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Review

Exploring How Reactive Oxygen Species Contribute to Cancer via Oxidative Stress

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Abstract

Cancer remains a major global health burden driven by genetic, metabolic, and microenvironmental alterations. Although reactive oxygen species (ROS) and oxidative stress have long been implicated in cancer biology, current understanding remains fragmented and, in several areas, conceptually disputed considering how ROS and oxidative stress thresholds determine the switch between tumor-promoting signaling and cytotoxic outcomes, and whether redox-based therapies can be safely and selectively applied across different cancer types. Moreover, existing studies often examine isolated pathways or single ROS, leaving unanswered the question of how spatial and temporal ROS dynamics and oxidative stress responses shape carcinogenesis, metastasis, and therapeutic resistance. This review moves beyond descriptive summarization by critically examining unresolved mechanistic gaps, including (i) how ROS and oxidative stress interact with epigenetic and metabolic reprogramming, (ii) the context-dependent role of ROS-driven oxidative stress within the tumor microenvironment and immune evasion, and (iii) why ROS-targeting and oxidative stress-modulating therapies have shown inconsistent clinical translation despite promising preclinical data. We highlight areas of consensus as well as conflicting evidence, synthesizing recent advances across multiple cancer types to clarify where ROS and oxidative stress function as drivers, modulators, or vulnerabilities. Finally, we outline emerging research priorities, such as real-time redox profiling, subtype-specific targeting strategies, and combination approaches, to guide the development of more precise and effective ROS- and oxidative-stress-based interventions.

Keywords: ROS; oxidative stress; redox imbalance; therapeutic resistance; tumor microenvironment; cancer progression; genetic alterations; epigenetic alterations; DNA damage

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1. Introduction

Cancer, a major global health burden, is not merely a consequence of genetic mutations but results from a complex interplay of cellular signaling alterations, metabolic reprogramming, and environmental influences [1]. Among these elements, reactive oxygen species (ROS) have emerged as key contributors to both the suppression and progression of

tumors [2]. ROS are highly reactive molecules that include free radicals such as superoxide anion ($O_2^{\bullet-}$) and hydroxyl radical (•OH), and also non-radical molecules such as hydrogen peroxide (H_2O_2). They are derived from molecular oxygen and can react with cellular components, including lipids, proteins, and nucleic acids, giving rise to oxidative stress. Whereas ROS have conventionally been regarded as deleterious metabolic products, they also play important roles in cellular signaling; thus, they exhibit a dual role in biological systems, contributing to both physiological functions and oxidative damage [3,4]. ROS are produced in multiple subcellular locations, including mitochondria, peroxisomes, and the endoplasmic reticulum, as byproducts of metabolic processes or in response to external stimuli [5,6]. The mitochondrial electron transport chain (ETC) is the primary source of intracellular ROS, where oxygen is reduced during oxidative phosphorylation. A small percentage of electrons leak to oxygen, generating superoxide anions. These anions are converted to hydrogen peroxide by superoxide dismutase (SOD), which is then detoxified by catalase or glutathione peroxidase [7]. Other important sources of ROS are the NADPH oxidases (NOXs), because they produce ROS as a primary product in the course of immune defense and signaling processes [8], whereas peroxisomes are organelles where hydrogen peroxide is produced during fatty acid β-oxidation [9]. The endoplasmic reticulum also participates in the production of ROS during protein folding, especially upon accumulation of misfolded proteins [10]. Another source for ROS production is external environmental factors that may involve UV radiation, ionizing radiation, and toxins, which may also induce ROS production by their direct action on cellular components or through the stimulation of ROS-producing enzymes (Figure 1) [11].

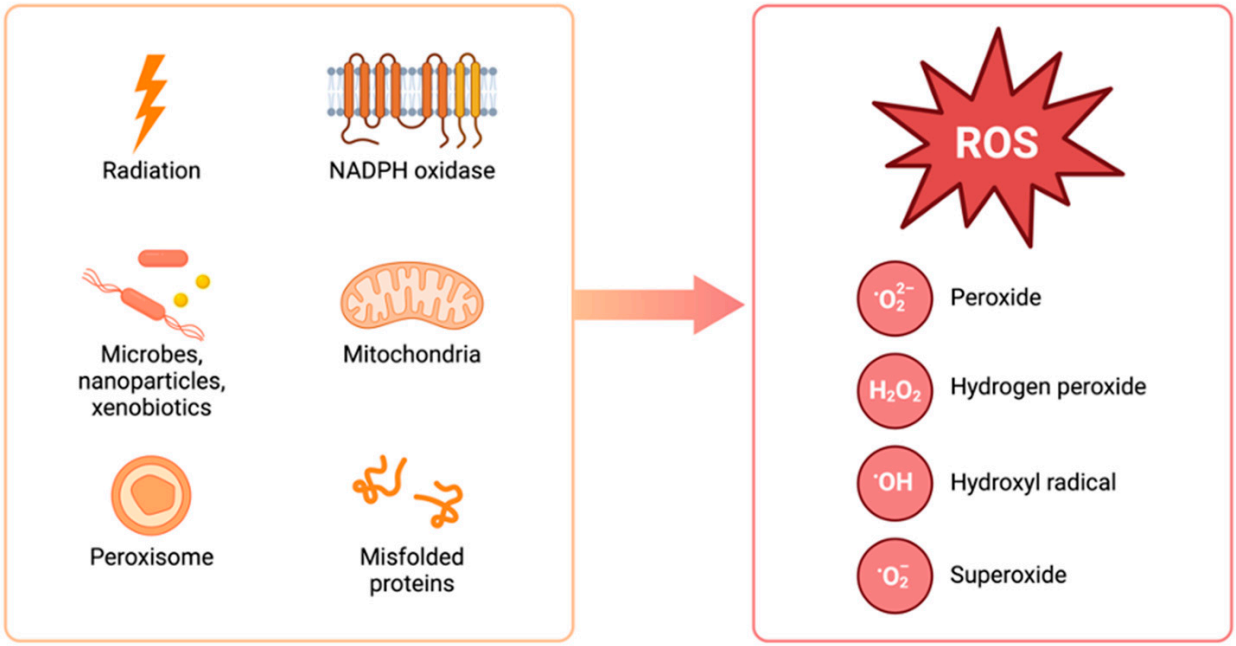

Figure 1. Sources of ROS generation.

The $O_2^{\bullet-}$ is one type of free radical formed mainly in mitochondria. It is relatively stable but acts as a precursor to more reactive species [12]. H_2O_2, by contrast, is a non-radical ROS, less reactive than superoxide, and is capable of diffusing through membranes; it may also act as a precursor to hydroxyl radicals [13]. The •OH, probably the most reactive and toxic form of ROS, results from the Fenton reaction between hydrogen peroxide and transition metals such as iron, among others [14]. Peroxyl radical species (ROO•), formed within the course of lipid peroxidation, intervene in the damage of membrane lipids [15,16]. Finally, singlet oxygen ($^1O_2$), in its excited high-energy form, is able to oxidize proteins

and DNA with subsequent cellular disruption [17]. The low to moderate levels of ROS modulate several cellular processes including growth, differentiation, and immune responses through the activation of pathways like mitogen-activated protein kinases (MAPK), phosphatidylinositol-3-kinase (PI3K)/AKT, and nuclear factor kappa B (NF-κB), or the post-translational modification of protein function via cysteine oxidation [6,13,18]. They also play an important role in immune defense, where the NADPH oxidases, produce ROS as a mechanism of eliminating pathogens [19]. Also, ROS at controlled levels may drive apoptosis by stimulating cytochrome C release and also the activation of caspases [7,20]. On the other hand, over-accumulation of ROS results in oxidative stress that can damage DNA, proteins, and lipids, resulting eventually in cell dysfunction, apoptosis, or necrosis [6]. This oxidative stress is very significant in cancer, where DNA damage induced by ROS contributes to mutations and chromosomal instability, conditions that promote carcinogenesis [14]. More than their role in disease, ROS enable metabolic adaptation, such as under hypoxic conditions, where mitochondrial ROS stabilize hypoxia inducible factor-1α (HIF-1α), enabling cells to survive and reprogram metabolism, an important process in cancer progression [21]. ROS-driven signaling, mediated through molecules like NADPH oxidases, plays a pivotal role in activating oncogenic pathways that encourage these malignant transformations [22]. Notably, branched-chain amino acid metabolism and other metabolic reprogramming pathways are intertwined with ROS production, underscoring the metabolic adaptations of cancer cells that rely on ROS-mediated signaling to support their rapid growth and adaptability under stress conditions [23]. Knowledge of ROS functions can shed new light on the research for therapeutic strategies [3]. Although ROS have been reviewed extensively, recent findings reveal previously underappreciated roles in metabolic reprogramming, redox adaptation, and therapeutic modulation. Emerging evidence shows that cancer cells remodel redox metabolism to sustain proliferation and resist treatment, while targeted manipulation of ROS is now being explored in clinical and preclinical settings. In this review, we aim to provide a comprehensive overview of ROS's complex role in cancer, examining its function as a promoter of tumor growth. By unraveling the redox tapestry of cancer, we explore how ROS-driven mechanisms contribute to carcinogenesis, metastasis, and resistance to therapy. Furthermore, we discuss emerging therapeutic approaches aimed at targeting ROS and redox signaling pathways, with the ultimate goal of improving cancer treatment outcomes by leveraging our understanding of ROS dynamics in cancer cells at modulating its action for preventive or curative purposes.

