucleus is particularly vulnerable to ROS even though it is not a major generator of them because even minute quantities of ($^{\bullet}OH$) can oxidize guanine to (8-oxoG), which can cause mutagenesis lesions. This compartmentalization is not absolute; aquaporin-mediated $H_2O_2$ transport, mitochondrial–ER contact sites, and vesicular trafficking all facilitate ROS interaction between organelles. Cancer cells often operate near a "redox cliff" that they remain just below the devastation threshold because their ROS levels are constantly increased to encourage growth and adaptability. This delicate equilibrium is the exploitable weakness of ROS-based therapies since a deliberate push over it results in irreversible oxidative collapse and tumor cell death.(33)

$O_2 \rightarrow O_2^{\bullet-} \rightarrow H_2O_2 \rightarrow {}^{\bullet}OH$ (mitochondria, cytosol, nucleus, peroxisomes) → low/moderate ROS → signaling (proliferation, differentiation, survival); high/excess ROS → oxidative stress → DNA/protein/lipid damage → cytotoxicity

If ROS exceed the capacity of these systems, oxidative damage accumulates. Cancer cells live close to this oxidative limit, using high ROS for growth but risking collapse if ROS increase further a weakness targeted in many therapies.

## 2. ROS Threshold Concept in Cancer Therapy

The "Redox Window" hypothesis suggests that cancer cells maintain a balanced oxidative state, with low to moderate ROS levels serving as critical signaling molecules for proliferation, survival, and metabolic adaptation.(34) However, excessive ROS accumulation surpasses the antioxidant buffering capacity, leading to cytotoxicity and cell death. Cancer cells upregulate antioxidant defenses like glutathione, thioredoxin, and enzymes to neutralize excessive ROS and prevent irreversible damage. This adaptive increase in antioxidant capacity expands the "redox window," allowing tumor cells to tolerate higher ROS concentrations compared to normal cells. Differential ROS tolerance is due to oncogenic signaling pathways in cancer cells, which rely on ROS-mediated reversible oxidation of cysteine residues on phosphatases and kinases to sustain proliferative signaling.(35) Normal cells, lacking such oncogenic stimuli, operate within a narrower redox range and are more susceptible to oxidative damage at comparable ROS levels. The mitochondrial electron transport chain in cancer cells exhibits altered efficiency, often producing increased superoxide due to electron leakage. Overloading this antioxidant system, through pharmacological agents, disrupts redox homeostasis and causes hydrogen peroxide and hydroxyl radical accumulation, leading to irreversible oxidation of protein thiols, lipid peroxidation, DNA strand breaks, and activation of intrinsic apoptotic pathways. (36)

Under physiological conditions, ROS remain below a threshold that allows signaling without toxicity. Therapeutic strategies such as chemotherapy, radiotherapy, photodynamic therapy, and nanoparticles aim to raise ROS above this threshold, inducing oxidative stress and forms of cell death, including apoptosis, ferroptosis, and necroptosis. Combining selective ROS elevation with inhibition of antioxidant defenses further enhances therapeutic efficacy.

The therapeutic strategy of ROS overloading involves using pro-oxidant drugs or radiation to push ROS levels beyond the cancer cell's expanded redox

window, selectively inducing cytotoxicity without harming normal tissue. Targeting NRF2-regulated pathways can sensitize tumors to oxidative damage. In summary, understanding and manipulating the nuanced interplay between ROS generation, scavenging, and redox-sensitive signaling enables selective tumor cell eradication through redox overload, marking a promising avenue for precision oncology interventions.(37)

