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Review Article

Reactive Oxygen Species and Drug Resistance in Cancer Chemotherapy

Jianli Chen*

Department of Pathology and Laboratory Medicine, Molecular Pathology Laboratory, USA

***Corresponding author:** Jianli Chen, Department of Pathology and Laboratory Medicine, Molecular Pathology Laboratory, SIUH, NSLIJ Health System, 476 Seaview Ave, Staten Island 11305, and Feinstein Institute for Medical Research, NSLIJ Health System, Suite 140, 225 Community Drive, Manhasset, NY 11030, USA, Tel: 516-918-4874; Email: jchen3@nshs.edu

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Abstract

Drug resistance in cancer chemotherapy represents a major obstacle to successful treatment of patients with cancer. Compelling research results suggest that reactive oxygen species (ROS) have been involved in many physiological and pathological processes including apoptosis, tumor hypoxia, regulation of some drug resistance-related proteins, and collateral sensitivity. All of these aspects are associated with drug resistance in cancer chemotherapy. This review will mainly focus on these aspects to sort out the relationship between ROS and drug resistance in cancer chemotherapy.

Keywords: Reactive oxygen species; Drug resistance; Apoptosis; Tumor hypoxia; P-glycoprotein; Dihydrodiol dehydrogenases; Collateral sensitivity; Chemotherapy; Neoplasms

Abbreviation

2-DG: 2-deoxy-D-glucose; AKR: Aldo-keto Reductase; ARE: Antioxidant Response Element; CS: Collateral Sensitivity; DDH: Dihydrodiol Dehydrogenase; DHE: Dihydroethidium; ERK: Extracellular Signal-regulated Kinase; GSH: Glutathione; H_2DCFDA: 2',7'-dichlorodihydrofluorescein Diacetate; H_2O_2: Hydrogen Peroxide; HIF: Hypoxia-inducibble Factor; JAK2: Janus Kinase 2; JNK: c-Jun N-terminal Kinases; MAPK: Mitogen-activated Protein Kinase; MDR: Multiple Drug Resistance; mTOR1: Mammalian Target Of Rapamycin Complex 1; NAC: N-acetylcysteine; NF-κB: Nuclear Factor Kappa B; NF-YA: Nuclear Transcription Factor Y Subunit Alpha; NO: Nitric Oxide; Nrf2: Nuclear Factor Erythroid 2 [NF-E2]-related Factor 2; PAH: Polycyclic Aromatic Hydrocarbon; P-gp: P-glucoprotein; PI3K: Phosphoinositide 3-kinase; PKC: Protein Kinase C; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species; siRNA: Small Interfering RNA; SNP: Sodium Nitroprusside

Introduction

Chemotherapy has become a more and more important weapon of fighting against cancer in clinical practice even although it has been only a little bit more than 50 years since the mid-term of last century, when Gilman et al found nitrogen mustard and applied it to humans after the World War II [1-2]. Currently chemotherapy in single or combined with other methods has been markedly improved survival of patients with cancers, even fortunately able to cure several kinds of tumors like those particularly originated from germ cells, including Choriocarcinoma [3], testes carcinoma [4], and so on. However, drug resistance, no matter intrinsic or acquired resistance, has become the major cause of treatment failure in cancer chemotherapy [5]. To understand and overcome drug resistance, many mechanisms of drug resistance have been proposed [6-8] which can be generally categorized as affecting the pharmacodynamics or pharmacokinetics of anticancer agents [6,8]. Pharmacodynamic resistance includes altered drug target sensitivity, increased DNA repair, and a reduced ability to produce an apoptotic response. Pharmacokinetic resistance usually includes alterations in the stability, metabolism, excretion and distribution of chemotherapeutic drugs at the tumor site [8]. Most recently, the lack of stratification of patients was also been suggested as a cause of resistance to targeted therapy [6].

Based on the observation of an increased GSH-redox cycling capacity in P-glycoprotein (P-gp)-over-expressing multiple drug resistance (MDR) cells, Kramer et al. [9] firstly put forward the theory of "dual mechanism of drug resistance", which brought forth the intriguing suggestion that the MDR should be broadened to include enhanced antioxidant defenses in addition to the typical enhanced drug efflux mediated by P-gp pump. In a sense, this theory actually has implicated the role of ROS in the development and/or the regulation of drug resistance to chemotherapeutic drugs, in particular in solid tumor where probably refers to hypoxia in the central region of tumor tissue, angiogenesis and reperfusion. Since ROS have been demonstrated to be broadly involved in many physiological and pathological processes [10], this review will mainly focus on this point and the relationship between ROS and drug resistance in cancer chemotherapy.

