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Expanding roles of superoxide dismutases in cell regulation and cancer

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Reactive oxygen species (ROS) have important roles in normal physiology and diseases, particularly cancer. Under normal physiological conditions, they participate in redox reactions and serve as second messengers for regulatory functions. Owing to aberrant metabolism, cancer cells accumulate excessive ROS, thus requiring a robustly active antioxidant system to prevent cellular damage. Superoxide dismutases (SODs) are enzymes that catalyze the removal of superoxide free radicals. There are three distinct members of this metalloenzyme family in mammals: SOD1 (Cu/ZnSOD), SOD2 (MnSOD) and SOD3 (ecSOD). SODs are increasingly recognized for their regulatory functions in growth, metabolism and oxidative stress responses, which are also crucial for cancer development and survival. Growing evidence shows that SODs are also potentially useful anticancer drug targets. This review will focus on recent research of SODs in cellular regulation, with emphasis on their roles in cancer biology and therapy.

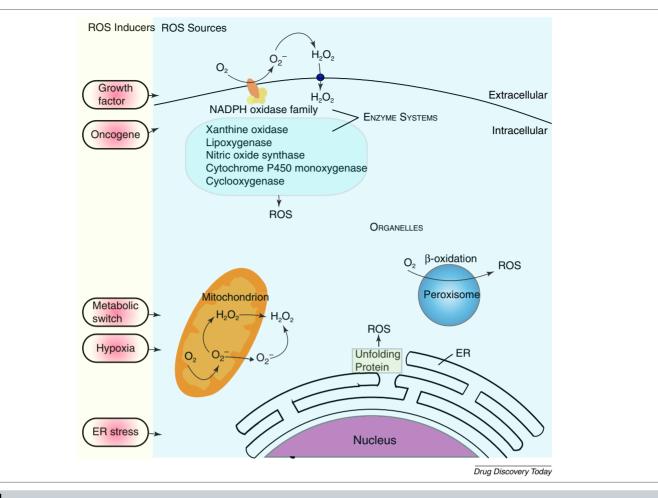## Reactive oxygen species and the cellular redox system

Reactive oxygen species (ROS) represent a group of oxygen-containing molecules derived from oxygen metabolism within the cells [1]. ROS include the superoxide (O_2^-) and hydroxyl (OH^-) free radicals, as well as other ROS such as hydrogen peroxide (H_2O_2) [2]. In eukaryotic cells, ROS are generated in metabolic processes during mitochondrial respiration, or in reactions catalyzed by enzymes such as NADPH oxidase (NOX), xanthine oxidase and cytochrome P450 [3] (Fig. 1). Mitochondrial respiration is a major source of ROS as a result of production of O_2^- from complex I and III of the electron transport chain, which is estimated to represent 1–2% of the oxygen consumed by the cell [4]. O_2^- is further converted into other ROS such as OH^- and H_2O_2.

At physiological levels, ROS are important modulators of many cellular functions from metabolism, signal transduction to stress responses [5,6]. For example, O_2^- oxidizes iron–sulphur (Fe–S) clusters in enzymes such as asconitase [7]. Asconitase functions in the tricarboxylic acid (TCA) cycle where it catalyzes the citrate-to-isocitrate reaction. Oxidation of the Fe–S cluster in aconitase by O_2^- inhibits its enzymatic activity, thereby reducing the rate of ATP synthesis by the TCA cycle, which serves as a negative feedback mechanism in modulating the major electron flow [8]. Another important ROS function is that H_2O_2 regulates activity of proteins, particularly those involved in cell signalling, through oxidation of cysteine residues, which causes conformational and functional changes [9–11]. A well-documented example is oxidation of the active site cysteine of protein tyrosine phosphatases (PTPs) and lipid phosphotases by H_2O_2, leading to their inactivation [12,13]. This increases tyrosine phosphorylation and lipid second messengers that stimulate cell growth, metabolism and proliferation. In addition to lipid and protein phosphatases, cysteine residues of many proteins can be oxidized, providing a convenient way for the redox system to regulate protein activity and related cellular functions [14].