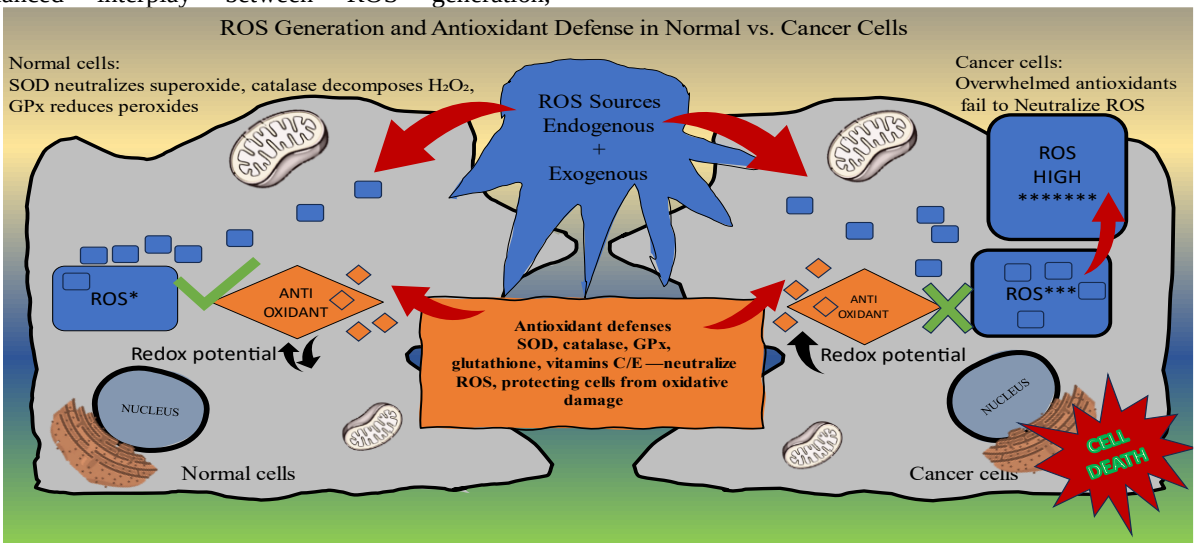


**Figure2.** Normal cells maintain redox balance through efficient antioxidant defenses, including SOD, catalase, GPx, glutathione, and vitamins C/E, which neutralize ROS. In contrast, cancer cells often exhibit elevated basal ROS and overwhelmed or dysregulated antioxidant systems, making them more susceptible to oxidative stress and ROS-mediated cell death

## 3. ROS in Cancer Initiation and Progression

ROS including superoxide, hydrogen peroxide, and hydroxyl radicals, are chemically reactive molecules derived from mitochondrial electron transport chain leakage, NADPH oxidases (NOX family), and enzymatic processes such as cytochrome P450 monooxygenase reactions. Low to moderate ROS levels serve essential roles in intracellular signaling and homeostasis, but their excessive accumulation precipitates oxidative stress that drives cancer initiation and progression via complex molecular mechanisms involving DNA damage, redox-dependent signaling modulation, metabolic reprogramming, and tumor microenvironment remodeling. ROS induced genomic instability is a key initiating event in oncogenesis, causing oxidative DNA lesions such as (8-oxoG), which mis pairs with adenine during replication, resulting in Guanine–Cytosine (G:C) → Thymine–Adenine (T:A) transversions. These mutations can activate oncogenes or inactivate tumor suppressors.(38)

ROS also induce a basic sites and single- and double-strand breaks (DSBs), overwhelming BER and homologous recombination pathways. Oxidative stress-mediated telomere shortening exacerbates chromosomal instability, promoting replicative immortality and clonal evolution. Beyond direct DNA damage, ROS function as modulators of oncogenic signaling cascades through selective oxidative modifications of key cysteine residues on phosphatases and kinases. (39) For instance, ROS reversibly oxidize the active site cysteine of phosphatase and tensin homolog (PTEN), impairing its lipid phosphatase activity and thereby hyperactivating the Phosphoinositide 3-Kinase/Protein Kinase B/Mammalian Target of Rapamycin (PI3K/AKT/mTOR) pathway. This signaling axis enhances glucose uptake via Glucose Transporters (GLUT) and anabolic metabolism, supporting proliferation and survival. Similarly, ROS inhibit Mitogen-Activated Protein Kinase (MAPK) phosphatases (MKPs) by sulfenylation, prolonging the phosphorylation state of Extracellular Signal-Regulated Kinases 1/2 (ERK1/2), fostering transcription of genes promoting cell cycle progression and anti-apoptotic responses.(40)

ROS also engage the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway by oxidative activation of the Inhibitor of kappa B (IκB) kinase (IKK) complex. Oxidation of redox-sensitive cysteines within Inhibitor of kappa B (IκB) kinase subunits triggers conformational changes that lead to degradation of the inhibitor Inhibitor of kappa B (IκB), freeing Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) to translocate into the nucleus and induce transcription of pro-inflammatory cytokines, anti-apoptotic proteins, and angiogenic factors such as Vascular Endothelial Growth Factor (VEGF).(41) This inflammatory signaling establishes a tumor-promoting

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microenvironment that enhances immune evasion and fosters metastatic potential. In metabolic reprogramming, ROS serve as key mediators adjusting the Warburg effect and mitochondrial function. Oxidative stress stabilizes Hypoxia-Inducible Factor 1-alpha (HIF-1α) by inhibiting Prolyl Hydroxylases (PHDs) via oxidation of their Ferrous ion ($Fe^{2+}$) centers, preventing Hypoxia-Inducible Factor 1-alpha (HIF-1α) degradation. Stabilized HIF-1α drives expression of glycolytic enzymes and Glucose Transporters (GLUT), thus promoting aerobic glycolysis even under normoxia. Concurrently, ROS influence mitochondrial biogenesis by regulating transcriptional coactivators like Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha (PGC-1α).(42)

Tumor microenvironment remodeling by ROS is multifaceted, primarily induced via Vascular Endothelial Growth Factor (VEGF) signaling and directly oxidizing cysteine residues on Vascular Endothelial Growth Factor Receptors (VEGFR), modulating receptor activation and downstream signaling cascades. ROS also activate Matrix Metalloproteinases (MMPs) such as Matrix Metalloproteinase-2 (MMP-2) and Matrix Metalloproteinase-9 (MMP-9) by oxidizing the cysteine switch that maintains these proteases in an inactive pro-form. At the biochemical level, ROS generation in cancer cells is orchestrated by several enzymatic systems. (43)Mitochondrial Complex I [Nicotinamide Adenine Dinucleotide (NADH): Ubiquinone Oxidoreductase] and Mitochondrial Complex III (Cytochrome $bc_1$ Complex, also called Ubiquinol–Cytochrome c Oxidoreductase) are major ROS sources via electron leakage to molecular oxygen, while the Nicotinamide Adenine Dinucleotide Phosphate Hydrogen (NADPH) oxidase family catalyzes electron transfer from NADPH to molecular oxygen ($O_2$) to form superoxide or directly $H_2O_2$, depending on the isoform. Cytochrome P450 monooxygenases contribute to ROS production during xenobiotic metabolism in tumors, where incomplete electron transfer leads to superoxide and $H_2O_2$ leakage.(44)