ROS and apoptosis

Apoptosis is an active cell death process initially proposed by Kerr in 1972 [11]. The concept between drug resistance and apoptosis has been well defined, by which drug resistance of chemotherapeutic agents is thought to be the result from inhibition of apoptosis. But this relationship between ROS and apoptosis is not a one-way story [12,13]. The real role of ROS in apoptosis still needs to explore further.

ROS induce apoptosis

In fact, most conventional chemotherapeutic and radiotherapeutic agents kill cancer cells by stimulating ROS generation as at least one part of the mechanisms [13,14]. Even many recently tested compounds with the potential of killing cancer cells were continuously reported to play their role in inducing apoptosis by generating ROS [15-18].

Many different mechanisms on how ROS induce apoptosis have

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been putting forward. Earlier research results showed that ROS might play a direct killing role in their cytotoxicity of chemotherapeutic agents and recombinant human tumor necrosis factor (rhTNF). Later ROS have been implicated as mediators of apoptosis by activating different caspases or up-regulating death receptor 5 and pre-treatment with N-acetyl-cysteine (NAC) or antioxidative protein can dramatically inhibit apoptosis [19,20]. Recently their molecular mechanisms have been further elucidated. Many different signaling pathways, such as mitogen-activated protein kinase (MAPK) pathway, extracellular signal-regulated kinase(ERK) pathway, phosphoinositide 3-kinase(PI3K) signaling pathway and so on, have been found to get involved in ROS-induced physiological or pathological processes including apoptosis [13,21-23].

ROS level in the resistant cancer cells are usually lower than that in their parental sensitive cells. Our preliminary study by siRNA knockdown and forced over-expressing transfection and other research have found that the resistant cancer cells often show higher level of antioxidants and lower level of ROS than the sensitive parental cell lines [24,25]. So generally speaking from above, ROS are usually considered to increase the chemo-sensitivity by inducing apoptosis [26,27].

ROS inhibit apoptosis

Even though the majority of the body of evidences support ROS induce apoptosis, however, there are also many evidences which showed that ROS could inhibit apoptosis [28,29] and apoptosis could be stimulated by inhibiting ROS with antioxidants [28]. As a matter of fact, this is also easily understandable. Normally, healthy cells are in a biological status characterized by a balance between low steady-state level of ROS and a constant level of reducing equivalents. However, if this balance was broken, usually by an increased ROS level and beyond the cellular ability of returning to the balance, it would cause cellular genomic instability, mutations, and finally even malignancy. Therefore, in this regard, malignancy as a result from apoptosis inhibition, could be caused by ROS stress [13,30,31]. Earlier research finding has already demonstrated this similar point. Caspases (cysteine aspartate proteases) have been well known to be involved in the final stage of apoptotic process; however, ROS could also prevent caspase activation in prolonged or excessive oxidative stress [32]. Recently different ROS species have also been reported to play different roles in ROS-associated apoptosis [13]. Azad et al. reported that superoxide anion played a pro-apoptotic role by causing down-regulation and degradation of Bcl-2 protein through the ubiquitin-proteasomal pathway. In contrast, nitric oxide (NO)-mediated S-nitrosylation of Bcl-2 prevented its ubiquitination and subsequent proteasomal degradation, leading to inhibition of apoptosis [33].

On the other hand, in the most recent years more and more natural plant extracts were found to have the potentials to kill cancer cells. Many these findings support the typical increased ROS-driven apoptosis pathway to kill cancer cells [34,35]. But many others found some extracts decreased ROS level when inducing apoptosis, which implies the reverse role of ROS in apoptotic process. For example, salidroside was found to significantly reduce the proliferation of human lung cancer A549 cells and to induce apoptosis but it decreased ROS generation in A549 cells in a dose- and time-dependent manner [36]. Cho et al reported that butein caused breast cancer cell death by the reduction of ROS production. In their research they also found that NAC, a free radical scavenger, also reduced ROS production and Akt phosphorylation, resulting in apoptotic cell death in butein-sensitive breast cancer cell lines [37]. Furthermore, the inhibition of apoptosis by ROS was reported to be seen in a variety of cell lines from different tissue origins including pancreatic cancer cell, smooth muscle cells, leukemia cells, colorectal cancer cells, and prostate cancer cells [28]. Although the mechanism involved is still controversial, redox status and/or hydrogen peroxide (H_2O_2) have both been proposed as critical factors [29,38]. This effect of ROS might also be mediated through antiapoptotic redox-sensitive pathways [28,39].

