

Targeting ROS for Cancer Therapy

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Abstract

Reactive oxygen species (ROS) are chemically reactive molecules containing oxygen. Examples include peroxides, superoxide, hydroxyl radical, and singlet oxygen. In a biological context, ROS are formed as a natural by-product of the normal metabolism of oxygen and have important roles in cell signaling and homeostasis. The rate of ROS produced faster in cancer cells compared to normal cells, but at the same time the cancer cell has a strong ROS scavenging system to maintain its homeostasis and immortal. ROS play crucial roles in development and progression of cancer, as they could induce mutations in DNA, causing genomic instability and release tumorigenic signals. On the other hand, high levels of ROS could also cause cancer cell death. To balance the oxidative stress and keep the steady status, cancer cells have a very strong antioxidant capacity. And then, if we make clear with functions of ROS and the mechanism of ROS clearance due to eliminate the high levels of ROS in cancer cells, which could be useful to find new strategies for preventing cancer.

Key words:

Preventing cancer; Genomic; Cell signalling; Reactive oxygen species

Introduction

Reactive oxygen species (ROS) act as a second messenger in cell signaling and participate in a variety of biological processes in normal cells. Under normal physiological conditions, ROS are produced and then eliminated by ROS scavenging system to maintain cellular redox balance. Levels of ROS could change with endogenous or exogenous reasons, leading to DNA damage, oxidative stress and abnormal cell signaling. Reduction of ROS could lead to interruption of cell signaling, thus influence the cellular homeostasis. Cancer cell metabolism that often appear in the redox imbalance and oxidative stress, in the situation, antioxidant mechanism needs to balance this pressure, which has been the symbol of tumorigenesis [1]. The role of ROS in cancer is two-fold. On the one hand, ROS could lead to cancer development by activating signaling pathways that regulate cell proliferation, survival, angiogenesis and metastasis pathways [2-4]. Cancer cells are characterized by an increased rate of spatially localized ROS production, compared to normal cells due to a loss in proper redox control. Cancer cells adapt to oxidative stress by up-regulating antioxidant proteins. However, on the other hand, excessive ROS could induce cell death, aging and cell cycle arrest [5,6]. For example, paclitaxel could induce breast cancer cell death by increasing ROS generation [7]. Previous studies demonstrated that cancer cells make them adapt the high level of ROS and activate the antioxidant pathways [8,9] resulting in increased ROS clearance [10] in order to maintain the level of ROS. Various studies showed that the use of

antioxidants inhibitors could selectively kill tumor cells, induce inhibition of tumorigenesis [11-15]. Compared with the cancer cells, the rate of producing ROS in normal cells is lower. Targeting the ROS signal to treat cancer is a very promising way. Elevating ROS and promoting ROS by using dietary antioxidants or ROS-generation drugs (paclitaxel) could selectively kill or arrest cancer cells. But most clinical trials have failed to show beneficial effects of dietary antioxidants in variety of cancer types or cause significant toxicity to normal cells [16]. The purpose of this review is to summarize the ROS key mechanisms in cancer development, as well as to target these potential redox mechanisms, present new strategy to prevent cancer.

The basic conception of ROS

The sources of ROS are mainly produced from mitochondria and NADPH oxidase (NOX_s) family. Different levels of ROS could directly regulate different cell signals and even adjust the ROS production. H₂O₂ generated by the NOX protein and mitochondria could damage proteins and iron-sulfur clusters. However, localized in mitochondria (SOD2), cytoplasm (SOD1) and extracellular matrix (SOD3) of SODs could be quickly transformed ROS into H₂O₂ [17]. The intracellular concentration of peroxide is very low. H₂O₂ is a more stable form of diffusion and ROS could be selectively applied to reaction with cysteine residues of protein, thereby controlling cell signals. There are many ways to make intracellular H₂O₂ transform into H₂O. During these processes, cysteine can be modified, to regulate active protein in relative signal pathways. Peroxiredoxins (PRXs) become a key regulator of quenching H₂O₂. PRXs regulates H₂O₂-mediated oxide by regulating the active site of cysteine [18]. The function of Glutathione peroxidase (GPXs) is similar with PRXs, transforming into oxidation of H₂O₂-mediated GSH while scavenging H₂O₂, and GPXs is the most

abundant intracellular antioxidant [19]. Once GSH levels reduced, it could be reactivated by glutathione reductase and NADPH.