In summary, ROS-mediated oxidative DNA damage leads to mutation accumulation and chromosomal instability foundational for cancer initiation. Redox-dependent modulation of PTEN, MAPK, NF-κB, and JAK/STAT pathways drives proliferation, survival, inflammation, and immune evasion. Metabolic shifts orchestrated by ROS regulate glycolysis and mitochondrial function, adapting energy production to tumor demands. in moderate ROS signaling range, the pathways (MAPK, NF-κB, PI3K/AKT) mostly promote cell survival and growth not death.(45)

Endogenous ROS: mitochondria (ETC leakage, Complex I/III), NADPH oxidase, xanthine oxidase, peroxisomes; Exogenous ROS: UV, ionizing radiation, chemicals, toxins → $O_2^{\bullet-}$ (superoxide) → SOD → $H_2O_2$ → $^{\bullet}OH$ (via Fenton/Haber-Weiss) / $^1O2$ → oxidative damage to DNA (base modifications, strand breaks, crosslinks), lipids (peroxidation), proteins (carbonylation, oxidation) → mutations → oncogene activation (Ras, Myc, Bcl-2) / tumor suppressor loss (p53, PTEN, RB) → sustained ROS → activation of redox-sensitive signaling pathways: NF-κB → inflammation/proliferation; MAPK/ERK → growth & survival; PI3K-Akt → proliferation, anti-apoptosis; HIF-1α → angiogenesis & metabolic reprogramming → enhanced tumor progression: cell proliferation, survival, angiogenesis, invasion, metastasis → adaptive antioxidant response (Nrf2, GSH, catalase, peroxiredoxins) → redox balance, therapy resistance → chronic ROS exposure → genomic instability → further cancer evolution.

## 4. ROS in the Tumor Microenvironment (TME)

In the tumor microenvironment (TME), reactive oxygen species (ROS) play multifaceted roles in orchestrating cellular and molecular interactions that drive tumor progression, immune evasion, and therapeutic resistance. Under hypoxic conditions commonly found in solid tumors, ROS critically stabilize hypoxia-inducible factor-1 alpha (HIF-1α) by inhibiting prolyl hydroxylase domain enzymes (PHDs) through oxidative modification of their $Fe^{2+}$-containing catalytic sites, preventing HIF-1α hydroxylation and subsequent proteasomal degradation. Stabilized HIF-1α translocates to the nucleus, initiating transcriptional programs that promote angiogenesis via VEGF, glycolytic reprogramming, and survival pathways, thereby facilitating tumor adaptation to oxygen deprivation. (46) Concurrently, hypoxia triggers antioxidant responses through nuclear factor erythroid 2–related factor 2 (NRF2) activation, enhancing expression of glutathione synthesis enzymes, thioredoxin reductases, and catalase, which mitigate excessive ROS to preserve cellular viability while maintaining redox signaling critical for tumor progression. Cancer-associated fibroblasts (CAFs), abundant stromal cells within the TME, respond to elevated ROS by undergoing phenotypic activation driven by redox-sensitive transcription factors such as NF-κB and AP-1, which induce secretion of matrix metalloproteinases (MMPs) and pro-fibrotic factors. This ROS-induced ECM remodeling facilitates cancer cell invasion and metastasis by degrading basement membranes and altering ECM stiffness through collagen crosslinking catalyzed by lysyl oxidase (LOX), whose expression is upregulated by ROS and HIF-1α signaling. (47)

Furthermore, ROS modulate fibroblast activation by

promoting the myofibroblast phenotype, characterized by α-smooth muscle actin (α-SMA) expression and increased contractility, which supports tumor growth and desmoplasia. Immune cells within the TME are similarly influenced by ROS; elevated oxidative stress impairs T-cell receptor (TCR) signaling through reversible oxidation of cysteine residues on key signaling proteins such as LCK and ZAP-70, reducing T-cell proliferation and cytokine production, thereby promoting immune suppression.(48) ROS also induce T-cell exhaustion by upregulating inhibitory receptors like PD-1 and CTLA-4 via redox-sensitive transcriptional pathways. Additionally, ROS promote the expansion and suppressive function of myeloid-derived suppressor cells (MDSCs) through activation of STAT3 and NF-κB, leading to enhanced production of arginase-1, inducible nitric oxide synthase (iNOS), and NADPH oxidase components, which further elevate ROS within the TME. This ROS-mediated feedback loop not only suppresses effector T-cell activity but also enhances MDSC survival and recruitment, reinforcing an immunosuppressive microenvironment. (49)