2. ROS and Carcinogenesis

ROS play a crucial role in multistep carcinogenesis, exerting impacts on all stages of cancer development, from its initiation to metastatic disease. Recent studies have elaborated that ROS plays a multifaceted role in the biology of tumors; it is not only a factor in tumor development and progression but also a target for intervention [24–27]. DNA damage induced by ROS is regarded as one of the key triggers in carcinogenesis, eventually giving rise to genetic alterations comprising mutations and genomic instability. In addition, ROS modulate some of the major signaling pathways driving cell proliferation, survival, and metastasis. ROS also impact the tumor microenvironment (TME) by influencing the behavior of immune cells and stromal cells, supporting tumor growth and angiogenesis. Therefore, the role of ROS in cancer will be of great use in developing therapies targeted to maximum exploitation of oxidative vulnerabilities in cancer cells with minimum damage to normal tissues (Figure 2) [24–27].

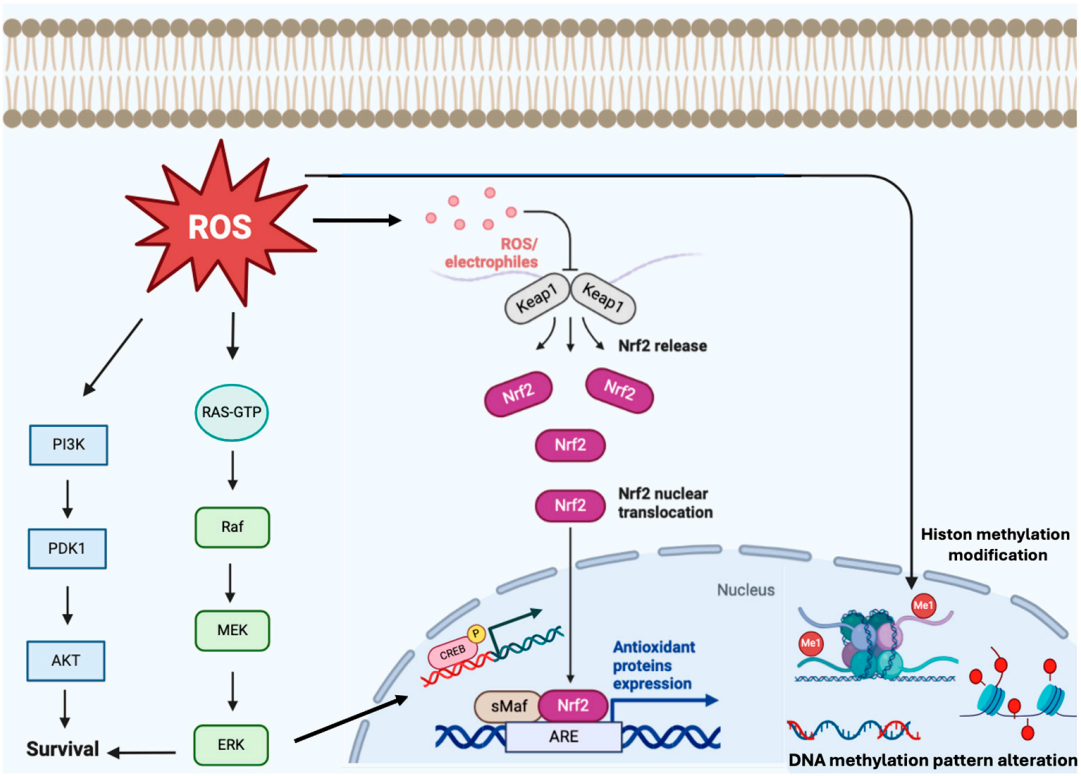

Figure 2. ROS generation and its genetic and epigenetic alteration mechanisms.

2.1. Genetic Alterations and Genomic Instability

The process of cancer initiation is characterized by various genetic alterations that disrupt cellular homeostasis and lead to an uncontrolled increase in cell proliferation [28]. The involvement of ROS in tumorigenesis directly results from their capability to induce oxidative DNA damage-one of the leading causes of genomic instability-a hallmark of cancer [29]. This encompasses an oxidative stress-driven process that leads to lesions such as 8-oxoguanine, strand breaks, and other DNA modifications that impairs genomic integrity and promotes mutagenesis [30]. Single-strand breaks (SSBs) occur when ROS directly attack the phosphodiester backbone of DNA, while double-strand breaks (DSBs) arise when SSBs are not properly repaired [31]. The DSBs are most dangerous because they can lead to extensive chromosomal rearrangements, which are a common feature in the initial stages of carcinomas [32]. Moreover, oncogenic events such as the loss of tumor suppressors like p53 and mitochondrial DNA mutations further increase ROS production, promoting tumor development and adaptability to the TME [33]. Accumulation of DNA damage more than the cellular repair capacity assists in the initiation of oncogenic transformation either through the activation of oncogenes or inactivation of tumor suppressor genes [34]. For instance, ROS can cause mutations in genes and oncogene activation, such as KRAS, while the inactivation of tumor suppressor genes like p53 may trigger cancer development [35,36]. In addition, at high levels, ROS disrupt the functions of T cells and NK cells and enhance the recruitment and polarization of M2 macrophages, further promoting tumor growth. In contrast, it has been reported that infiltration by T cells, NK cells, and M1 macrophages is associated with restraint on tumor growth in breast cancer [37]. Furthermore, overproduction of ROS suppresses the phosphorylation of eukaryotic initiation factor 2B (eIF2B), which then further reduces the expression level of NKG2D and its ligands. Due to such downregulation, cytotoxic granule release from NK cells is significantly reduced, thereby hindering their functions in antibody-dependent cell-mediated cytotoxicity and leading to tumor growth and metastasis of the breast cancer [38,39]. ROS generation may

occur through multiple signal transduction pathways, including RTKs, with activation involving EGF, PDGF, FGF, TNF, IFN-γ, and interleukins [40]. The Ras-Raf-MEK signaling cascade is considered the one through which ROS-activated signal transduction usually occurs. Oncogenic Ras is highly active in conditions associated with increased activity and expression [36,41]. Activity of ERK 1/2, due to increased oncogenic Ras activation, is thus heightened. ERK then activates several oncogenes, including c-myc, c-Jun, and CREB, through phosphorylation, promoting cellular proliferation and decreasing apoptosis, two of the critical hallmarks of oncogenesis (Figure 2) [42].

Recent studies have further elucidated ROS-mediated mutagenesis. Saxena et al. demonstrated that ROS-induced replication stress enhances micronuclei formation, which leads to chromothripsis—a catastrophic genome rearrangement process in early tumorigenesis [43]. Furthermore, a study by Chen et al. revealed that oxidative DNA damage tends to occur at topologically associating domain boundaries, leading to destabilization of 3D genome organization and driving enhancer hijacking, which may activate proto-oncogenes [44]. It is previously described that ROS directly oxidize cysteine residues on regulatory subunits of ATM and ATR, master kinases of DNA damage response, leading to faulty checkpoint activation and incorrect DNA repair [45]. Simultaneously, novel evidence shows that ROS-modified alterations in long non-coding RNAs (lncRNAs) control DNA repair accuracy and chromatin accessibility and thus contribute to transcriptional reprogramming in pre-malignant cells [46]. This adds yet another layer of control to ROS-induced genomic instability.

2.2. Epigenetic Alterations, Cell Proliferation and Signaling Pathways

Apart from genetic damage, ROS have been implicated in the regulation of tumorigenesis through epigenetic mechanisms with an unaltered DNA backbone [47]. The oxidative DNA methylation patterns are a simple mode of action through which ROS can interfere with the epigenome [48]. ROS have been known to oxidize 5mC into 5hmC, thereby interfering with normal methylation processes [49]. Aberrant DNA methylation may cause the silencing of tumor suppressor genes or activation of oncogenes, which could lead to early stages of carcinogenesis [50]. Another important epigenetic mechanism is histone modifications that can also be influenced by ROS. Modifications, such as methylation, acetylation, and phosphorylation, are changes that can occur in histones post-translation [51]. ROS have been found to alter the activities of the histone-modifying enzymes such as HDACs and HATs, which further alter chromatin conformation and gene expression profiles in cancerous cells. According to Mongelli et al., this can create epigenetic disruption in cell cycle checkpoints, apoptosis, and DNA repair, thereby facilitating the malignant transformation of cells [52]. The fact that oxidative stress can modulate m6A RNA methylation connects the accumulating level of ROS to the intensity of such modulation which could be highly relevant also for tumor development. Accordingly, different experiments showed that the levels of ROS can modulate the activity of methylation writers and erasers involved in the regulation of gene expression and carcinogenesis [53]. On the other hand, oxidative stress can induce gene silencing by mechanisms involving aberrant hypermethylation of tumor suppressor gene promoters that confer a more malignant phenotype [54]. For instance, it was recently demonstrated that exposing hepatocellular carcinoma cells to H_2O_2 induced hypermethylation of the E-cadherin gene promoter [55]. The present effect was associated with induction of Snail, a transcription factor known to repress E-cadherin expression [56,57]. Snail recruits histone deacetylase 1 and DNA methyltransferase 1, which in turn induce methylation of the E-cadherin promoter [58]. ROS also play a role in the functional loss of other tumor suppressor genes through genetic mutation and epigenetic silencing such as PTEN and RB1 [59]. For instance, Trinh et al. describe how ROS, par-

ticularly H_2O_2, oxidize PTEN's active-site cysteine, inhibiting its function. The oxidation is reversible, and enzymes such as thioredoxin (Trx) and peroxiredoxins (Prxs) play key roles in restoring PTEN activity [60]. Additionally, Ying Zhang et al. further emphasize the reversible redox regulation of PTEN, noting the critical roles of Trx and Prxs in maintaining PTEN's tumor-suppressive activity [61]. On the other hand, Peng et al. discuss how prolonged oxidative stress disrupts epigenetic machinery, such as chromatin-modifying enzymes, potentially leading to stable repression of genes like RB1 [62] and facilitation of survival and proliferation of cancer cells accelerates the initiation of tumorigenesis [63].