ROS and tumor hypoxia

Hypoxia is a common phenomenon existed in the central region of solid tumors because of insufficient penetration and diffusion of oxygen and nutrition. Before the formation of new abnormal vessels, malignant solid tumors can be only about 1 to 2 mm^3 in diameter [40]. Rapidly growing malignant solid tumors are very susceptible to deficiency of nutrients (mainly glucose deprivation) and oxygen (hypoxia) by expanding beyond the perfusion capacity of its blood supply.

ROS and glucose deprivation

Studies showed that during glucose deprivation, decreased peroxide scavenging (by pyruvate and NADPH dependent pathways) could result in increased ROS level (H_2O_2) by mitochondrial electron transport chain, which has been shown to further cause cytotoxicity, activation of signal transduction (ERK1/2, JNK, and Lyn kinase), and increased expression of genes associated with malignancy (bFGF and c-Myc) in MCF-7/ADR human resistant breast cancer cells [41]. Malignant tumors usually support their growth by stimulating blood vessel development (angiogenesis) [42]. However, blood flow within these new vessels is often chaotic, causing periods of hypoxia followed by reperfusion and consequent generation of ROS. So it is easily understandable about some change of biological characteristics induced by hypoxia and ROS due to serials of genes expression including drug resistance.

Most research in vitro on glucose deprivation employed 2-deoxy-D-glucose (2-DG) to imitate the state of glucose deprivation. 2-DG is a glucose analog molecule which has replaced 2-hydroxyl group by hydrogen. It acts to competitively inhibit the production of glucose-6-phosphate from glucose. Glucose hexokinase phosphorylates 2-deoxyglucose, trapping the product 2-deoxyglucose-6-phosphate intracellularly and therefore stops further glycolysis. Earlier evidence showed that 2-DG caused cytotoxicity via a mechanism involving perturbations in thiol metabolism and 2-DG was found to cause a 50% of decrease in intracellular total glutathione (GSH) content. Simultaneous treatment with antioxidant NAC protected HeLa cells against the cytotoxicity effects from 2-DG [43]. Currently more and more findings have supported the conclusion that glucose deprivation as well as treatment with 2-DG induces the generation of ROS (including superoxide and H_2O_2) and subsequently causes cytotoxicity [44-47]. However, in the meanwhile, it was also found that 2-DG could cause chemoresistance by up-regulating the expression of P-glycoprotein through ROS stimulation [48,49]. Actually, our laboratory findings also supported that 2-DG could

induced chemoresistance in human ovarian and breast cancer cells by up-regulating the expression of dihydrodiol dehydrogenases (DDHs) and many other different drug resistance-associated target genes(unpublished data) and dihydrodiol dehydrogenases have been demonstrated to regulate the generation of ROS and cisplatin resistance [25].

ROS and oxygen deficiency

For the oxygen deficiency of tumor cells, the most important adaptive mechanism is activation of hypoxia-inducible factor 1 (HIF1). HIF1 consists of two subunits: HIF1α and HIF1β. Under normal oxygen condition, HIF1β is stable but HIF1α is hydroxylated by prolyl hydroxylases. However, when in hypoxic conditions, HIF1α is stabilized and dimerized with HIF1β and regulates the expression of the large number of genes involved in the hypoxic response [50,51]. ROS have been involved in the regulation of HIF1 under various conditions but the role of ROS is still in controversy and the mechanism underlying the HIF-1 regulation by ROS is not completely understood. Insulin and angiotensin II were reported to produce cellular ROS, which were indispensable to increases of HIF-1a protein translation in normoxia. In human prostate carcinoma cell line, it was found that JNK and JAK2 pathway regulated the ROS-induced HIF1α expression as an upstream of AMPK signaling [52]. Conversely, ROS could also down-regulate expression of P-gp in Nox-1 overexpressing prostate tumor spheroids. Nox-1 is an enzyme to generate intracellular ROS. Pretreatment with free radical scavengers increased the expression of P-gp and HIF1α [53].