ROS (from cancer cells, stromal cells, immune cells; endogenous: mitochondria/NADPH oxidase, exogenous: hypoxia, radiation, chemo) → HIF-1α stabilization (via PHD inhibition) → transcription of VEGF, glycolytic enzymes, survival genes → angiogenesis & metabolic adaptation; ROS → NRF2 activation → glutathione, thioredoxin, catalase → redox balance; ROS → CAF activation (NF-κB/AP-1) → MMPs, LOX, pro-fibrotic factors → ECM remodeling, collagen crosslinking, myofibroblast phenotype → invasion/metastasis; ROS → immune suppression: TCR oxidation (LCK/ZAP-70) → T-cell dysfunction & exhaustion (↑PD-1/CTLA-4), MDSC activation via STAT3/NF-κB → arginase-1/iNOS/NADPH oxidase ↑ → further ROS → immunosuppressive TME → tumor progression & therapy resistance

Moreover, mitochondrial ROS in MDSCs contribute to metabolic reprogramming favoring glycolysis and fatty acid oxidation, which supports their immunosuppressive phenotype. Collectively, the interplay between hypoxia, ROS production, and antioxidant defense mechanisms in the TME orchestrates a complex signaling network that remodels the extracellular matrix, activates stromal fibroblasts, and subverts immune surveillance, thereby promoting tumor growth, metastasis, and resistance to therapy.(50) Understanding these intricate redox-dependent mechanisms offers promising avenues for therapeutic intervention aimed at disrupting ROS signaling pathways to restore anti-tumor immunity and inhibit tumor progression. (Table 2)

## 5. Molecular Mechanisms of ROS-Mediated Cancer Cell Death

ROS serve as pivotal regulators of diverse cell death modalities and intricate tumor microenvironment (TME) interactions, profoundly shaping cancer progression and therapeutic response at the molecular level. In apoptosis, ROS-induced mPTP opening results from oxidative modifications of mitochondrial membrane lipids and proteins, destabilizing membrane potential and enabling cytochrome c release into the cytosol.(34) This release triggers apoptosome formation, activating initiator caspase-9 and effector caspases-3/-7, culminating in controlled proteolytic cleavage of cellular substrates. ROS also potentiate p53 tumor suppressor activity via oxidative DNA damage, promoting transcription of pro-apoptotic genes such as Bax, Puma, and Noxa, further sensitizing cells to mitochondrial outer membrane permeabilization (MOMP).(51) In ferroptosis, a non-apoptotic form of programmed cell death, ROS-mediated lipid peroxidation targets polyunsaturated fatty acid (PUFA)-rich membrane phospholipids through iron-dependent Fenton reactions, generating lethal lipid hydroperoxides. This is exacerbated by glutathione peroxidase 4 (GPX4) inactivation and glutathione (GSH) depletion, which normally detoxify lipid hydroperoxides, thereby tipping the balance toward ferroptotic cell demise.(52) The catalytic role of $Fe^{2+}$ in ROS amplification underscores the iron-ROS nexus central to ferroptosis execution. Necroptosis, governed by the receptor-interacting protein kinases RIPK1 and RIPK3, and the pseudokinase mixed lineage kinase domain-like protein (MLKL), is modulated by ROS through oxidative activation of RIPK1 and enhancement of mitochondrial ROS production, which amplifies death signaling in a feed-forward loop. (53)

The oxidative environment facilitates MLKL oligomerization and membrane translocation, disrupting plasma membrane integrity and causing necrotic cell death. Autophagy is intricately regulated by ROS via the AMPK-mTOR axis, wherein ROS activate AMP-activated protein kinase (AMPK), inhibiting mTOR and promoting autophagic flux to remove damaged organelles and proteins, notably through mitophagy that the selective autophagic clearance of ROS-producing dysfunctional mitochondria triggered by oxidative damage markers such as oxidized cardiolipin and PINK1/Parkin pathway activation.(54) Pyroptosis, an inflammatory programmed cell death, is initiated by ROS-driven activation of the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, where mitochondrial ROS oxidize thiol groups on NLRP3 and associated components, facilitating its oligomerization. (55) activates caspase-1, which

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cleaves gasdermin D, forming membrane pores that allow cytokine release and pyroptotic cell lysis. Immunogenic cell death (ICD) is another ROS-dependent pathway wherein oxidative stress induces endoplasmic reticulum (ER) stress responses, leading to the exposure of damage-associated molecular patterns (DAMPs) such as calreticulin on the cell surface, and the release of ATP and high-mobility group box 1 (HMGB1), which stimulate dendritic cell maturation and anti-tumor immunity.(56) Within the tumor microenvironment, hypoxia and ROS interplay dynamically; hypoxia stabilizes hypoxia-inducible factor 1-alpha (HIF-1α) by ROS-mediated inhibition of prolyl hydroxylases that normally mark HIF-1α for degradation. Stabilized HIF-1α upregulates glycolytic genes and VEGF, promoting angiogenesis and metabolic reprogramming. Hypoxia also induces antioxidant responses via NRF2 activation, allowing cancer cells and stromal elements to tolerate increased ROS.(57) Cancer-associated fibroblasts (CAFs), key components of the TME, are activated by ROS through TGF-β signaling and redox-sensitive transcription factors, driving extracellular matrix (ECM) remodeling via MMP secretion and collagen crosslinking, which facilitates tumor invasion. ROS also induce fibroblast senescence-associated secretory phenotype (SASP), amplifying inflammatory cytokine secretion. Immune cells in the TME are profoundly influenced by ROS; elevated ROS levels induce T-cell dysfunction by oxidizing critical signaling proteins and impairing receptor activation, reducing cytotoxic activity.(58) Furthermore, ROS promote expansion and suppressive functions of myeloid-derived suppressor cells (MDSCs) by activating redox-sensitive transcription factors such as STAT3 and NF-κB, which upregulate arginase-1 and inducible nitric oxide synthase (iNOS), leading to T-cell suppression and immune evasion.(59) Collectively, these molecular events depict ROS as central modulators of cancer cell fate and TME remodeling, intricately balancing pro-survival and pro-death signals through redox-dependent post-translational modifications, transcriptional reprogramming, and intercellular crosstalk, offering critical insights into therapeutic strategies that exploit redox vulnerabilities to enhance cancer treatment efficacy.(60)