Recent studies have pointed out how the cellular balance of ROS may influence tumor growth; accordingly, moderate levels facilitate proliferative signaling, and high levels trigger cellular damage and death [24–27]. ROS mainly stimulate tumor cell proliferation by triggering essential growth pathways, including PI3K/AKT and the MAPK/ERK cascades, crucial for both the cell cycle and survival (Figure 2) [64]. A study showed that the KRAS gene is a well-known proto-oncogene that suffers frequent mutations from ROS-induced oxidative damage in several cancers, such as lung and colorectal cancers [65]. Mutations within KRAS cause constitutive activation of the RAS/RAF/MEK/ERK signaling pathway, which then promotes uncontrolled cell proliferation and survival (Figure 2) [66]. On the other hand, ROS can cause mutations in TP53 that disrupt its function and prevent such protective responses by the cell, hence allowing damaged cells to survive and proliferate [67]. The inactivation of TP53 is observed in over 50% of all cancers, underscoring the important role played by ROS in the inactivation process [68]. Furthermore, the heightened content of ROS in cancer cells is a product of high mitochondrial activity and expression of NOX enzymes that produce superoxides, further dissimulated to hydrogen peroxide—the more stable ROS involved in signaling [69,70]. These molecules activate various transcription factors like HIF-1, which, in turn, can help in cancer cell survival and proliferation, especially under hypoxic conditions prevailing in a tumor [71]. More importantly, ROS also drive cellular metabolism to switch towards aerobic glycolysis or the Warburg effect, which facilitates rapid cell division and generates additional ROS [72]. This therefore acts as a self-reinforcing feedback loop wherein the increased metabolic needs of growing tumor cells result in higher levels of ROS, thus further stimulating growth. ROS can modify key glycolytic enzymes through oxidative post-translational modifications [73]. These modifications enhance the activity of enzymes like pyruvate kinase M2 (PKM2), further promoting aerobic glycolysis in cancer cells, a loop between ROS and metabolic reprogramming [74]. Ngo et al. found that ROS-induced activation of the NRF2 pathway increased the expression of antioxidant genes, which in turn supported the high metabolic demands of rapidly proliferating tumor cells (Figure 2) [75]. First, in order to avoid excessive oxidative damage, the antioxidant systems of cancer cells are increased, including superoxide dismutase and catalase, both of which detoxify ROS by maintaining a pro-proliferative balance [76]. Targeting these antioxidant systems has emerged as a potential therapeutic strategy to push the levels of ROS beyond a critical threshold, leading to the initiation of cell death and oxidative stress in cancer cells [77]. However, it is still a daunting task to selectively enhance the levels of ROS in cancer cells without affecting the normal cells, which also depend on them for physiological signaling [78]. In addition, ROS control the transitions of the cell cycle by regulating the activity of cyclin-dependent kinases and promote the replication of tumor cells [79]. In consequence, ROS are complex molecules; their involvement in the process of tumor cell proliferation requires the modulation of important signaling pathways, metabolic pathways, and cell-cycle machinery. Therefore, disruption of ROS homeostasis in cancer cells might be a promising avenue toward the control of tumor growth [80,81].

2.3. Angiogenesis and Tumor Vascularization

ROS are pivotal in regulating tumor angiogenesis and vascularization, both essential for tumor growth and metastatic spread [24–27]. Beyond their classical damaging role, ROS act as signaling molecules that modulate endothelial cell behavior and neovascularization [82]. For instance, ROS generated by NOX enzymes, especially NOX4, directly stimulate endothelial sprouting and migration [83]. Endothelial NOX4–derived H_2O_2 activates Ca^{2+} dependent TRPM2/eNOS pathways, enhancing angiogenic capacity [84]. In glioma models, selective NOX4 inhibition reduced vessel density and tumor progression highlighting the therapeutic potential of redox modulation [85]. ROS levels higher than normal in the TME activate various pathways like HIF-1α that increases the expression of vascular endothelial growth factor (VEGF), a potent stimulator of angiogenesis [82]. ROS activate the ATM–CHK2–HIF-1α axis, directly linking oxidative stress to VEGF induction and tumor angiogenesis. These abnormal leaky blood vessels allow the uninterrupted growth of tumors but show inefficiency in supplying oxygen, therefore creating more hypoxia and, accordingly, further stimulating the production of ROS in a vicious circle [86]. Not only do ROS support tumor angiogenesis, but they also disrupt the normalization process in tumor vasculature [87]. ROS have been involved in interfering with proteins such as Secreted Protein Acidic and Rich in Cysteine (SPARC) that normally is involved in vascular stabilization, contributing to promoting greater permeability of tumor vessels and thus very irregular blood flow [88]. The end result is poor drug delivery and poor immune cell infiltration, which accounts for tumor resistance to therapies [89]. Also, endothelial cells of the tumor show expression of galectins, which represent a family of proteins whose expressions are targeted by ROS and contribute to angiogenesis through interacting with VEGF and other growth factors. For instance, it has been documented that hypoxia and oxidative stress induce galectin-3, thus promoting angiogenesis while suppressing anti-tumor immune responses [90]. This therefore underscores a very promising rationale for the therapeutic targeting of ROS-driven pathways, which inhibits angiogenesis, hence normalizing tumor vasculature with consequences for improved outcomes of treatments [91].

2.4. Epithelial–Mesenchymal Transition (EMT) and Metastasis

ROS play a significant role in the EMT and metastasis of tumor cells. In this biological process, the epithelial cells lose their characteristics and mesenchymal features are ultimately acquired; this enhances motility and invasiveness, features very important for metastasis [92,93]. Recent studies have indicated that ROS can stimulate EMT by controlling the key transcription factors like SNAIL, ZEB1, and TWIST that are mainly involved in lower expression of epithelial markers including E-cadherin and higher expression of mesenchymal markers like vimentin (Figure 3) [94,95]. ROS is intracellularly produced either as a result of hypoxia or due to extracellular stresses [96]. Once upregulated, ROS activate many signaling pathways, among which TGF-β, PI3K/AKT, and MAPK are all implicated in EMT and metastasis [97]. For example, the TGF-β pathway, frequently activated by ROS, initiates EMT by stimulating certain transcription factors known to repress epithelial markers (Figure 3) [98]. ROS can also facilitate the invasive capabilities of malignant cells through enhancing the activity of matrix metalloproteinases, which degrades extracellular matrix (ECM) components that enable metastasis [99]. In addition, it has been elaborated that ROS-induced EMT enriches the cancer cells with stemness, helping them to survive even under strict conditions and escape apoptosis. This stemness promotes not only metastasis but also the acquisition of resistance against various therapies [100]. There are other interesting interactions of ROS with other signaling mechanisms. For example, ROS also interact with purinergic signaling whereby ATP release from stressed cells drives EMT and metastasis through purinergic receptors activating cell motility and invasive behavior [96].

In other words, ROS are deeply related to EMT and metastasis, in which many pathways and transcription factors all together regulate cancer development and resistance through different mechanisms. Understanding the relationship between ROS and EMT can be very helpful in achieving targeting therapies against ROS in order to inhibit such processes involved in cancer progression [94].