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FIGURE 1

Overview of intracellular mechanisms of reactive oxygen species (ROS) production. Eukaryotic cells generate ROS through four different mechanisms. The first is mitochondrial electron transfer which is a main source of superoxide ion (O_2^-) and hydrogen peroxide. The second is enzymatic reactions, including those catalyzed by NADPH oxidases (NOX), xanthine oxidase, lipoxygenase, nitric oxide synthase, cytochrome c monoxygenase and cyclooxygenase. The third is peroxisomal oxidation of long-chain fatty acids. The fourth is endoplasmic reticulum (ER)-unfolding protein stress response. A number of physiological and pathological stimuli (inducers) can cause increased ROS production, including growth factors, oncogenes, hypoxia, metabolic switch (e.g. Warburg effect in cancer) and ER stress.
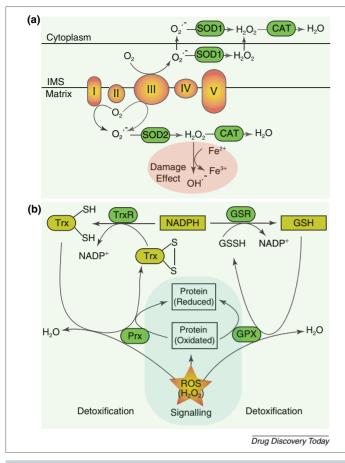
Cellular ROS homeostasis is maintained by balancing production of ROS and activity of the antioxidant system. ROS can reach excessive levels as a result of imbalance of two opposing forces, ROS production and antioxidants, particularly under pathological situations. Excessive ROS oxidize macromolecules such as DNA, proteins and lipids, causing elevated mutations, damage to cellular organelles and other structures and, in extreme circumstances, apoptotic cell death [7,15,16]. Such a condition is called oxidative stress. ROS-producing (inducer) pathways and ROS-detoxifying (scavenger) pathways are tightly regulated to avoid oxidative stress. Eukaryotic cells have developed a sophisticated antioxidant network (Fig. 2). Dismutation of O_2^- is catalyzed by superoxide dismutases (SODs), giving rise to H_2O_2 and molecular oxygen. H_2O_2 is further converted to water and oxygen in a reaction catalyzed by catalase and peroxiredoxin. In addition to enzymatic reactions to remove ROS, eukaryotic cells employ the thioredoxin (Trx) system to facilitate reversal of oxidized cysteine residues. Trx are small protein antioxidants that reduce substrates through cysteine thiol–disulfide exchange [17]. There are two Trx: Trx1 and Trx2. Trx1 is the cytoplasmic form and Trx2

is the mitochondrial form. They are responsible for reducing peroxiredoxins and other oxidized cellular proteins.

To control the cellular redox environment in a precise manner, antioxidant genes are transcriptionally regulated in response to cellular and environmental conditions. When ROS reach a cytotoxic level, an oxidative stress response is triggered that, through transcription factors, upregulates antioxidant and cellular repair genes. A well-studied regulatory system is the Keap1/the nuclear factor erythroid 2–related factor 2 (Nrf2) pathway [18]. Elevated ROS cause oxidation of cysteine residues in Keap1, resulting in escape of Nrf2 from the Keap1–cullin-3 E3 ubiquitin ligase complex. Stabilized Nrf2 protein translocates into the nucleus and activates a program of oxidative stress response genes.

SODs and their physiological functions

SODs are present in all aerobic living cells, which is probably because O_2^- is a common product of oxygen metabolic reactions. In mammals, there are three distinctive SODs: the copper/zinc SOD (Cu/ZnSOD or SOD1), the manganese SOD (MnSOD or SOD2) and the extracellular SOD (ecSOD or SOD3, also a Cu/ZnSOD).
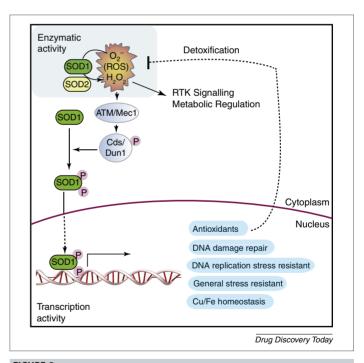
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FIGURE 2