Excess ROS ($O_2^{\bullet -}$ , $H_2O_2$, $^{\bullet}OH$, $^1O2$; sources: mitochondria, NADPH oxidase, peroxisomes, chemotherapeutics, radiation, photodynamic therapy) → mitochondrial outer membrane permeabilization → cytochrome c release → apoptosome formation → caspase-9/-3 activation → apoptosis; ROS → lipid peroxidation (PUFAs) → ferroptosis via GPX4 inhibition and iron accumulation; ROS → DNA damage (strand breaks, base oxidation) → p53 activation → cell cycle arrest/apoptosis; ROS → protein oxidation → ER stress → unfolded protein response → apoptosis/autophagy; ROS → RIPK1/RIPK3 activation → necroptosis; ROS → lysosomal membrane permeabilization → cathepsin release → cell death; antioxidant systems (GSH, thioredoxin, catalase, SOD) modulate susceptibility; excessive ROS overwhelms defense → selective cancer cell cytotoxicity

## 6. Strategies to Harness ROS in Cancer Therapy

Strategies to harness ROS in cancer therapy exploit the delicate balance between ROS generation and antioxidant defenses to selectively induce cancer cell death while minimizing damage to normal cells. Direct ROS inducers such as ionizing radiation and photodynamic therapy (PDT) generate overwhelming oxidative stress by producing large quantities of ROS, including hydroxyl radicals, singlet oxygen, and superoxide, through radiolysis of water or photosensitizer activation by light, respectively.(61) These ROS inflict widespread macromolecular damage DNA strand breaks, lipid peroxidation, and protein oxidation triggering apoptosis or necrosis. Redox-active chemotherapeutics like doxorubicin and arsenic trioxide further elevate intracellular ROS by redox cycling or mitochondrial electron transport chain disruption, driving cancer cells beyond their oxidative stress threshold. Complementarily, indirect ROS amplification strategies focus on crippling cancer cells' antioxidant systems to potentiate endogenous ROS toxicity. (62)

Glutathione (GSH) depletion using agents such as buthionine sulfoximine (BSO) inhibits γ-glutamylcysteine synthetase, impairing GSH biosynthesis and disrupting the critical thiol-based redox buffering capacity. Similarly, inhibition of thioredoxin reductase (TrxR), an essential enzyme in maintaining the reduced state of thioredoxin (Trx), using compounds like auranofin, disrupts cellular redox homeostasis by preventing reduction of oxidized proteins and scavenging of ROS.(14) The resulting accumulation of hydrogen peroxide and lipid peroxides exacerbates oxidative damage, sensitizing cancer cells to death. ROS-based combinational approaches have garnered considerable interest to overcome therapeutic resistance and enhance efficacy. Combining ROS inducers with conventional chemotherapy exploits synergistic cytotoxicity, where chemotherapy drugs impair DNA repair or mitochondrial function, amplifying ROS-mediated damage. (62)

For instance, platinum-based agents combined with ROS-inducing compounds enhance mitochondrial ROS generation, promoting apoptosis. Moreover, integrating ROS modulation with immunotherapy capitalizes on ROS's dual role in immune regulation:

moderate ROS levels enhance antigen presentation and T-cell activation, whereas excessive ROS suppress immune cell function. Agents that transiently elevate ROS can improve immunogenic cell death (ICD), increasing exposure of damage-associated molecular patterns (DAMPs) such as calreticulin and HMGB1, which stimulate dendritic cell maturation and cytotoxic T lymphocyte priming.(14) Conversely, inhibitors targeting ROS-producing enzymes in myeloid-derived suppressor cells (MDSCs) or tumor-associated macrophages (TAMs) alleviate ROS-mediated immunosuppression, restoring T-cell cytotoxicity. At the molecular level, these therapeutic strategies manipulate critical redox-sensitive signaling pathways such as NRF2-mediated antioxidant response, MAPK cascades, and p53-dependent apoptosis, tipping cancer cells from survival into programmed cell death.(13)Targeting the mitochondrial electron transport chain complexes or NADPH oxidases increases mitochondrial and cytosolic ROS, disrupting ATP production and triggering intrinsic apoptosis. Concurrent inhibition of antioxidant enzymes like superoxide dismutase (SOD) and catalase further impedes ROS detoxification, fostering a pro-oxidant milieu that preferentially kills cancer cells due to their already elevated basal ROS levels.(41) Additionally, the exploitation of ferroptosis via ROS-induced lipid peroxidation is emerging as a novel approach, where agents like erastin or RSL3 inhibit cystine uptake or GPX4 activity, enhancing iron-dependent ROS damage to lipid membranes.(7) Ultimately, successful ROS-based cancer therapies require precise modulation to surpass cancer cells' "redox window," achieving cytotoxic ROS accumulation without overwhelming normal tissue. Advances in nanotechnology and targeted delivery systems improve specificity and minimize off-target effects, enabling combination regimens that harness ROS generation, antioxidant inhibition, and immune activation to synergistically dismantle tumor survival networks at the molecular level, presenting a promising frontier in oncology.(56)