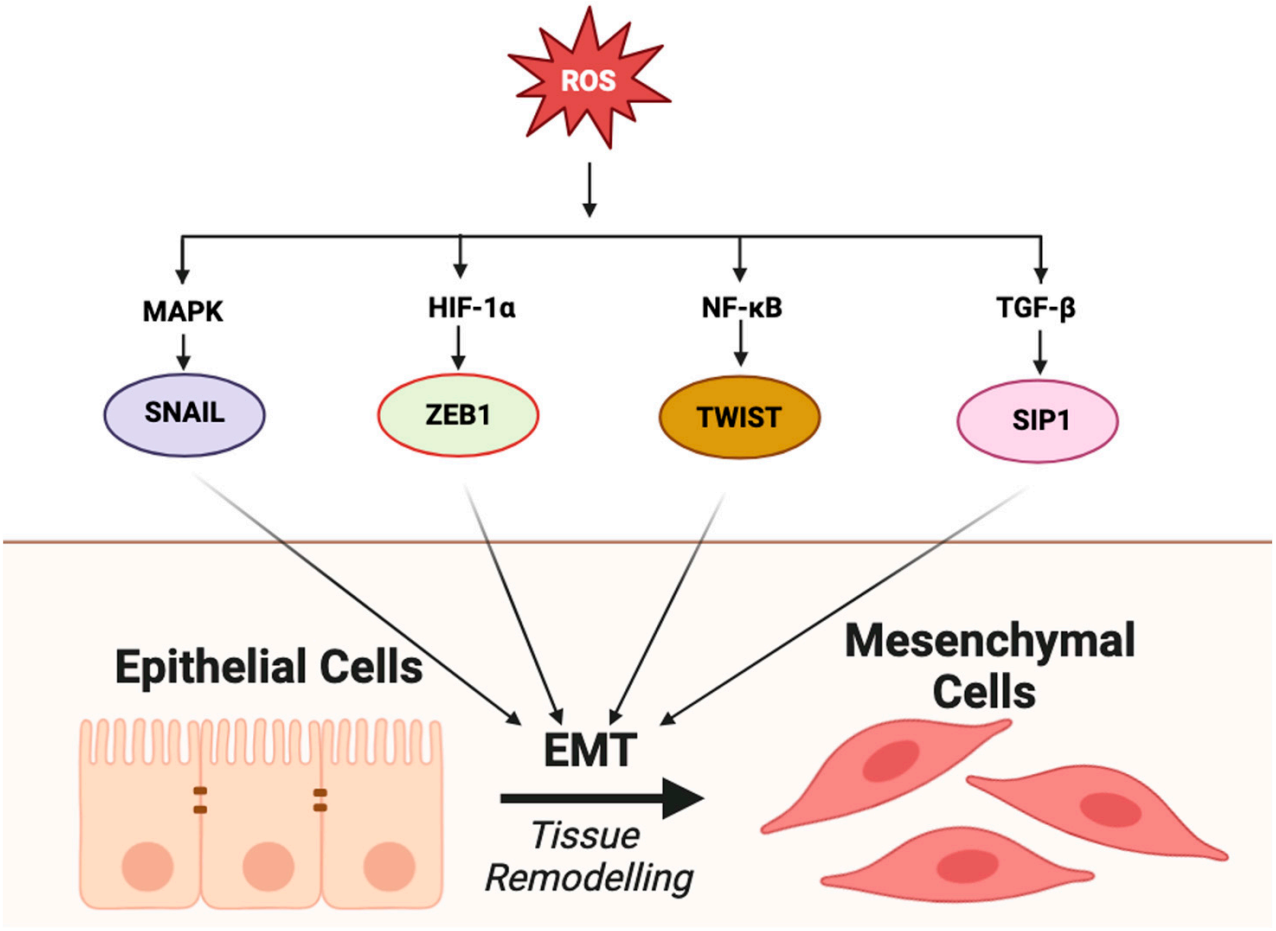

Figure 3. EMT mechanisms induced by ROS.

2.5. Tumor Microenvironment (TME) and Immune Response

ROS have been at the center of the TME, whose influence on tumorigenesis and also on stromal and immune cells in the TME [33]. ROS, being produced both by tumor cells and the cells in the TME, are critical mediators of oxidative stress in a process that promotes inflammation, immune suppression, and survival of cancer cells [101]. Within the TME, ROS play critical roles in many processes, including differentiation of Cancer-Associated Fibroblasts (CAFs), which produce factors contributing to tumor growth and metastasis [102]. These fibroblasts, upon oxidative stress, secrete pro-inflammatory cytokines such as IL-6 and TGF-β, further promoting tumor development (Figure 4) [103]. Immune modulation in the TME by ROS also seems to play a role to induce the accumulation of immunosuppressive cells such as Tregs and Myeloid-Derived Suppressor Cells (MDSCs), thus promoting immune evasion of tumors [102]. Tumor-derived ROS may lead to the expression of immune checkpoint molecules such as PD-L1, further inhibiting T-cell activity and promoting an immunosuppressive TME [104]. Moreover, mitochondrial ROS have been shown to enhance the production of extracellular vesicles carrying immune-modulatory signals, reinforcing the immunosuppressive nature of the TME (Figure 4) [105].

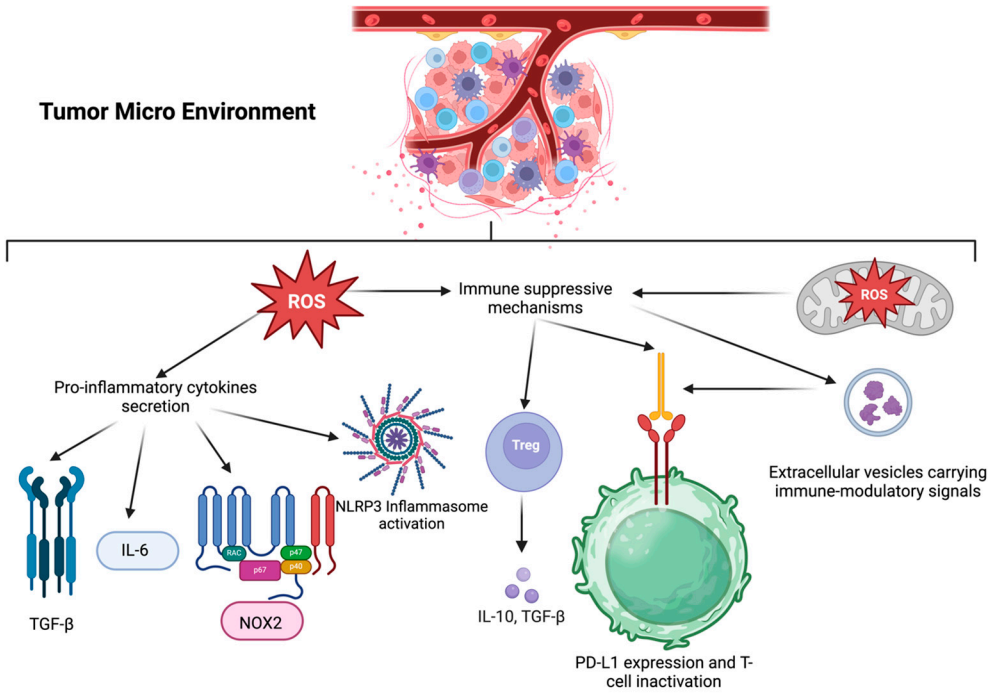

Figure 4. ROS role in tumor microenvironment.

Furthermore, ROS are implicated in the regulation of immune response, affecting several types of immune cells including T cells, macrophages, and dendritic cells [106]. For instance, low to moderate levels of ROS are required for T-cell activation, proliferation, and cytokine production, activities critical for mounting an effective immune response against tumors [107,108]. One of the key ways ROS modulate the immune system is through the production of ROS in response to pro-inflammatory signals by NADPH oxidase (NOX) enzymes [109]. In particular, NOX2 and NOX4 have been considered to contribute to the TME and influence immune surveillance [109]. High levels of ROS are also known to drive the expansion of MDSCs and polarization of M2-like TAMs, both of which promote tumor progression through immune suppression [110,111]. ROS also modulate the activation of inflammasomes such as the NLRP3 inflammasome that further contributes to inflammation and immune cell recruitment (Figure 4) [112]. Chronic activation of these pathways can establish an immunosuppressive microenvironment suppressing efficient immune responses [113]. While ROS may favor immune activation in some circumstances, their dysregulation in the TME commonly causes the immunosuppressive effect driving tumor immune evasion. Therapeutic strategies centered on ROS modulation and NOX enzymes hold great promise for improving the efficacy of cancer immunotherapies [114].

2.6. Remodeling of the Extracellular Matrix (ECM)

ROS play a very important role in the remodeling of the ECM during tumor development [115]. This process is quite essential for metastasis and invasion of cancers because the changes in the ECM will lead to changes in the TME and result in cellular migration [116]. ROS regulate many components of the ECM that include the matrix metalloproteinases, which degrade a number of ECM proteins [117]. It has also been associated that the overexpression of especially MMP-2, MMP-9, and MMP-14 facilitates the degradation of ECM, allowing tumor cell invasion and metastasis [118]. These enzymes degrade collagen and other structural proteins, allowing easy passage of tumor cells through tissues to spread at distant sites (Figure 5) [119,120].