As a master switch for hypoxic gene expression, HIF1α could be regulated by H_2O_2 through several possible molecular mechanisms and it was estimated that about 5% of the human genome comes under HIF-1 control [54]. Multidrug resistance transporter P-gp is one of HIF1α-targeted genes [55-57]. HIF1α –mediated P-gp expression to hypoxia-induced drug resistance has been reported in many different cancer cell lines including gastric cancer, glioma, breast cancer, and colon cancer. Inhibition of HIF1α with specific siRNA was also found to significantly decrease the expression of P-gp and the regulation of P-gp by HIF1α was due to a direct effect of HIF1α binding to P-gp gene promoter [57].

Hypoxia causes ROS generation in solid tumors. Persistent oxidative stress may cause other adaptive responses like up-regulation of antioxidants within tumor cells that confer resistance to apoptosis. All of this up-regulation of anti-ROS defenses may eliminate ROS-induced cytotoxicity and apoptosis to increase the detoxification ability (resistance) of tumor cells to chemotherapeutic agents [58].

ROS and some MDR-associated proteins

ROS and P-gp

P-gp belongs to a family of plasma membrane proteins encoded by the MDR gene(s). Increasing studies show that ROS can regulate expression of P-gp [53,56,57,59]. Both transient and chronic ROS stress were found to up-regulate P-gp expression in rat brain microvessel endothelial cells [48,60] and ROS could induce P-gp expression on RNA, protein and functional levels and this effect could be counteracted by antioxidants. On the other hand, ROS could also work as negative regulator to down-regulate P-gp expression [59,61-63]. In fact, the recent findings showed that ROS could regulate P-gp expression biphasically. When human colon cancer Caco-2 cells were exposed to low concentration of H_2O_2 (1μM), P-gp expression was increased; however, when exposed to high concentration of H_2O_2 (10mM), P-gp expression was decreased [64]. Furthermore, Duan et al. [65] reported that P-gp expression and function could be even biphasically regulated by ROS through a time-dependent mode under the same ROS level stress. Short-term exposure (4-hour) to nitric oxide (NO) donor like sodium nitroprusside (SNP) increased intracellular ROS and reactive nitrogen species (RNS) in human colon cancer Caco-2 cells and impaired P-gp function and expression, whereas long-term exposure (24-hour) stimulated P-gp function and expression. This is compatible with the earlier finding reported by Wartenberg et al. that low levels of ROS down-regulated P-gp expression whereas high concentrations of prooxidants resulted in up-regulation of P-gp in multicellular prostate tumor spheroids [53,56]. Therefore, the final biological effect of P-gp regulation by ROS could be dependent on the duration and the intensity of ROS exposure.

The mechanism that ROS regulate P-gp expression is not completely clear. Recent research showed PI3K inhibitor, p38 inhibitor and PKC inhibitor could reverse the P-gp stimulation induced by long-term exposure to SNP, which suggested that 24-hour exposure to NOx donors stimulated the expression and activity of P-gp via the PI3K/Akt, PKC and p38 MAPK pathways [65]. Wild type p53 is generally known to repress the expression of P-gp through interaction with basal transcription factors, such as TATA-binding protein. Interestingly, mutant p53 is still capable of interacting with TATA-binding protein but is unable to repress MDR1 transcription. On the contrary, mutant p53 has been demonstrated to activate P-gp gene promoter [66]. Furthermore, certain kinases existing in various signaling pathways such as ERK1/2, PKC, SAPK and Akt are activated by ROS exposure. It seems that the NF-kappaB (NF-κB) pathway, in particular, plays a significant part in modulating ROS-mediated P-gp expression. Earlier study showed that up-regulation of P-gp was via NF-κB activation [56]. By depressing NF- κB signaling, H_2O_2 may still augment P-gp expression when ERK1/2, PKC or SAPK are inhibited [67,68].

ROS and DDHs

DDHs are a superfamily of aldo-keto reductases (AKRs) that normally convert PAH (polycyclic aromatic hydrocarbon) to PAH *o*-quinones, which is cytotoxic and mutagenic. During the metabolic process of PAH to PAH *o*-quinones, large amount of ROS and *o*-semiquinone anion radicals are produced. However, this does not mean that ROS are just only byproduct during this process. Research suggested that DDH1 (AKR1C1) was also reversibly inducible by ROS and multiple classes of xenobiotics. Under the stimulation of oxidative stress with H_2O_2 and GSH depletion, DDH1 could be induced up to a 10-fold increase. This implies the role of DDH1 as an antioxidant response element in redox systems [25,69].