ROS and Cancer

ROS regulate cell signaling

The traditional views considered that ROS are the toxic metabolic by-products, leading to cell damage [20]. Recently, research demonstrates that low levels of ROS could maintain biological functions and cellular homeostasis [21]. ROS levels fluctuating, and then influence cell signaling and the regulation of biological functions, including the regulation of cell signaling could be directly, or through structural modification of proteins, genes and transcription factors, regulate their functions. H₂O₂ could be reversible with oxidation of cysteine residues of the protein. This type of redox regulation targets phosphorylation, which could produce dephosphorylated proteins in cell signaling and lead to inactivation of kinases [22]. Of course, kinases, transcription factors and antioxidant proteins such as glutathione and PRX could also be directly regulated by H₂O₂ [23,24]. The active site of the protein tyrosine phosphatases are susceptible to redox regulation, because they have a common complex (cysteine-X5-arginine), which presents the state of the active site cysteine thiol acid (SH) of the (S-) form [25]. H₂O₂ signaling pathways including the regulation of cell proliferation and PI3K/AKT, HIF and MAPK/ERK signaling cascade and death-inducing pathways similar to JNK and P38 MAPK signaling pathway [26,27]. However, the reaction of superoxide with protein thiols enough to compete with the powerful SOD enzyme, SOD enzyme rapidly degraded by peroxide, allowing the cells to maintain homeostasis [28].

Cancer cells adapt ROS stress

ROS homeostasis is necessary for cell survival. Low ROS levels could effectively regulate mitosis, cell survival, cell growth, cell proliferation and angiogenesis [20]. However, high ROS levels show toxic to cells, which could trigger a signal transduction pathway involving cell proliferation inhibition or cell death. It's a very novel character that ROS levels of cancer cells are higher than normal cells, and it is often due to the self-needing of cancer cells [29]. P53 plays a crucial role in regulating antioxidant genes, thereby preventing damage to DNA and protein, and restore the redox balance [30]. P53 mutations or loss is about more than 50% of cancer, which is related with ROS stress [31]. In addition, the proto-oncogene increase production of ROS [32]. Downstream of RAS, PI3K/AKT/mTOR pathways are activated survival signal in most tumors [33]. AKT phosphorylation and inhibition of FOXO transcription factors, could lead to anti-oxidation blocked, leading to increased production of ROS.

ROS promote pro-tumorigenic cell signaling

The increased rate of ROS production in cancer cells play causal roles in acquiring hallmarks of cancer: sustained cell proliferation and mitogenic signaling, increased cell survival and disruption of cell death signaling, EMT, metastasis and angiogenesis [34-37].

ROS promote cancer cell proliferation

In various cancer cells, ROS could enhance cell proliferation by increasing pro-proliferative pathways like PI3K/AKT/mTOR and MAPK/ERK cascades. ROS-mediated cancer cell proliferation was observed in various cancer cells and could be prevented by the

addition of ROS-scavenging antioxidants [38-40]. Recently, study showed that mitochondrial-derived ROS are required for cell growth in KRAS-driven lung cancer cells through the regulation of MAPK/ERK signaling, and increasing ROS by disruption of mitochondrial function could reduce tumorigenesis.

ROS promote cancer cell survival

Aberrant ROS levels could activate PI3K/AKT pathway through inhibiting PTEN in various cancers [41,42]. Oncogenes including KRAS and AKT could also activate and stabilize the antioxidant regulator NRF2 [43], which plays a critical role in protecting against oxidative stress to promote cancer cell survival [44]. Furthermore, ROS could also promote cell survival through activating redox sensitive NFκB signaling in cancer cells [45,46]. NFκB upregulating Bcl-2, caspase inhibitors and antioxidant proteins leads to enhance cell survival in response to ROS accumulation [47,48].

ROS promote angiogenesis and metastasis

Tumor angiogenesis, invasion and metastasis are inter-related processes and the most severe inducements of tumorigenicity. Angiogenesis vascularizes solid tumors in order to provide enough nutrients and oxygen for tumor growth. The main angiogenic growth factor triggering formation of new blood vessels is VEGF, which is activated by HIFs [49]. As we know, hypoxia is an important character of cancers and could increase ROS production [50,51]. ROS play crucial roles in stabilization of HIFα, leading to VEGF activation [52]. And then induce angiogenesis and tumor progression, but the antioxidant of N-acetyl-cysteine (NAC) could prevent the effects [53]. NAC treatment also prevented HIF stabilization and diminished MYC-mediated tumorigenesis [38]. Angiogenesis allows for cancer cell migration and metastasis. Metastasis requires extracellular remodeling and intracellular adaptations including EMT, reduced cell adhesion, increased migration and degradation of tissue barriers and ECM [54]. ROS have been shown to mediate metastasis in various cancer cells through regulating transcription factors and MAPK and PI3K/AKT pathways, HIFs and the EMT regulator Snail [55-57]. ROS could also modulate structural changes in tumor cells like the formation of invasive microdomains, which promote cell invasion and metastasis [58]. Furthermore, ROS promote the activation of MMPs that participate in the degradation of membranes and help detach primary tumor cells from ECM [59-61]. Taken together, these ROS-mediated events promote tumor progression.