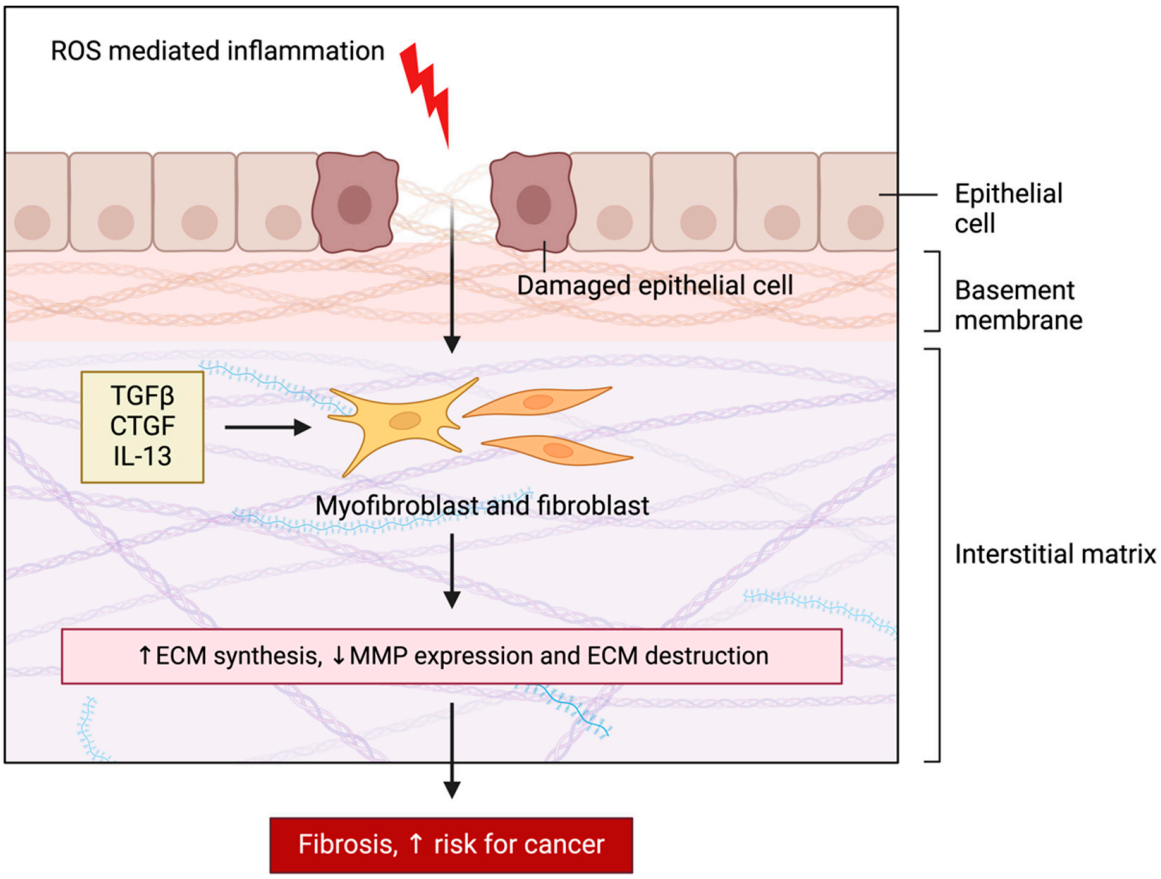

Figure 5. ROS and extracellular matrix remodeling in cancer.

Moreover, ROS regulate other enzymes related to ECM, such as heparanase, which degrades heparan sulfate proteoglycans and releases growth factors that also contribute to tumor growth, and angiogenesis [121,122]. The degradation of the ECM allows cancer cells to evade immune detection and adapt the mechanical and biochemical signals inside the TME [123]. Moreover, ROS also contribute to premetastatic niche formation by the enhancement of collagen cross-linking through enzymes like Lysyl oxidase (LOX), which stiffens the ECM and hence serves as a scaffold for tumor cells to invade [124,125]. Besides being involved in the degradation process of the ECM, ROS regulate the expression and activity of a number of other important proteins and signaling pathways related to the ECM that are implicated in tumor development and progression [115]. For instance, ROS can stimulate TGF-β signaling, which is well known to induce the fibrosis of ECM and enhance the expression levels of the components of ECM such as fibronectin and collagen (Figure 5) [119,120]. This fibrotic environment not only supports tumor cell adhesion and migration but also provides a physical barrier that protects tumor cells from immune surveillance and therapeutic agents [126]. Furthermore, ROS-induced ECM remodeling leads to the activation of integrins and other cell surface receptors that mediate cell–ECM interactions, which promote cell survival, proliferation, and metastasis [80,81]. In addition, ROS are involved in the mechanical properties of the matrix, such as stiffness and elasticity, and are necessary for the invasive behavior of cancer cells [24–27]. Finally, ROS are capable of inducing exosome and other types of extracellular vesicle secretion, which transport ECM-modifying enzymes and signaling molecules, further contributing to dynamic remodeling of the TME [127]. These multifunctional roles of ROS in ECM remodeling highlight their importance for cancer progression and underscore the targeting of ROS and ECM interactions as a potential therapeutic strategy.

3. Therapeutic Targeting of ROS in Cancer

High levels of ROS may result in oxidative stress in the tumor cells, leading to cellular damage, apoptosis, or even necrosis [128]. This has formed the basis of the pursuit of pro-oxidant approaches, whereby cancer treatments seek to further increase levels of ROS beyond the cell's capacity to neutralize them, thereby inducing cell death [129]. Agents like doxorubicin, cisplatin, and paclitaxel act to elevate intracellular ROS to induce apoptosis in tumor cells [130,131]. Other medical interventions have been antioxidants that deplete the levels of ROS; these, in protecting normal cells from damage in the course of treating cancer, have sought to preserve quality of life [132]. For instance, pharmacological interference with therapies targeting the Keap1-Nrf2 pathway, which controls antioxidant responses, either activates the production of ROS in cancer cells or modulates redox signaling in an effort to maintain cellular homeostasis [133]. In addition, plasma-based therapies and natural compounds are new ways to modulate the levels of ROS. For instance, atmospheric gas plasma has been used to induce ROS-mediated apoptosis in melanoma cells [134]. Similarly, research is underway with inhibitors of mitochondrial pathways of ROS production and inhibitors of NADPH oxidase, all of which are being explored to enhance treatment success [135,136].

Pro-oxidant therapies aim at further increasing the levels of ROS in cancer cells and driving them towards cell death due to oxidative stress [137]. Agents such as arsenic trioxide and certain chemotherapeutic drugs enhance the production of ROS in the cancerous cells, leading to oxidative damage that culminates in selective killing of the cancerous cells while normal cells are spared [138]. For instance, carotenoids like β-carotene were shown to act also as pro-oxidants in cancer cells by inducing apoptosis through ROS-mediated pathways when those have high intrinsic levels of ROS [139]. Other examples include the combination of drugs that induce ROS with drugs that modulate their levels to achieve higher effectiveness [140]. While on the other hand, antioxidant strategies tend to decrease ROS levels in order to evade oxidative stress damage to normal tissues [2]. Antioxidants like vitamins C and E were researched for their protective roles against chemotherapy-induced oxidative damage [141]. Targeted antioxidants to mitochondria have shown even more promise in reducing excessive ROS production and hence shielding healthy cells during cancer treatment [142]. However, the specific role of antioxidants in cancer therapy is complex; sometimes, they may even protect cancerous cells from oxidative damage, leading to treatment resistance [143]. Therefore, what makes the therapeutic utility in targeting ROS is to strike a proper balance between the induction of lethal oxidative stress in cancer cells and protection of normal cells [144]. Clinical trials are underway that further refine these approaches and provide more detailed understanding of the conditions under which pro-oxidant or antioxidant strategies can be effectively deployed in cancer therapy [145].

Recently, ROS have attracted much attention with regard to their therapeutic implications for cancer treatment because they exert a double-edged sword in promoting and inhibiting tumorigenesis [146]. Attacking the ROS detoxification systems of the cancer cells can selectively disrupt their survival, rendering them therapeutically vulnerable [147]. The challenge will be finding that delicate balance, with too much reduction in ROS levels possibly protecting the very cancer cells and enabling them to evade death and continue proliferating [148]. Despite these promising approaches, challenges persist due to the heterogeneous nature of ROS levels within tumors and the elaboration of resistance mechanisms [149]. Therefore, tumoral cells may upregulate antioxidant pathways that counteract ROS-inducing therapies, and such adaptive mechanisms ultimately limit the long-term efficacy of these therapies [150]. Combination therapies targeting both ROS and key survival pathways are thus currently under active exploration in efforts to surmount these challenges [151].

One of the most promising approaches in cancer treatment has been the combination of ROS with both immunotherapies and targeted therapies [152]. Targeted therapies, as in the case of inhibitors of the EGFR or KRAS pathway, increase ROS levels; these increased ROS levels result in cell death in cancer [153]. However, this increases tumor immune evasion. Once immunotherapies such as Immune Checkpoint Inhibitors (ICIs) are added, one manages to neutralize this aspect by reactivating the immune system and allowing it to recognize and destroy tumor cells [154]. Perhaps more excitingly, ROS-modulating therapies combined with ICIs have indeed been shown to possess the potential for improving the efficacy of treatments [155]. Moreover, ROS can increase the immunogenicity of the tumors and make them more visible for the immune system, thus effectively acting in concert with ICIs [156]. For example, gut microbiota metabolites known to impact ROS production have been shown to increase CD8+ T cell infiltration in the TME, leading to an overall better response to immunotherapies in cancers such as triple-negative breast cancer [157,158]. Further, CAR-T cell therapies in combination with ROS modulation have been utilized to attack the solid tumors more effectively [159]. The clinical trials against glioblastoma and other solid tumors indicated that in combination with CAR-T therapy, the increased intracellular levels of ROS can mediate pro-inflammatory cytokine release and tumor regression, as in case of glioblastoma and neuroblastoma [157,160]. Overall, given the central role of ROS in cancer initiation, progression, and therapy resistance, therapeutic strategies that modulate ROS levels have gained significant attention.