In view of its inducible antioxidant property of DDHs, our research and other authors have demonstrated that DDHs also contributes to chemotherapeutic resistance in many human cancer cell lines [69-74]. Our recent findings showed that DDHs, particularly DDH1, could directly regulate intracellular ROS level by forced over-expression and siRNA techniques in human ovarian cancer

cell lines; DDH1 over-expression attenuated intracellular ROS level and increased resistance to cisplatin; on the other hand, DDHs knockdown by siRNA significantly increased intracellular ROS level and decrease drug resistance to cisplatin [25,75]. Even though cisplatin has been widely known that it can induce intracellular ROS generation, and our findings indicated that nuclear transcription factor Y subunit alpha (NF-YA) can regulate the basal transcription of DDH1 in human ovarian, lung and liver carcinoma cells and the cisplatin-induced CCAAT box-dependent transcription in human ovarian carcinoma cells [76], however, the mechanisms how DDHs are regulated by ROS involved in drug resistance still need to be elucidated further.

A growing body of evidence indicates that ROS are important intracellular signaling regulators in many physiological and pathological processes, including carcinogenesis [13,77] and development of drug resistance to anticancer agents [13,78]. ROS consist of various free radicals, which exert different effects on cellular signaling. By signal transduction, cells communicate with their environment or neighbor cells, connecting extracellular stimuli into specific transcription factors and thereby converting these signals into cellular responses. ROS have been reported to activate the extracellular signal-regulated kinases (ERKs), the c-Jun N-terminal kinases (JNKs), and the p38, which are three subgroups of mitogen-activated protein kinases (MAPKs) (see recent review [79]). Our research group found that treatment of human ovarian cancer cell lines to cisplatin induced increasing intracellular ROS level with H_2DCFDA (for H_2O_2) and DHE (for superoxide) probles and consequently phosphorylated JNK/p38, which was compatible with subsequent levels of apoptosis/necrosis and changes of mitochondrial membrane potential with JC-1 probe; On the other hand, the above changes of cisplatin-induced ROS and subsequent JNK/p38 activation in this pathway could be attenuated by corresponding DDH1 expression level. With external H_2O_2 and antioxidant NAC further demonstrated the above findings (Figure 1). These findings are also compatible with our previous report about the relationship between ROS and DDHs expression level [25]. DDHs are classic antioxidant response element (ARE) genes that are transcriptionally up-regulated by Nrf2 and Nrf2 was originally identified as protective transcription factor from ROS stress. Chen et al recently reported that knockdown of Nrf2 not only decreased the levels of DDH1, DDH2, and DDH3 mRNA and protein but also reversed oxaliplatin resistance in gastric carcinoma S3 cells [69]. This further suggested the relationship with drug resistance and the inter-regulation between ROS and DDHs.

PI3K-Akt-mTOR1 signaling axis and its regulation by Notch1 was also recently reviewed in resistant T-cell acute lymphoblastic leukemia [80,81]. Lee et al reported that cadmium treatment induced increasing intracellular ROS level and DDH3 expression, which was suppressed by NAC and therefore it was believed that up-regulated DDH3 expression was due to the activation of Nrf2 and the PI3K-Akt pathway by cadmium-induced ROS generation [21]. Furthermore, the activation of mTOR1 pathway by cadmium-induced ROS was also reported by another group [23]. Similarly, Lee et al. also demonstrated that ROS generation and/or activation of PI3K/Akt signaling regulated cell survival and HO-1 expression by Nrf2 transcriptional regulation in sulforaphane-treated human mesothelioma MSTO-211H cells [22]. This is easily understandable since like DDHs, heme oxygenases are also one of the target genes by Nrf2 [82].

Signaling transduction is indeed important since almost all kinds of biological processes cannot go without it. Although more and more molecules in signaling pathways are being as targets for designing new anticancer agents to fight against cancer and chemoresistance, however, these anticancer drugs on new targets could also come to resistance finally [80,83]. Thus unfortunately we might come back to the beginning point after hard hunting. Therefore, creative ideas and innovative thoughts to combat against drug resistance are definitely needed in this field of signal transduction research on chemotherapy.