ROS promote anti-tumorigenic cell signaling

While ROS are associated with the activation of pro-tumorigenic survival and growth pathways, oxidative stress could also lead to the induction of cell death and cell cycle arrest.

ROS promote cell death through ASK1/JNK/P38 MAPK pathways

Apoptosis signal-regulating kinase 1 (ASK1) acts as a redox sensor by mediating JNK and P38 MAPK, resulting in apoptosis upon excessive ROS [62]. P38 MAPK is also a tumor suppressor and ROS sensor in cancer cells [63]. So we could target P38 MAPK activation to induce cell death in cancer cells by identifying its high levels of ROS [64].

ROS regulate cell cycle arrest

High levels of ROS inhibit cell proliferation to prevent cell division by negatively regulating pro-proliferative kinases. For example, ROS-induced P38/JNK MAPK signaling could lead to down-regulate cyclins and the induction of cyclin-dependent kinase (CDK) inhibitors resulting in cell cycle arrest [65,66]. ROS could also induce cell cycle arrest directly through the oxidation of various cell cycle regulators. The H₂O₂-mediated oxidation and inactivation of the cell cycle phosphatase CDC25 is required for cell cycle progression from G₂ to M phase [67].

In summary, ROS play causal roles in tumorigenesis but could also be toxic to the cell and could potentially induce cancer cell death, cell cycle arrest and inhibit cancer progression. Therefore cancer cells are dependent on maintaining high enough ROS levels that allow for pro-tumorigenic cell signaling, but they still need to keep ROS at limit levels to avoid causing cell death.

Regulating ROS Levels to Treat Cancer

Decrease ROS levels

Due to the high levels of ROS in promoting cancer, various antioxidant promoters like NRF2 are considered as tumor suppressors [68,69]. Antioxidant treatments include supplementation of natural ROS scavengers, treatment with antioxidants and also other strategies that decrease oxidative stress like the disruption of the ROS-producing mitochondrial electron transport chain [2,70-72]. The most effective antioxidant treatment is the regulation of HIF1 levels because that ROS could regulate hypoxic activation of HIF [52]. Antioxidants like NAC and vitamin C could prevent HIF stabilization and diminish MYC-mediated tumorigenesis [38]. Other studies also reported anti-tumorigenic results of antioxidant treatments, including over-expression of SOD3, which inhibited breast cancer metastasis indicating the potential anti-tumorigenic effect of restoring extracellular superoxide scavenging capacity [73-75]. However, most clinical trials were failed to show beneficial effects of antioxidants on a variety of cancer [76,77]. Long-term study showed that vitamin E could significantly increase the risk of prostate cancer in healthy men [78]. Supplementation with β -carotene, vitamin A or E could increase the incidence of lung cancer [79,80]. A recent study demonstrated that using NAC and vitamin E could accelerate lung cancer progression in mice by reducing ROS [81]. Long-term antioxidant supplements treatment for cancer prevention did not provide evidence that they are beneficial in primary cancer prevention [82-86]. Antioxidants are not effective in targeting the locally ROS producer requiring for tumorigenic signaling due to poor efficacy of anticancer. Mitochondrial targeted antioxidants would be a way. These targeted antioxidants have shown efficacy in diminishing tumorigenic potential [87]. Recently, study showed that reduction in reactive oxygen species contributes to dihydromyricetin induced apoptosis in human hepatocellular carcinoma cells [88]. However, we should pay attention to antioxidant-based therapy, because these two problems could not be solved simultaneously. (1). ROS and ROS-dependent cell signaling are essential for normal cell function; (2). Antioxidants could interfere with chemotherapy depending on ROS-induced cytotoxicity [89]. Therefore, elevating ROS levels, either by increasing ROS generation or decreasing ROS scavenging potential, could be a way to selectively kill or arrest cancer cells without causing significant toxicity to normal cells.