Cellular antioxidant systems. **(a)** Superoxide dismutase (SOD) and catalase-based reactive oxygen species (ROS)-scavenge system, including SODs and catalases (CAT), which is NADPH-independent. SOD1 is responsible for dismutating O_2^- generated in the mitochondrial intermembrane space by the electron transfer chain, and from other locations in the cytoplasm. SOD2 is responsible for dismutating O_2^- in the mitochondrial matrix. Catalases further catalyze the reaction from H_2O_2 into H_2O and O_2. **(b)** The glutathione peroxidase and thioredoxin ROS-scavenge systems that require NADPH. H_2O_2 can be converted to H_2O by glutathione peroxidase (GPX) and peroxiredoxin (Prx), which require the reducing power from glutathione (GSH) and thioredoxin (Trx). NADPH is utilized to reduce oxidized glutathione (GSSH) and Trx by glutathione reductase (GSR) and thioredoxin reductase (TrxR), respectively. GPX and Prx also reduce oxidized proteins, which control redox-dependent signalling pathways.

SOD1 is the major intracellular form of SOD, accounting for ~80% total SOD protein. Early studies reported that SOD1 is primarily cytosolic [19]. However, later studies found it throughout the cell, including in the mitochondrial intermembrane space and nucleus [20,21]. Interestingly, SOD1 protein is also prominently in the nuclei of normal and cancer cells or tissues according to the Human Protein Atlas Project (http://www.proteinatlas.org/). The discrepancy is probably caused by early studies that primarily used subcellular fractionation to apply mechanical disruption of cells, which might have caused cellular stress and hence redistribution of the protein. SOD2 is exclusively localized in the mitochondrial matrix (MM) [19], whereas SOD3 is the secreted form that is mainly associated with the extracellular matrix of different tissues [22]. SOD1 scavenges O_2^- in the cytosol generated by NOX, xanthine oxidase and cytochrome P450 [3] (Fig. 1). It is also responsible for O_2^- in the mitochondrial intermembrane space

during electron transport. Thus SOD1 protects much of the cellular structures except the MM. By contrast, SOD2 is exclusively localized in the MM [19]. In addition, it is associated with mtDNA, and has been proposed to prevent mtDNA and mtDNA polymerase c from oxidative damage or inactivation [23]. Mutant mice lacking SOD2 die shortly after birth but SOD1-deleted animals are fully viable. Interestingly, even though SOD1 is partially localized to mitochondria, SOD1 overexpression cannot rescue the lethal phenotype of SOD2-deficient mice, suggesting that SOD1 and SOD2 have distinct functions [24]. SOD3 is the secreted form of SOD with expression restricted mainly to the lung, kidney and adipose tissues to prevent oxidative tissue damage. Together, these SOD enzymes ensure timely removal of the damaging O_2^- free radicals from cells and tissues.

In addition to their classical function as detoxification enzymes against O_2^-, increasing evidence indicates that SOD1 and SOD2 are actively involved in modulating diverse cellular processes. One well recognized mechanism is that H_2O_2, the dismutating product of O_2^- by SOD can serve as a second messenger to regulate growth and metabolic processes [10,11] (Fig. 3). Based on the rate of mitochondrial respiration, SOD1 controls the level of H_2O_2, which in turn sets a threshold for mitogen signalling such as receptor tyrosine kinase (RTK) signalling to determine the rate of cell proliferation [25]. SOD1 is also engaged in metabolic regulation

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FIGURE 3

Role of superoxide dismutases (SODs) in the regulation of redox homeostasis and cell signalling. In addition to the classical function of SODs [i.e. to dismutate superoxide ion into hydrogen peroxide (H_2O_2)], SODs are increasingly recognized to regulate diverse cellular processes from mitogenic signalling to oxidative stress response. The H_2O_2 product in turn can activate receptor tyrosine kinase (RTK) signalling and metabolic regulation. SOD1 also acts as a transcription factor regulating oxidative stress response. When H_2O_2 reaches an excessive level, it activates the checkpoint kinase ataxia-telangiectasia mutated (ATM) kinase, which promotes SOD1 phosphorylation by Cds/Dun1 kinase and SOD1 localization into the nucleus where SOD1 acts as a transcription factor for a large panel of genes involved in oxidative stress responses.

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in response to the presence of glucose and oxygen. SOD1 represses respiration in the presence of glucose and oxygen to promote glycolysis [26]. SOD1 binds to, and regulates the stability of, two casein kinases involved in glucose-mediated respiratory repression through localized production of H_2O_2 [26]. In this fashion, SOD1 engages in control of metabolic switches between aerobic glycolysis and oxidative phosphorylation (OXYPHOS).