4. Metabolic Reprogramming and Redox Adaptation in Cancer

Metabolic reprogramming is a hallmark of cancer that supports rapid proliferation, survival under stress, and adaptation to hostile microenvironments. Cancer cells model core pathways, including glycolysis, the tricarboxylic acid (TCA) cycle, oxidative phosphorylation (OXPHOS), glutaminolysis, and lipid metabolism to meet their bioenergetic and biosynthetic demands [161]. This metabolic rewiring is tightly intertwined with redox homeostasis, altered metabolism increases ROS production, while ROS themselves act as signaling molecules that further modulate metabolic enzymes and pathways [162]. A growing body of work indicates that ROS both shape and are shaped by metabolic reprogramming. Elevated mitochondrial and NADPH oxidase-derived ROS can enhance glycolytic flux, divert glucose into the pentose phosphate pathway (PPP) to generate NADPH, and influence glutamine metabolism to support antioxidant defenses [163]. In this context, ROS act not merely as byproducts of dysfunctional metabolism but as upstream regulators that tune the balance between ATP generation, anabolic growth, and redox buffering capacity. Oncogenic signaling further reinforces this loop; for example, KRAS- and NRF2-driven tumors exhibit sustained ROS production together with enhanced PPP and glutamine utilization, illustrating how oncogenes couple metabolic reprogramming to redox control [164]. Key glycolytic enzymes, including PKM2 and GAPDH, are selectively inhibited by ROS, redirecting glucose toward the PPP to boost NADPH and glutathione synthesis and prevent metabolic collapse.

Beyond glucose metabolism, cancer cells upregulate glutaminolysis and lipolysis to sustain TCA cycle intermediates and redox buffering when glycolysis is impaired [165–167]. Importantly, these metabolic–redox adaptations create therapeutic vulnerabilities. For instance, combination metabolic–inhibition strategies can selectively induce apoptosis in redox-dependent tumors by disrupting multiple cellular defense systems. Several studies have demonstrated that simultaneous targeting of the glutathione and thioredoxin antioxidant pathways effectively eliminates cancer cells. In particular, co-administration of buthionine sulfoximine (BSO) and auranofin produces synergistic cytotoxic effects across multiple tumor types, including pancreatic cancers, head-and-neck malignancies, and

B-cell neoplasms [168–172]. Emerging evidence also supports the therapeutic potential of combining metabolic inhibitors such as mTOR pathway blockers with thioredoxin reductase inhibition to induce oxidative stress and suppress tumor growth. These combination approaches act by overwhelming the antioxidant buffering capacity of cancer cells, leading to lethal ROS accumulation while largely sparing normal tissues [169]. Specifically, recent findings demonstrated that mTOR and TrxR inhibitors cooperate to induce cell death by activating oxidative stress, autophagy, and stress signaling pathways in cancer cells. In xenograft models, auranofin combined with everolimus significantly suppressed tumor growth in HCT116 and SGC-7901 cancer models with no significant toxicity [173] (Table 1).

Table 1. Metabolic reprogramming and redox adaptation in cancer.

Category	Key Mechanisms/Findings	Pathways and Molecules Involved	Therapeutic Implications	Supporting Refs
Core metabolic reprogramming	Cancer cells remodel metabolism to sustain proliferation, survival, and stress adaptation	Glycolysis, TCA cycle, OXPHOS, glutaminolysis, lipid metabolism	Supports growth in hypoxic and nutrient-limited microenvironments	[162]
ROS–metabolism interdependence	Altered metabolism increases ROS; ROS feed back to regulate metabolic enzymes	Mitochondrial ROS, NADPH oxidases	ROS act as signaling molecules rather than byproducts	[163]
ROS-driven metabolic shifts	Elevated ROS enhance glycolysis and divert glucose to PPP for NADPH generation	PPP activation, glutamine metabolism	Maintains redox buffering and prevents metabolic collapse	[164]
Oncogene-linked redox rewiring	Oncogenic signaling sustains ROS and metabolic flux	KRAS, NRF2 activation; increased PPP and glutamine use	Couples metabolic reprogramming to redox control	[165]
ROS-sensitive glycolytic regulation	Key enzymes inhibited by ROS, redirecting glucose metabolism	PKM2, GAPDH inhibition	Boosts NADPH and glutathione synthesis	[166]
Compensatory pathways	Upregulation when glycolysis is impaired	Glutaminolysis, lipolysis, TCA replenishment	Maintains ATP and antioxidant capacity	[167,168]
Dual antioxidant pathway targeting	Simultaneous inhibition of glutathione and thioredoxin systems induces tumor cell death	BSO (GSH depletion) + auranofin (TrxR inhibition)	Synergistic cytotoxicity in pancreatic, head-and-neck, and B-cell cancers	[169–173]
Metabolic–mTOR combination therapy	mTOR inhibitors cooperate with TrxR blockade to trigger oxidative stress and autophagy	Everolimus + auranofin	Suppresses tumor growth with minimal toxicity in xenograft models	[174,175]
Therapeutic mechanism summary	Cancer cells can be pushed beyond antioxidant capacity	Lethal ROS accumulation; stress signaling activation	Selective killing of redox-dependent tumors while sparing normal cells	[174,175]

5. ROS in Specific Cancer Types

ROS have been shown to play important roles in a variety of cancers and influence tumor biology in underappreciated contexts [174]. Recent studies have emphasized the double-edged sword of ROS in driving tumorigenesis and providing a mechanism of therapeutic resistance, thus making it a very important area of cancer research [2].

5.1. Neuroendocrine Tumors (NET)

ROS have become established drivers of proliferation and survival in less-studied tumors, such as NET, making them targets for therapy. For instance, one study has documented that high levels of ROS in NET cells are associated with enhanced cell proliferation and reduced apoptosis, suggesting that targeting ROS might provide novel therapeutic ap-

proaches for these tumors [175]. Moreover, ROS modulate the TME through the induction of inflammation and angiogenesis, shifting the behavior of immune and stromal cells toward a supportive environment that favors tumor growth and metastasis [176]. Often, NETs are resistant to conventional therapies, and ROS participate in such resistance by inducing antioxidant defenses and survival pathways that render the tumor cells resilient against treatments [101]. Targeting ROS in NETs represents a very promising therapeutic approach, with strategies ranging from the administration of pro-oxidant agents, which increase ROS above the tolerable threshold of cancer cells, thus forcing them to undergo cell death, to the use of antioxidants that disrupt the redox balance, sensitizing them to other treatments [177]. Neuroendocrine tumors demonstrate a distinct dependency on ROS-mediated signaling. Elevated ROS levels enhance proliferation and survival through redox-sensitive regulatory pathways and support angiogenesis within the hypoxic tumor microenvironment. Neuroendocrine tumors exhibit heightened susceptibility to ROS-driven proliferation due to their dependence on redox-regulated secretory signaling, elevated mitochondrial activity, and strong HIF-1α–mediated angiogenic responses, making moderate ROS levels growth-promoting rather than cytotoxic. Hematologic cancers demonstrate a highly regulated approach to ROS management. Leukemic stem and progenitor cells maintain low ROS levels to preserve self-renewal capacity [178], whereas leukemic blasts deliberately elevate mitochondrial ROS to promote proliferation and genomic instability while remaining vulnerable to oxidative overload [179]. In contrast, solid tumors such as pancreatic cancer adapt through fundamentally different mechanisms. Oncogenic *KRAS* mutations support low intracellular ROS by activating antioxidant gene programs and reshaping metabolic pathways [180] while the hypoxic tumor microenvironment drives chronic ROS accumulation through mitochondrial and glycolytic rewiring and enhanced antioxidant responses [2]. A recent study reported a significant increase in ROS levels in peripheral blood mononuclear cells (PBMCs) from patients with neuroendocrine tumors following therapy. This increase was accompanied by elevated expression of inflammatory mediators, including COX-2 and iNOS, as well as higher circulating levels of pro-inflammatory cytokines such as IL-2, IL-6, and TNF-α. Notably, in vitro experiments demonstrated that exosomes isolated from post-treatment samples induced a marked rise in ROS production in recipient cells compared to controls, suggesting a potential role for exosome-mediated redox signaling. Despite these changes, the study did not detect alterations in DNA damage-associated gene expression. While these findings highlight a possible link between treatment-related oxidative stress and inflammatory responses in NETs, they derive from a single investigation, and further studies are required to clarify the clinical and mechanistic significance of ROS in NET progression and therapeutic response [181]. This underlines the possibility that ROS-targeting therapies hold potential for improving treatment outcomes in NET by tackling tumor progression and resistance mechanisms.

5.2. Melanoma

Evidence has shown that oxidative damage in these types of tumors drives their aggressive behavior and makes them resistant to treatments; thus, the need for ROS-targeting therapies to improve treatment outcomes [182]. ROS play a significant role in the pathogenesis and development of melanoma. Increased intracellular levels of ROS enhance proliferation, migration, and invasion of melanoma cells due to the activation of particular signaling pathways, such as MAPK/ERK and PI3K/AKT [183]. Further, ROS can be involved in the development of therapeutic resistance in melanoma, achieved by turning on survival pathways and antioxidant defenses that render the cells more resistant to chemotherapy and radiotherapy treatments [184]. Despite this pro-tumorigenic and resistance-conferring role of ROS, these molecules may also induce apoptosis in melanoma

cells and thus carefully modulated levels of ROS could represent a therapeutic strategy for the selective killing of cancer cells, sparing normal cells [185]. Recent evidence confirms that ROS are involved in multiple stages of melanoma development, from early transformation of melanocytes through to metastatic dissemination. The findings underscore a delicate redox balance, wherein lower ROS levels activate protective signaling pathways that support cell survival, while excessive ROS concentrations induce oxidative damage and genomic instability. Notably, melanocytes are inherently vulnerable to oxidative stress due to their melanin-synthesizing activity and high basal redox burden, making ROS a critical determinant of malignant progression in melanoma [186,187]. Targeting ROS and related pathways has emerged as a promising approach with strategies including the use of pro-oxidant agents to increase ROS levels beyond a tolerable threshold for melanoma cells or the use of antioxidants to disrupt the redox balance and sensitize cells to other treatments [188].