Increase ROS levels

Many chemotherapeutic agents could induce cancer cell death or cell growth inhibition by increasing ROS production [90,91]. Chemotherapeutic drugs such as paclitaxel, vinca alkaloids and anti-folates could cause cell death through releasing cytochrome c and also disrupt the mitochondrial electron transport chain which leads to ROS increase [92]. Cisplatin, carboplatin and doxorubicin could also significantly increase ROS, which is the basis of their anti-tumor ability [93,94]. Procarbazine is approved for the treatment of lymphoma and primary brain tumors by increasing ROS [95]. Monoclonal antibodies like rituximab, an anti-CD20 antibody that is used for non-Hodgkin's lymphoma, which is targeted ROS production [96]. Arsenic trioxide (ATO) agents could effectively treat ROS-dependent leukemia [97]. Elesclomol (STA-4783) is another ROS-generating candidate in clinical trials for malignant melanoma. Either it was given as a single agent or combination with paclitaxel seems to be effective in phase II clinical trials. But antioxidants could suppress Elesclomol's curative effect [98]. The same problem restricts anti-tumor drugs which increase ROS is their toxic effect on normal cells.

Target antioxidants to decrease ROS scavenging capacity

Only thinking about increasing ROS seems not very ideal for cancer therapy, because cancer cells could adjust the ROS scavenging system to adapt ROS enhancing, which may induce cancers become resistant to chemotherapeutics. Various cancer cells increase antioxidant proteins, such as activation of NRF2 to maintain ROS levels that allow pro-tumorigenic signaling pathways to be activated without inducing cell death [99,100]. GSH increasing seems to play an active role in protecting cancer cells from cell death and also from ROS-inducing therapy strategies [101]. In fact, ROS scavenging pathway blocking could more efficiently trigger ROS-mediated cell death than solely increasing ROS in various cancer cells [102-104]. Phenethyl isothiocyanate (PEITC) conjugates with GSH, depleting the GSH pool and leading to oxidative stress induced cell death. Additionally, PEITC inhibits GPX activity, which leads to cell death in ovarian cancer cells and leukemia cells. The compound also prolonged survival in an ovarian cancer cell xenograft model [102]. L-Buthioninesulfoximine (BSO) targets de novo GSH synthesis as an inhibitor of glutamylcysteine synthetase (g-GCS) [105]. BSO depletes GSH and exhibits anticancer activity through apoptosis as a single agent and in combination with ATO in solid tumors and APL cells [106,107]. BSO also increased efficacy of cisplatin in preclinical studies [108]. Similar to BSO, Imexon has GSH-depleting induced ROS accumulating, and death-inducing potential as shown in a phase I study of non-Hodgkin's lymphoma and melanoma patients [109,110]. Recently, using a cell-based molecular screen for pro-apoptotic effects in cancer identified the natural compound piperlongumine (PL), which could induce ROS accumulating by binding and modulating the antioxidant enzyme glutathione transferase and therefore change the ROS-stress response. PL induces apoptosis in several cancer cells but has little effect on normal cells [103]. Sulphasalazine (SASP) could decrease cysteine and GSH levels, and then increases ROS, lead to reduce pancreatic cancer cell growth and viability [111]. Another thiol-based antioxidant is thioredoxin (TRX). TRXs are up-regulated in various cancer cells and the TRX inhibitor PX-12 showed anti-tumor activity [112]. Furthermore, motexafin gadolinium is a TRXR inhibitor which showed anti-tumor activity in phase II and III clinical trials [113]. Auranofin is a TRX inhibitor and has been shown to have sensitivity effects in several cancers by causing ROS-mediated cell death [114].

Furthermore, the antioxidant SOD1 has been proved to be a potent target to selectively kill cancer cells. The SOD1 inhibitor methoxyestradiol (2-ME) increases superoxide and is currently in phase I and II clinical trials for prostate and metastatic breast cancer [115,116]. It also induces ROS-mediated apoptosis selectively in cancer cells [117]. Furthermore, recent studies identified the SOD1 inhibitor ATN-224 could cause cancer cell death and growth impairment in various cancer cells through ROS mediated mechanisms [117-119]. ATN-224-induced cancer cell death was mediated through ROS dependent activation of P38 MAPK [104]. Interestingly, extracellular SOD3 is differentially expressed in cancers. SOD3 mRNA was shown to be decreased in some clinical mammary adenocarcinoma samples compared to normal mammary tissues and research found that overexpression of SOD3 inhibited breast cancer metastasis [120]. On the other hand, SOD3 is shown to be amplified in some other cancers making it a potential target for therapy. NRF2 inhibition has the potential to suppress antioxidant systems and induce ROS-mediated cancer cell death. Effective NRF2 inhibitors have been developed and tested for anti-cancer effects.