As discussed above, although SOD1 has been widely regarded as a cytosolic enzyme, it is also found prominently in the nucleus in normal and cancer cells or tissues. An early study in chicken DT40 cells shows that interfering with nuclear SOD1 causes genomic DNA damage [27]. Consistently, loss of SOD1 or its copper chaperon LYS7 sensitizes yeast to DNA damage agents [28]. These observations indicate that nuclear SOD1 plays a key part in maintaining genomic DNA stability. Interestingly, nuclear localization of SOD1 is promoted by H_2O_2 in yeast and fibroblasts, which is dependent on phosphorylation of SOD1 at S60 and S99 by the ATM/Mec1 pathway [29]. Considering O_2^- is generated in the cytoplasm and has a very short half-life in aqueous solutions, and thus has limited ability to reach the nucleus, these observations suggest that nuclear SOD1 has other functions. Indeed, SOD1 is found to bind to the promoters and regulates a large set of genes involved in oxidative stress, replication stress, DNA damage response, general stress response and Cu/Fe homeostasis [29] (Fig. 3). In an independent study in which human recombinant proteins were systematically assayed for DNA binding, SOD1 was identified as a sequence-specific DNA-binding protein, suggesting a direct role in gene regulation [30]. In support of this role, SOD1 also binds estrogen receptor alpha (ERα) and enhances its transcriptional activity [31]. The precise mechanism of how SOD1 is involved in transcriptional regulation is currently not understood. It could regulate specific transcription factors through redox reactions by its catalyzed product H_2O_2, although nuclear O_2^- appears to be limited. Alternatively, SOD1 might act as a transcription factor itself, but this remains to be established.

SODs and cancer

During recent years, a growing body of evidence has formed that clearly indicates that SODs have crucial roles in many aspects of human cancer. Although all three SODs carry out the same enzymatic reaction of superoxide dismutation, they have very different roles in human cancer owing to their distinct cellular localizations, tissue distributions and biological functions. Below is a summary of the current knowledge of each SOD in cancer, focusing primarily on recent findings.

SOD1 in cancer

SOD1 is a well-known disease-causing gene because germline mutations in SOD1 are associated with a majority of familial amyotrophic lateral sclerosis (fALS) cases, a fatal, early-adulthood-onset neurodegenerative disease primarily affecting motor neurons [32,33]. Over the past two decades, fALS has been a main focus in SOD1 research to elucidate the pathobiology of this neurodegenerative disease. By sharp contrast, its role in cancer is much less well studied. Because redox homeostasis and oxidative stress are instrumental in carcinogenesis, it is not surprising that SOD1 is closely linked to cancer. Much like ROS, SOD1 appears to have a paradoxical role in cancer. On one hand, loss of SOD1

increases ROS level, which is naturally thought to cause oxidative DNA damage and promote carcinogenesis. On the other hand, cancer cells are known to have a high ROS content and become increasingly dependent on activated antioxidants such as SOD1 to prevent excessive cellular damage and apoptosis during tumor progression.

Constitutive SOD1 knockout mice provide some insights into how SOD1 is involved in cancer. Although there is no obvious developmental deficiency and adult animals are relatively normal, SOD1-null animals develop several age-related diseases, including muscle atrophy and macular degeneration. Interestingly, despite whole-body-deficiency of SOD1, spontaneous tumors are only observed in the liver of aged mice [34]. It is intriguing to note that, despite extensive oxidative DNA damage, a known carcinogenic event, the mice do not develop other tumors, suggesting that SOD1 has an essential function important for tumor development, which is discussed below. Liver is the major organ for iron transport and storage, and is prone to injury in the absence of SOD1, which could explain why only hepatocellular carcinomas are favored [34]. In recent years, it has become increasingly clear that malignant cells have high ROS content, which leads to oxidative stress responses and upregulation of the antioxidant system [35]. For example, some tumors exhibit constitutive activation of Nrf2 [36,37], either through gain-of-function mutation or inactivation of Keap1, which is crucial for the growth and survival of these cancer cells [38]. Consistently, overexpression of SOD1 has been observed in lung [39] and mammary [40] carcinomas. Analysis of SOD1 in human mammary tumors also revealed that SOD1 is localized in the cytoplasm as well as nucleus of breast cancer cells [40,41]. These observations indicate that SOD1 is generally pro-oncogenic rather than tumor suppressive in late stages of cancer. Consistent with the above notion, in vitro studies show that SOD1 is essential for non-small-cell lung cancer (NSCLC) because knockdown or pharmacological inhibition of SOD1 potently inhibits growth of lung adenocarcinoma cell lines driven by oncogenic K-Ras and epidermal growth factor receptor (EGFR) [39,42].