Cancer therapy ↑ ROS selectively (chemotherapy, radiotherapy, photodynamic therapy, nanoparticles) → exceed ROS threshold → apoptosis/ferroptosis/necroptosis; combined with ↓ antioxidants (GSH, SOD inhibitors) → enhance ROS-mediated cancer cell death; targeted delivery → minimize normal tissue damage

Metallic and metal-based devices have been used in cancer therapy to control ROS in order to provide tailored treatment. These techniques make use of metals' redox-active properties to produce ROS only in cancer cells, killing them while reducing harm to healthy organs. Through Fenton and Fenton-like reactions, metal-based nanoparticles such as gold, silver, and platinum have been designed to increase the formation of ROS. Hydrogen peroxide is catalyzed into reactive hydroxyl radicals by iron-based nanoparticles, which causes oxidative stress and the death of cancer cells. Nanoparticles of copper and manganese encourage the production of ROS, which damages cellular constituents and triggers apoptosis. ROS-induced cytotoxicity can be increased by combining these nanoparticles with chemotherapy or photodynamic treatment (PDT). Therapeutic compounds and photosensitizers have been delivered via metal-organic frameworks (MOFs).(23)

## 7.Limitation & future perspective

The clinical application of ROS-based cancer therapies faces significant limitations and challenges that must be addressed to fully harness their therapeutic potential. A primary concern is off-target oxidative damage, as elevated ROS levels indiscriminately affect both cancerous and normal cells due to the ubiquitous nature of ROS, leading to toxicity in healthy tissues such as cardiac, neural, and hematopoietic systems. This collateral damage stems from ROS-induced DNA strand breaks, lipid peroxidation, and protein oxidation, which compromise cellular integrity and function beyond the tumor site. Furthermore, tumors exhibit remarkable adaptability through the upregulation of intrinsic antioxidant defenses, including increased expression of glutathione synthesis enzymes, thioredoxin system components, and phase II detoxifying enzymes regulated by NRF2 signaling. (47)

This antioxidant plasticity allows cancer cells to survive and proliferate despite elevated oxidative stress induced by therapy, thus contributing to drug resistance and tumor recurrence. Compounding these challenges is the current lack of reliable, real-time ROS monitoring tools in clinical settings, which limits the ability to dynamically assess ROS levels and redox status during treatment. This hinders personalized dosing and temporal modulation of ROS-inducing agents, often resulting in suboptimal therapeutic windows and adverse side effects. Future perspectives emphasize the development of precision ROS modulation strategies aimed at generating tumor-selective ROS bursts that maximize cancer cell cytotoxicity while sparing normal cells.(53) Molecular targeting of tumor-specific redox vulnerabilities, such as aberrant mitochondrial metabolism or dysregulated NADPH oxidase activity, can exploit differential redox homeostasis. Integration with high-throughput genomic and proteomic profiling enables identification of redox-sensitive mutations, antioxidant gene signatures, and metabolic reprogramming unique to individual tumors, facilitating tailored therapeutic regimens.(21)

Moreover, advances in artificial intelligence (AI)-guided drug design and predictive modeling can optimize ROS-inducing compounds and combinational strategies by simulating complex redox networks and cellular responses at the molecular level. AI can also aid in identifying novel molecular targets within ROS regulatory pathways, enhancing specificity and efficacy.(60) Theranostic platforms integrating ROS-sensitive imaging probes with targeted drug delivery systems provide real-time visualization of intratumoral ROS dynamics coupled with controlled therapeutic release, enabling feedback-controlled treatment adjustments. These platforms employ molecular sensors that fluoresce or emit signals upon reaction with specific ROS species, permitting spatiotemporal resolution of oxidative stress at the cellular and subcellular levels.(23) Collectively, overcoming the current barriers through multidisciplinary approaches that combine molecular redox biology, systems pharmacology, and cutting-edge technology promises to transform ROS modulation from a broad cytotoxic strategy into a precise, adaptive cancer therapy paradigm, minimizing toxicity and overcoming tumor resistance mechanisms at the molecular and cellular interface.(3)