Combination therapy

The difference between normal cells and cancer cells is the rate of ROS production and results in redox regulation. Combination therapy need to solve these two problems we would meet: (1) decrease the toxicity of chemotherapeutics to normal cells, (2) augment efficacy of anti-tumor. Upon the previous states, metabolic modulation is a suitable candidate for combination therapy with ROS-generators or ROS-scavenging inhibitors. We target the deference of ROS regulation between cancer cell and normal cell to design combination therapy. For example, regulating redox balance particularly through the production of reducing equivalents like NADH and NADPH, which are required for the function of various antioxidant proteins inducing cancer-killing ROS. The metabolic pathway predominantly involved in redox modulation is glutamine metabolism. It plays a central role in redox regulation and antioxidant response. Glutamine is the precursor of glutamate, which, as previously mentioned, is required for GSH synthesis and therefore antioxidant response. Glutamine metabolism has been shown to be required for cancer cell survival leading to the notion that some cancers are glutamine addicted [121]. Inhibition of glutaminase 1 (GLS1), the enzyme that converts glutamine to glutamate for entry into the TCA cycle, inhibits oncogenic transformation [122,123]. Furthermore, an approved agent for the treatment of leukemia has been shown to deplete glutamine levels and therefore GSH synthesis. The drug L-asparaginase was thought to function through its role in limiting asparagine levels, however recent data has shown that the anticancer effect of the drug could be attributed to its effect on glutamine levels [124]. Finally, the alternative glutamine pathway, mediated by the aspartate transaminase GOT1 has been shown to be required for KRAS-driven pancreatic ductal adenocarcinoma (PDAC) growth *in vitro* and *in vivo* [125]. GOT1 is a key enzyme in the aspartate-malate shuttle, producing pyruvate and increasing the NADPH/NADP⁺ ratio, which in turn maintains reduced GSH levels and therefore redox homeostasis. Indeed, GOT1 inhibition led to a decrease in the ratio of reduced-to-oxidized GSH, an increase in ROS levels and suppression of PDAC growth. The role of glutamine metabolism in NADPH production and GSH synthesis makes glutamine pathway inhibitors potentially suitable partners for pro-oxidants in anti-cancer therapy [126].

Conclusion

Studies have established a causal role of ROS in maintaining cellular homeostasis and in triggering cell signaling events. Cancer cells, compared to normal cells, have an increased rate of ROS production and have aberrant ROS regulation mechanisms to adapt their unique redox status. ROS play roles in promoting and maintaining tumorigenicity, and antioxidants could prevent or reduce tumorigenesis by targeting ROS regulation. Some clinical trials showed that dietary antioxidants could not affect cancer development. In fact, dietary antioxidants contribute to tumorigenesis by reducing the potentially death-inducing oxidative stress in cancer cells. This failure of therapeutic antioxidants might be due to the fact that they are unlikely to diminish the local ROS required for cancer survival. Thus, recent studies have focused on the aberrant redox status of cancer cells by exploiting pro-oxidant approaches to cancer therapy. Chemotherapy and radiation could induce cancer cell death by increasing intracellular ROS. However, cancer cells are master of adaptation to oncogene mutations, reprogrammed metabolism, extreme microenvironments and nutrient starvation induce highly stressful conditions. Hence, cancer cells have the ability to develop resistance to therapeutics that exogenously raise ROS by increasing their antioxidant mechanisms. With that, tumor cells can maintain ROS levels that allow pro-tumorigenic signaling without inducing cell death, but at the same time they also rely on ROS detoxification. Redox scavenging and antioxidant system provide new strategy to selectively induce cancer cell death via oxidative stress, while sparing normal cells. In fact, studies have shown that disabling antioxidant mechanisms trigger ROS-mediated cell death in a variety of cancer cell types. Hence, the design of dual pro-oxidant therapies has the potential to be efficacious in selectively killing cancer cells. Combining ROS-generating agents with ROS-scavenging inhibitors like GSH, TRX or SOD inhibitors could diminish the ability of cancer cells to adapt to sole chemotherapeutics.

Various antioxidant proteins and regulators are upregulated in cancers, but cancers have very complicated systems and strong adaptation ability to cope with ectogenic toxicity. To targeting ROS signals for cancer therapy, we still need to study the mechanism of the endogenous ROS regulation in cancer cells comprehensively and systematically.

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