SOD2 in cancer

SOD2 has long been thought to be a tumor suppressor because early studies showed that SOD2 expression is decreased in tumors [43]. However, recent evidence shows considerable heterogeneity in the expression and activity of SOD2 in different cancer cells, suggesting that SOD2 expression in human cancer might be stage- and/or tumor-type-dependent [44,45]. Reduced SOD2 expression tends to be lower in early-stage tumors, suggesting that SOD2 loss is associated with tumor initiation, which is consistent with the general theme of reduced antioxidants being associated with increased ROS and oxidative genomic DNA damage, and thus carcinogenesis. By contrast, SOD2 level is generally higher in late-stage tumors, especially metastatic tumors. However, the situation might be more complex because SOD2 level could also be determined by specific oncogenic drivers and the overall state of the entire redox system. For example, reduced SOD1 expression has been shown to cause a compensatory increase in SOD2 in some breast cancer cells [40]. The SOD2 gene is subjected to regulation by a number of intrinsic and extrinsic stimuli including growth factors, inflammatory cytokines, chemotherapeutic agents and UV irradiation, involving a wide array of transcription factors,

including AP-1, CCAAT/enhancer binding proteins (C/EBP), nuclear factor (NF)-κB, p53 and SP-1, as well as epigenetic and post-transcriptional regulations [44]. One or more of these transcription factors and processes is typically altered during carcinogenesis, which is likely to reflect specific changes in SOD2 expression in a particular tumor context.

Mitochondria have important roles in human cancer [46] and SOD2 has been shown to be required for maintaining mitochondrial integrity and functions [44,47]. Because SOD2 is exclusively localized in the MM where mtDNA resides, it has been presumed that a main function of SOD2 is to protect mtDNA against oxidative damage. Surprisingly, however, in human cancers, mtDNA mutations appear to be mainly caused by mtDNA replication errors rather than oxidative damage [48]. Similar mtDNA mutation patterns were also observed in aged fruit flies in the absence of SOD2, which suggests that SOD2 protects mitochondrial proteins rather than mtDNAs [49]. One of the main processes affected by SOD2 is energy metabolism. It has been shown that downregulation of SOD2 impairs oxidative phosphorylation whereas SOD2 overexpression causes an increase in ATP production through mitochondrial respiration [44]. One study recently showed that increased SOD2 expression in cancer cells sustains the flow of H_2O_2 originating from mitochondria, which is required for maintaining AMP-activated protein kinase (AMPK) activity, causing a metabolic switch from mitochondrial respiration to glycolysis [50], a phenomenon commonly seen in human cancer known as the Warburg effect [51]. It has been generally recognized that high levels of SOD2 are often associated with invasive and metastatic cancer. The aforementioned increase in H_2O_2 as a result of SOD2 overexpression affects membrane localization of key regulators of cell migration such as p130cas and phosphatase and tensin homolog (PTEN) [47], and epithelial–mesenchymal transition through CD44 expression [52], which results in altered invasion and metastasis of tumor cells. Another relevant function is that SOD2 activates NF-κB signalling by increasing the I kappa B kinase (IKKβ) transcription, which results in cancer progression by stimulating anchorage-independent growth and invasion of lung cancer cells [53].
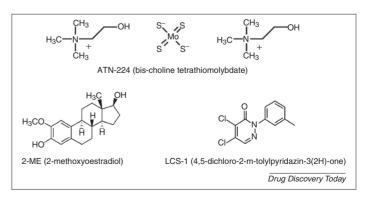
SOD3 in cancer