**Table 1.** Comprehensive Molecular Landscape of Reactive Oxygen Species (ROS)

| Source | Molecular Site/Enzyme | ROS Generated | Molecular Mechanism | Representative Reaction(s) | Relevance in Cancer | Ref |
|---|---|---|---|---|---|---|
| **Mitochondria – ETC Complex I** | NADH: ubiquinone oxidoreductase | $O_2^{\bullet-}$ (Superoxide) | Leakage of electrons from FMN or Fe-S clusters to $O_2$ | $NADH + H^+ + 2\ O_2 \rightarrow NAD^+ + 2\ O_2^{\bullet-}$ | Elevated in hypoxia; supports HIF-1α stabilization and metabolic shift | (63) |
| **Mitochondria – ETC Complex III** | Cytochrome bc1 (Qo site) | $O_2^{\bullet-}$ (both matrix & IMS sides) | Semiquinone at Qo site donates $e^-$ to $O_2$ | $QH_2 + O_2 \rightarrow Q^{\bullet-} + O_2^{\bullet-} + 2H^+$ | Major ROS hotspot; promotes angiogenesis | (64) |
| **Mitochondrial enzymes (TCA-linked)** | α-KGDH, PDH | $O_2^{\bullet-}$, $H_2O_2$ | Incomplete transfer of $e^-$ during oxidative decarboxylation | $\alpha\text{-KG} + NAD^+ \rightarrow$ Succinyl-CoA + $CO_2$ + NADH $\rightarrow$ NADH donates $e^- \rightarrow O_2^{\bullet-}$ | Links metabolism to ROS signaling | (65) |
| **NADPH Oxidases (NOX1–5, DUOX1/2)** | Plasma membrane, ER | $O_2^{\bullet-}$, $H_2O_2$ | $e^-$ transferred from NADPH to $O_2$ via FAD & heme | $NADPH + 2\ O_2 \rightarrow NADP^+ + 2\ O_2^{\bullet-} + H^+ \rightarrow O_2^{\bullet-}$ dismutates $\rightarrow H_2O_2$ | Drives PI3K/AKT, MAPK, JAK/STAT signaling | (66) |
| **Peroxisomes** | Acyl-CoA oxidase, Xanthine oxidase | $H_2O_2$, $O_2^{\bullet-}$ | Direct generation of $H_2O_2$ in fatty acid β-oxidation & purine catabolism | $R\text{-}CH_2\text{-CoA} + O_2 \rightarrow$ trans-$\Delta^2$-enoyl-CoA + $H_2O_2$ ; Xanthine + $O_2 \rightarrow$ Uric acid + $O_2^{\bullet-}$ | Links lipid/purine metabolism to redox stress | (67) |
| **Endoplasmic Reticulum (ER)** | ERO1, PDI | $H_2O_2$ | Oxidative protein folding couples disulfide formation to $O_2$ reduction | $ERO1\text{-}FADH_2 + O_2 \rightarrow ERO1\text{-}FAD + H_2O_2$ ; PDI-SH + ERO1 $\rightarrow$ PDI-S-S + $H_2O_2$ | Triggers ER stress → UPR → apoptosis | (68) |
| **Cytochrome P450 enzymes** | CYP monooxygenases | $O_2^{\bullet-}$, $H_2O_2$ | "Uncoupled" oxygen cycle leaks electrons to $O_2$ | $RH + O_2 + NADPH \rightarrow ROH + H_2O$; uncoupling: $O_2 + e^- \rightarrow O_2^{\bullet-}$ / $H_2O_2$ | Contributes to drug-induced ROS, tumor initiation | (69) |
| **Nitric Oxide Synthases (NOS)** | eNOS, iNOS | $O_2^{\bullet-}$, $ONOO^-$ | Uncoupling (lack of $BH_4$ or L-arginine) → $O_2$ reduction; $O_2^{\bullet-}$ reacts with NO | $O_2 + NADPH \rightarrow O_2^{\bullet-}$ ; $O_2^{\bullet-} + NO\bullet \rightarrow ONOO^-$ | $ONOO^-$ nitrates DNA/proteins; promotes inflammation-driven tumorigenesis | (70) |
| **Myeloperoxidase (MPO)** | Neutrophils, TAMs | HOCl | Uses $H_2O_2$ to oxidize $Cl^-$ | $H_2O_2 + Cl^- \rightarrow HOCl + OH^-$ | Causes mutagenic DNA adducts; modifies TME | (71) |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Transition metals (Fenton/Haber–Weiss)** | $Fe^{2+}$, $Cu^{+}$ | •OH (Hydroxyl radical) | Fenton chemistry converts $H_2O_2$ → •OH | $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + {}^{\bullet}OH$ | Highly toxic → DNA breaks, lipid peroxidation | (72) |
| **Radiation / UV / Chemo** | Water radiolysis | •OH, $H_2O_2$, $O_2^{\bullet-}$ | Ionizing radiation splits $H_2O$ molecules | $H_2O \rightarrow {}^{\bullet}OH + H^{\bullet}$; $2\ {}^{\bullet}OH \rightarrow H_2O_2$ | Used in therapy (radiotherapy, PDT), but also mutagenic | (73) |