5.3. Neuroblastoma

In neuroblastoma and other pediatric tumors, production of ROS is associated with the activation of oncogenic pathways promoting metastasis [189]. Very recent data indeed suggest that alterations in ROS levels have a profound impact on tumor growth and dissemination in these patients, thus providing a rationale for further studies into ROS-targeting approaches [190]. ROS is an important participant in tumor progression and metastasis of neuroblastoma by turning on critical oncogenic pathways such as oxidative phosphorylation, mTORC1, and MYCN amplification [191]. High levels of ROS promote such cellular events as proliferation, migration, and invasion in especially hypoxic conditions of the neuroblastoma environment [189]. Multiple studies demonstrate the complex involvement of ROS in neuroblastoma biology. Recent findings show that ROS can promote pyroptosis through mitochondrial signaling pathways, while other work has revealed a ROS-dependent contribution to ferroptosis, an iron-dependent form of regulated cell death. In addition, MYCN-amplified neuroblastomas exhibit increased ROS production and a heightened reliance on glutathione-mediated detoxification, indicating a metabolic vulnerability in this high-risk subgroup. Critically, emerging evidence emphasizes that ROS responses in neuroblastoma are highly context-dependent, varying according to the type and magnitude of ROS, cellular metabolic state, and disease stage [192–194]. These conditions are conducive to the EMT phenomenon and higher metastatic potential typical for high-risk neuroblastoma, where MYCN amplification is a major driver of aggressive disease and poor prognosis [195].

5.4. Leukemia

Recent data show that different leukemia types have their peculiar ROS profile, contributing to their microenvironment modulation and conferring drug resistance [178]. These observations underline the complexity of the interaction between ROS in different tumor types and the possibility of new therapeutic interventions based on ROS modulation [196,197]. More importantly, emerging data suggest that each leukemia subtype has its hallmark ROS profile, which is indeed critical in the development of its microenvironment and for drug resistance acquisition [198]. Indeed, in chronic lymphocytic leukemia, high ROS levels were associated with high expression of anti-apoptotic proteins such as Bcl-2, promoting the survival and expansion of leukemic cells [199]. Similarly, high levels of ROS in acute myeloid leukemia are associated with metabolic rewiring promoting cancer cell growth while inducing DNA damage and genomic instability to further drive leukemogenesis [200]. ROS also play an important role in the bone marrow microenvironment of leukemias and modify the interactions between leukemic cells and stromal cells. Recent

evidence highlights ROS as key regulators of cellular signaling in leukemia. Physiologically, low ROS levels are essential for maintaining hematopoietic stem cell (HSC) self-renewal, whereas elevated ROS in leukemic blasts has been associated with increased proliferation, metabolic rewiring, and enhanced invasiveness. In acute myeloid leukemia (AML), high ROS levels drive glycolysis and broader metabolic reprogramming, supporting leukemogenesis and contributing to treatment resistance and relapse, as summarized in recent reviews of current literature. Moreover, ROS-mediated survival signaling promotes drug tolerance across multiple leukemia subtypes. Conversely, modulation of oxidative stress, such as the use of antioxidants, has been reported to reduce therapy-associated toxicity and improve patient outcomes, although clinical evidence remains limited [201,202]. For instance, oxidative stress in the microenvironment may trigger signaling cascades such as NF-κB and STAT3, which form an inflammatory niche that promotes the growth of leukemia [203].

5.5. Breast Cancer

Breast cancer is one of the most common malignancies, and ROS play a significant role in its pathogenesis [204]. ROS have been shown to contribute to the progression of breast cancer by promoting genomic instability, enhancing metastatic potential, and influencing the TME [205]. The Warburg effect, which is a hallmark of many cancers, including breast cancer, involves a shift toward aerobic glycolysis [206]. ROS production is elevated in breast cancer cells as a consequence of mitochondrial dysfunction and metabolic alterations [207]. Interestingly, antioxidants, which are used to neutralize ROS, can paradoxically accelerate the progression of certain cancers, including breast cancer. For instance, in murine models, antioxidant treatments have been linked to accelerated metastasis and decreased efficacy of chemotherapy [208]. Recent studies demonstrate the significant influence of ROS in breast cancer progression. Experimental evidence shows that elevated ROS levels can induce mitochondrial DNA damage, activate proto-oncogenes, and suppress tumor-suppressor pathways, thereby promoting malignant transformation. In addition, a large clinical analysis involving 6245 breast cancer patients reported that high ROS burden is associated with more aggressive tumor biology, increased mutational load, and poorer overall survival. Together, these findings reinforce the contribution of oxidative stress to breast cancer development and highlight its potential prognostic and therapeutic relevance [209]. This finding underscores the delicate balance of ROS levels in cancer, where both excessive ROS and excessive antioxidant activity can be detrimental.

5.6. Lung Cancer

Lung cancer is another malignancy heavily influenced by ROS [210]. Exposure to environmental carcinogens, such as tobacco smoke and air pollution, generates ROS, which in turn initiate DNA damage and mutations, leading to the transformation of normal lung cells into malignant ones [211]. ROS also play a key role in regulating various signaling pathways involved in cell survival, apoptosis resistance, and metastasis in lung cancer [212]. For example, ROS activate NF-kB, a transcription factor that regulates genes involved in inflammation and immune evasion, contributing to the aggressive behavior of lung cancer cells [213]. In non-small cell lung cancer, a subset of patients exhibits altered redox homeostasis due to mutations in the KEAP1-NRF2 pathway, which is responsible for regulating antioxidant responses [214]. Activation of NRF2 leads to the upregulation of antioxidant enzymes, which protect the tumor cells from oxidative damage but also support tumor progression and chemoresistance. Additionally, ROS can induce the EMT in lung cancer cells, a critical process for metastasis [133]. Lung cancer is strongly shaped by exogenous ROS sources, including tobacco smoke and environmental pollutants. These

exposures initiate oxidative DNA damage and mutational events that drive malignant transformation. In established tumors, endogenous ROS support EMT, immune evasion, and therapy resistance, particularly in KEAP1–NRF2–altered subtypes with heightened antioxidant capacity [215].

Recent evidence reveals that ROS exert dual and context-dependent functions in lung cancer progression. During precancerous stages, ROS contribute to malignant initiation by inducing oxidative stress, DNA damage, and mutations in proto-oncogenes, while at more advanced stages they facilitate tumor invasion and metastasis through activation of signaling pathways such as NF-κB and MAPK. Critically, when intracellular ROS levels exceed a cytotoxic threshold, they can trigger cell-cycle arrest and apoptosis in cancer cells. This complexity underscores that the effects of ROS are highly dependent on their concentration, duration, and spatial distribution within the tumor microenvironment, making redox regulation a challenging yet promising therapeutic target. Consequently, researchers emphasize that a refined and mechanistic understanding of ROS dynamics will be essential for designing effective lung cancer interventions [216,217].

5.7. Colorectal Cancer

ROS contribute to colorectal carcinogenesis through various mechanisms, including the induction of DNA damage, epigenetic alterations, and activation of pro-inflammatory pathways [218]. One of the key sources of ROS in colorectal cancer is the microbial dysbiosis observed in the gut certain bacteria, such as Fusobacterium nucleatum, promote oxidative stress in the colonic epithelial cells, enhancing tumorigenesis and metastasis [219]. For example, a study that incorporated squalene, a minor constituent present in extra virgin olive oil, showed a disruption in the redox balance of a colon cancer cell line through an increase in ROS [20]. Moreover, ROS play a crucial role in the progression of colorectal cancer by regulating the TME [220]. Chronic inflammation in the colon, often caused by persistent ROS production, leads to the activation of pro-inflammatory cytokines and the recruitment of immune cells that support tumor growth and immune evasion [221]. Moreover, the NOX family have been implicated in colorectal carcinogenesis by promoting ROS-mediated DNA damage and inflammation [222]. Colorectal cancer demonstrates a unique ROS-driven pathogenesis where dysbiosis-associated bacteria generate ROS that fundamentally reshape the tumor microenvironment through epithelial damage, metabolic reprogramming, and metastatic signaling. Multiple studies provide strong evidence for this mechanism. It has been documented that ROS generated by tumor microenvironment cells like macrophages and neutrophils promote cellular proliferation, epithelial-to-mesenchymal transition, and cancer cell migration [223]. Specifically recent findings highlighted how dysbiosis causes inflammation that triggers immune cells to release ROS and reactive nitrogen species (RNS), causing direct DNA damage [224]. Further confirmed that bacterial metabolites can modulate ROS concentrations, either protecting against or contributing to oxidative stress [225]. Recent studies reveal that ROS are essential mediators of cancer cell survival in colorectal cancer, regulating key processes such as cellular proliferation, epithelial-to-mesenchymal transition, evasion of cell death, migration, and angiogenesis. Evidence spans multiple mechanisms, some reports show that ROS contribute to the cytotoxic effects of chemotherapy, while others highlight their involvement in DNA damage, regulated cell death pathways, and metabolic reprogramming. Critically, emerging work emphasizes that cancer cells adapt to oxidative stress through genetic and metabolic rewiring, indicating that ROS are not merely byproducts of cellular activity but active drivers of tumor progression. The strength of the current evidence is substantial, with multiple independent studies converging on the pivotal role of ROS in colorectal cancer development

and supporting the exploration of redox-modulating strategies as potential therapeutic interventions [223,226–228].