ROS and collateral sensitivity

Collateral sensitivity (CS) was originally used in 1952 and currently has been extended to broadly describe the observation that the development of resistance to one agent can confer greater sensitivity to another agent than seen in the original parental line [84]. The underlying mechanism of CS has not completely understood. However, the potential role of ROS in CS has been proposed recently [84,85]. Based on the evidences available right now, there are two possible different pathways which might get ROS involving in CS: P-gp-based ATPase stimulation and non-P-gp dependent ROS hypersensitivity (see recent review for details) [84,85].

P-gp-based ATPase stimulation pathway has been supported by earlier studies and recent evidence [85,86]. The non-P-gp dependent pathway is also being gradually demonstrated by more increasing findings. Most recently, Krzyzanowski et al. reported for the first time that BCRP- overexpressing MDCKII-BCRP cells are more vulnerable to ROS. These cells have significantly lower GSH level and decreased activities of glutathione S-transferase and glutathione reductase, implying the possibility of using agents that induce ROS to selectively kill cells overexpressing BCRP [87]. Another group also reported that natural flavonoids and some synthetic derivatives could induce CS

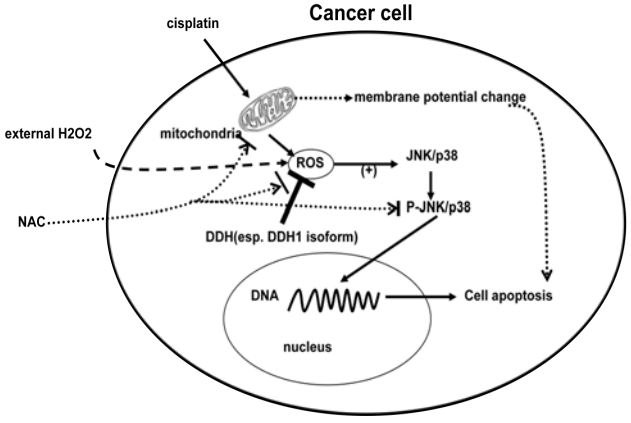

Figure 1: Cisplatin stimulated cancer cell to generate intracellular ROS through mitochondria. ROS subsequently activated JNK/p38 pathway and the phosphorylated JNK/p38 translocated into nucleus and bound to DNA to cause cellular apoptosis, which could also be reflected by the change of mitochondrial membrane potential following cisplatin treatment. Through the same mechanism, external H2O2 exposure could activate the JNK/p38 pathway and antioxidant NAC inhibit it. More interestingly, DDHs, especially DDH1 isotype, as member of intracellular antioxidant system, could directly attenuate intracellular ROS and prevent JNK/p38 pathway from activating and consequent apoptosis to cause chemoresistance.

activity through GSH efflux (which results in increased intracellular ROS level) in resistant MRP1-overexpressiong cells [88]. As ATP-binding cassette (ABC) efflux transporters, there is substantial overlap in substrate recognition among P-gp, BRCP and MRP1, but BRCP and MRP1 have not been definitively demonstrated to contribute to MDR in patients [84]. Hall et al. recently also demonstrated the drug tiopronin-induced non-P-gp dependent mechanism for CS. They found the CS activity of tiopronin was mediated by the generation of ROS and the inhibition of glutathione peroxidase (GPx) and all these CS activity can be reversed by ROS-scavenging compounds including NAC [89].

Summary

ROS are important mediators in drug resistance of chemotherapeutic agents. In this review, we have discussed recent findings illustrating the correlation of ROS with drug resistance in several aspects. In fact, theoretically drug resistance is an inevitable event as a protective mechanism of cell survival. Therefore, for better fighting against drug resistance, novel points of view or strategies are still needed to dig out the Achilles' heel of chemoresistance to overcome this challenging obstacle in clinical treatment of patients with tumor. The potential role of ROS in collateral sensitivity calls for more attention too.

Furthermore, conventionally we always look at antioxidants as "good guy" since they attenuate ROS produced in normal cellular processes and may protect cells from oxidative damage. However, clinical trials have surprisingly shown that antioxidant supplementation increases the risk of lung and skin cancers. Recent studies on electron transferring reported that, compared to oxidative damage caused by ROS, *reductive damage* by electron transferring might represent another previously unrecognized important mechanism for DNA damage and could even double the DNA damage caused by *oxidative damage* from ROS [90,91]. If so, electron transferring and chemotherapeutic agents, reductive damage and chemotherapy and their relationship with chemosensitivity will definitely need to be investigated further for the benefits of patients with cancer in future treatment.

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