**Table 2.** Comprehensive Overview of ROS Roles and Therapeutic Strategies in Cancer

| Category | Key Concepts | Molecular Mechanisms | Impact on Cancer | Therapeutic Implications / Strategies | Ref |
|---|---|---|---|---|---|
| **ROS in Cancer Initiation & Progression** | ROS act as signaling molecules regulating proliferation, survival, and genomic stability. | - ROS induce DNA mutations via 8-oxoguanine formation. - Activate oncogenes (e.g., Ras, Myc) and inactivate tumor suppressors (e.g., p53). - Modulate signaling pathways like NF-κB, MAPK, PI3K/Akt. | - Low to moderate ROS promote tumorigenesis and metastasis. - Chronic ROS exposure contributes to genomic instability and cancer hallmarks. | - Antioxidants may prevent initiation but could protect established tumors. - ROS modulation can influence tumor growth and invasion. | (74) |
| **ROS Threshold Concept in Cancer Therapy** | ROS exhibit a dual role: moderate levels promote survival; high levels trigger cell death. | - ROS threshold dictates cell fate: • Sub-lethal: proliferation, survival signaling. • Lethal: apoptosis, ferroptosis, necroptosis. - Cancer cells have higher basal ROS, making them selectively vulnerable. | - Exploiting ROS threshold selectively kills cancer cells while sparing normal cells. - Threshold modulation is context-dependent on tumor type and microenvironment. | - Pro-oxidant therapies (e.g., chemo, radiotherapy) elevate ROS beyond lethal threshold. - Combining ROS-inducing drugs with antioxidant inhibitors enhances selectivity. | (75) |
| **Molecular Mechanisms of ROS-Mediated Cancer Cell Death** | ROS can induce apoptosis, autophagy, ferroptosis, and necroptosis. | - Mitochondrial pathway: ROS → cytochrome c release → caspase activation. - Ferroptosis: ROS → lipid peroxidation → iron-dependent cell death. - Necroptosis: ROS → RIPK1/RIPK3/MLKL activation. - Autophagy: ROS → AMPK activation → autophagic flux. | - High ROS triggers cancer cell death. - Resistant cells may upregulate antioxidant defenses (e.g., Nrf2, GSH, SOD). | - Ferroptosis inducers, ROS-generating chemotherapeutics, photodynamic therapy (PDT). - Target antioxidant systems to overcome resistance. | (74) |
| **ROS in the Tumor Microenvironment (TME)** | ROS modulate interactions between tumor cells, immune cells, and stromal cells. | - ROS regulate immune cell function: T-cell exhaustion, macrophage polarization (M1/M2). - Modulate angiogenesis via VEGF signaling. - Alter ECM remodeling and cancer-associated fibroblast activation. | - ROS in TME influence metastasis, immune evasion, and therapy resistance. - Can promote immunosuppressive environment at moderate levels. | - Target ROS to normalize TME. - Combine ROS modulation with immunotherapy (e.g., checkpoint inhibitors). - ROS-sensitive drug delivery systems in TME. | (76) |

| | | | | | |
|---|---|---|---|---|---|
| **Strategies to Harness ROS in Cancer Therapy** | Aim: push ROS beyond lethal threshold in cancer cells or inhibit adaptive antioxidant responses. | - Pro-oxidant drugs: doxorubicin, cisplatin, arsenic trioxide. - Photodynamic therapy: light-activated ROS production. - Nanoparticles delivering ROS inducers. - Targeting antioxidant defenses: Nrf2, GSH, Trx system inhibitors. | - Enhanced selective killing of cancer cells. - Overcome chemoresistance and radio resistance. - Synergistic effect with immunotherapy or conventional therapy. | - Combination therapy: ROS-inducing agents + antioxidant inhibitors. - Nanocarriers for tumor-selective ROS delivery. - ROS-responsive drug release systems. | (77) |

## 4. Conclusion

Reactive oxygen species (ROS) are a crucial molecular switch in cancer biology, regulating proliferation, survival, and metabolic adaptation. However, excessive ROS accumulation can disrupt cellular redox homeostasis, leading to regulated cell death. This makes ROS an attractive therapeutic target, as they can selectively exploit the heightened oxidative stress characteristic of cancer cells. Therapeutic strategies that induce ROS bursts beyond the cancer cell's redox buffering capacity have shown potential to selectively eradicate tumor cells while sparing normal tissues. Combinational therapies integrating ROS modulation with chemotherapy or immunotherapy also enhance cancer cell vulnerability by amplifying oxidative damage and improving immune-mediated tumor clearance. Clinical translation of ROS-targeted therapies requires precise control over ROS dynamics to minimize off-target effects and overcome tumor adaptation. Cancer cells often counteract oxidative stress by upregulating endogenous antioxidants through NRF2 and other redox-regulatory networks, fostering resistance and survival. The lack of reliable real-time ROS monitoring tools limits the ability to personalize and optimize ROS-based interventions. Future progress will involve deeper integration of molecular redox biology with genomic, proteomic, and metabolomic profiling to identify tumor-specific redox vulnerabilities and resistance mechanisms. Advances in artificial intelligence and systems pharmacology offer tools to model redox networks, predict cellular responses, and tailor ROS-modulating regimens with enhanced efficacy and safety. Understanding the interplay between ROS and the tumor microenvironment provides additional therapeutic targets and strategies to disrupt tumor-supportive niches.

### Acknowledgments

We would like to extend our appreciation and thanks to all participants, staff, and managers who made this study possible.

### Ethical Considerations and Compliance with Ethical Guidelines

Not applicable

### Funding

No specific funding was received for this study.

### Conflict of interest

The authors declare no conflict of interest, financial, or otherwise.
The authors declare that they have no conflicts of interest.

### AI Using Declaration

The authors declare no artificial intelligent chatbot use.

### Author's contributions

All authors equally contributed to the preparation of this article.

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