5.8. Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC) is the most common form of liver cancer and is strongly associated with chronic liver disease, particularly cirrhosis and hepatitis [229]. ROS are central players in the pathogenesis of HCC, as they contribute to both liver injury and tumor progression [230]. The liver is particularly prone to ROS-induced damage due to its role in detoxifying metabolic byproducts [231]. In HCC, oxidative stress is driven by a combination of factors, including viral infection (hepatitis B and C), alcohol consumption, and metabolic disorders like metabolic dysfunction-associated steatotic liver disease [232–236]. For instance, an investigation that incorporated squalene, a minor constituent present in extra virgin olive oil, demonstrated a diminution in ROS generation in hepatocytes subjected to oxidative and endoplasmic reticulum stress [237,238]. ROS contribute to the pathogenesis of HCC by inducing genomic instability, promoting EMT, and enhancing metastasis [239]. Additionally, ROS can modulate the immune response in the liver TME, leading to immune suppression and evasion [240]. Elevated ROS levels also interfere with the effectiveness of chemotherapy and targeted therapies, rendering HCC cells resistant to treatment [241]. Numerous studies have explored targeted modulation of ROS, and recent reviews of emerging redox-based therapeutics suggest promising new treatment directions. ROS-induced programmed cell death has been identified as a key contributor to HCC development and progression, as summarized in the current literature. In addition, ROS-related gene signatures have been shown to correlate with prognosis, immune infiltration patterns, tumor stemness, and drug sensitivity in HCC, with recent bioinformatics-based models providing new prognostic tools. Experimental data further demonstrate that STK25 knockdown increases HCC cell proliferation, migration, and invasion, supporting the functional relevance of redox-associated pathways in tumor aggressiveness [242–244].

5.9. Pancreatic Cancer

Pancreatic cancer is characterized by poor prognosis due to its late-stage diagnosis and resistance to conventional therapies. ROS have been implicated in the initiation and progression of pancreatic ductal adenocarcinoma (PDAC) [245]. In PDAC, ROS are generated by activated oncogenes such as Kras, which leads to metabolic alterations and enhanced ROS production [246]. The accumulation of ROS contributes to the aggressive nature of pancreatic cancer by promoting tumor cell proliferation, invasion, and metastasis [247]. Interestingly, the TME in PDAC is known for its dense stroma, which is rich in reactive species [248]. ROS within this stroma promote fibrosis and create a pro-inflammatory milieu that supports tumor progression [249]. ROS also play a crucial role in chemoresistance, particularly in response to drugs like gemcitabine, by activating survival pathways and inhibiting apoptosis [250]. Recent evidence reveals that ROS play a critical and nuanced role in pancreatic cancer development, with both pro-tumorigenic and potentially therapeutic implications. Studies have shown that oncogenic KRAS mutations promote the accumulation of hydrogen peroxide in pancreatic cancer cells, altering cellular metabolism and supporting cancer cell survival. Additional findings indicate that ROS exert contrasting effects depending on their levels, lower ROS concentrations can facilitate premalignant tumor development, whereas increased ROS enhances metastatic potential. Further research notes that pancreatic cancer cells adapt to sustained oxidative stress through metabolic and antioxidant reprogramming, contributing to tumorigenesis, metastasis, and resistance to therapy. Importantly, these observations suggest that strategically elevating ROS beyond

a tolerable threshold may trigger cancer cell death, highlighting redox modulation as a promising therapeutic strategy in pancreatic cancer [251].

5.10. Ovarian Cancer

Ovarian cancer is another malignancy where ROS play a significant role in tumorigenesis and therapy resistance [252]. ROS are involved in the development of ovarian cancer through DNA damage, activation of survival pathways, and promotion of EMT [253]. The ovarian cancer microenvironment is characterized by chronic inflammation and hypoxia, both of which contribute to elevated ROS levels [254]. Hypoxia-inducible factor 1-alpha (HIF-1α), which is stabilized under low oxygen conditions, induces the expression of pro-oxidative enzymes and promotes ROS production, further enhancing cancer cell survival [63]. Moreover, ROS influence the sensitivity of ovarian cancer cells to chemotherapy. High levels of ROS can activate protective antioxidant pathways, leading to chemoresistance. Therefore, targeting ROS-producing pathways in ovarian cancer has emerged as a potential therapeutic strategy [255]. Recent evidence reveals that ROS play a critical and complex role in ovarian cancer development and progression, with studies from 2021 to 2024 demonstrating that ROS can both promote and inhibit tumor behavior through highly coordinated cellular mechanisms. Specifically, ROS contribute to ovarian cancer by inducing DNA damage and genomic instability, activating oncogenic signaling pathways, and promoting tumor cell proliferation, survival, and metastatic spread. Critically, ROS effects are dose-dependent, moderate increases can drive malignant progression, whereas excessively high ROS levels can trigger oxidative collapse and cancer cell death. These findings indicate that ROS are not passive metabolic byproducts but active modulators of ovarian cancer dynamics, highlighting redox regulation as a promising avenue for therapeutic intervention [256–258]. A summary of the roles, mechanisms, and therapeutic implications of ROS in different cancers is provided in Table 2.

Table 2. Roles of ROS in cancer, mechanisms and therapeutic implications across cancer types.

Cancer Type	Role of ROS	Mechanisms	Therapeutic Implications
Neuroendocrine Tumors [175–177]	Drives tumorigenesis Therapeutic resistance Immune evasion	Enhanced proliferation Reduced apoptosis, Inflammation, Angiogenesis	Targeting ROS with pro-oxidants or antioxidants to modulate redox balance
Melanoma [183–185,188,259,260]	Promotes aggressive behavior Metastasis Resistance to therapies	Oxidative damage to DNA Activation of MAPK/ERK, PI3K/AKT pathways	Pro-oxidants to increase ROS for apoptosis; antioxidants to sensitize cells to therapies
Neuroblastoma [189–191,195]	Drives tumor progression EMT Metastasis (especially in hypoxic conditions)	Activation of oxidative phosphorylation mTORC1, MYCN pathways	ROS-targeting strategies to reduce proliferation and metastasis
Leukemia [196–200,203]	Modulates microenvironment Promotes drug resistance	Increased ROS linked to anti-apoptotic proteins (e.g., Bcl-2) Metabolic rewiring, DNA damage	Therapies targeting ROS profiles specific to leukemia subtypes
Gastrointestinal Malignancies [208,261–264]	Influences tumor-associated inflammation Immune evasion	Chronic inflammation via ROS-driven cytokine release	Anti-inflammatory agents targeting ROS-mediated pathways

Table 2. *Cont.*

Cancer Type	Role of ROS	Mechanisms	Therapeutic Implications
Breast Cancer [204–208,265]	Contributes to tumor growth Metastasis Therapy resistance	Elevated ROS from mitochondrial dysfunction Promotion of genomic instability Influence on TME	Balancing ROS levels for targeted therapies to prevent progression and metastasis
Lung Cancer [210–214]	Drives initiation Progression Resistance	DNA damage from environmental ROS Activation of NF-kB and NRF2 pathways Promotion of EMT	Targeting oxidative damage pathways to reduce metastasis and chemoresistance
Colorectal Cancer [218–222,266]	Facilitates carcinogenesis Metastasis Immune evasion	ROS-induced DNA damage Pro-inflammatory cytokines Microbial dysbiosis	Targeting NOX enzymes and ROS-induced inflammatory pathways
Hepatocellular Carcinoma [229–232,239–241]	Promotes tumor progression EMT Metastasis	ROS from chronic liver diseases Viral infections Metabolic dysfunction	Therapies to counteract ROS-driven genomic instability and immune suppression
Pancreatic Cancer [245–250]	Drives aggressive behavior and resistance	ROS from Kras mutations Stromal inflammation Fibrosis	Modulating ROS in tumor–stromal interactions to reduce chemoresistance
Ovarian Cancer [63,252–255]	Promotes tumorigenesis EMT Therapy resistance	Hypoxia-induced ROS production Activation of HIF-1α Antioxidant pathways	Targeting ROS production and antioxidant defenses for improved therapy outcomes

6. Conclusions

ROS play a multifaceted role in cancer biology, acting as both promoters and suppressors of tumor growth. Their involvement in cellular signaling, metabolic reprogramming, and TME underscores their significance in cancer progression and therapy resistance. While ROS can drive carcinogenesis through DNA damage and epigenetic alterations, they also offer potential therapeutic targets. Strategies that modulate ROS levels, either by increasing oxidative stress to induce cancer cell death or by inhibiting antioxidant defenses to sensitize tumors to treatment, hold promise for improving cancer therapy. However, the challenge lies in selectively targeting cancer cells without harming normal cells. Future research should focus on understanding the intricate balance of ROS dynamics in cancer and developing combination therapies that leverage ROS modulation to enhance treatment efficacy and overcome resistance mechanisms.

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