Compared with the two intracellular SODs, the role of SOD3 in cancer is less well understood. The general consensus of several studies is that the SOD3 level is reduced in human cancer, which has a pro-tumorigenic effect. Downregulation of SOD3 has been examined in lung and mammary carcinomas and found to be due to DNA copy number change or hypermethylation in the promoter of methylation [54,55]. For example, SOD3 expression is decreased in pancreatic ductal adenocarcinoma (PDA), correlating with poor prognosis. Overexpression of SOD3 in PDA cells results in decreased growth and invasiveness [56]. It has been shown that overexpressed SOD3 causes hypoxic accumulation of hypoxia-inducible factor (HIF)-1α in PDA cells. Hypoxic induction of vascular endothelial growth factor (VEGF) is also suppressed by SOD3 [57]. Because SOD3 is extracellular, it is possible that the effect in cancer is mediated through the tumor microenvironment, explaining why downregulation of SOD3 promotes cancer metastasis, which is in contrast to SOD1 and SOD2.

SODs as anticancer therapeutic targets

SODs, SOD1 in particular, are increasingly recognized for their diagnostic and therapeutic values. Much of the past efforts in therapeutic targeting of SOD1 have been focused on fALS, but several SOD1 small-molecule antagonists have been identified with anticancer activity. So far, two SOD1 inhibitors, and one SOD1 and SOD2 dual inhibitor, have been reported in the context of cancer drug discovery. Another interesting potential application of SODs is in radiation therapy [58]. ROS are important effectors of ionic radiation. As a major class of ROS regulator, modulating the level or activity of SODs is expected to affect the efficacy of radiotherapy significantly in tumors as well as side-effects in normal tissues.

ATN-224, a bis-choline tetrathiomolybdate, is orally bioavailable (Fig. 4) and is the most advanced SOD1 inhibitor in development. ATN-224 is a copper chelator, which was inspired by early observations that copper chelating has antiangiogenic and antitumor benefits. Further studies showed that SOD1 is inhibited with an IC_{50} value of 330 nM [59]. Because there are many Cu enzymes, off-target effect is an obvious concern. However, even at 100 μM, ATN-224 has little effect toward cytochrome c oxidase, also a copper-dependent enzyme. These observations suggest that SOD1 is the primary target in cancer. ATN-224 inhibits cancer cells as well as endothelial cells, indicating that the compound has antitumor activity by blocking cancer cell proliferation and angiogenesis. Interestingly, ATN-224 induces apoptosis in tumor cells but not endothelial cells, suggesting that its cytotoxicity is selective toward cancer. ATN-224 has been tested in early-stage human clinical trials. A Phase I trial in patients with solid tumors demonstrates that the drug is well tolerated without adverse cardiac events previously associated with copper-deficient diet in animal studies [60]. Another randomized Phase II trial in patients with relapsed prostate cancer achieved some promising results [61]. In general, the overall therapeutic effect is less than the results seen with preclinical studies. One possible reason is that insufficient drug concentration is achieved at tumor sites because on-target SOD1 inhibition was only measured in blood samples during clinical trials. Therefore, improved rational design of clinical trials will be important for further development of ATN-224. In addition, identification of surrogate biomarkers might be necessary for selecting an appropriate patient population that will respond to ATN-224.

ATN-224 (bis-choline tetrathiomolybdate)

2-ME (2-methoxyoestradiol)

LCS-1 (4,5-dichloro-2-m-tolylpyridazin-3(2H)-one)

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FIGURE 4

Small-molecule superoxide dismutase (SOD)1 inhibitors. Shown are three known SOD1 inhibitors: ATN-224 (bis-choline tetrathiomolybdate); 2-ME (2-methoxyoestradiol); and LCS-1 (4,5-dichloro-2-*m*-tolylpyridazin-3(2H)-one).

The mechanism of action by ATN-224 has been investigated. It has been shown to induce apoptotic cell death in the A549 NSCLC cells, as did *SOD1* knockdown, in cultured cells and cell-line-derived xenograft tumors [39]. Curiously, despite strong inhibition of the superoxide dismutase activity of SOD1, ATN-224 or siRNA-mediated knockdown actually increases intracellular H_2O_2 levels [39]. Although more ROS probes are needed for verification, this is unexpected because H_2O_2 is the product of SOD1-catalyzed product and inhibition of SOD1 is expected to increase the H_2O_2 level if its enzymatic activity alone is considered. This observation suggests that an unconventional SOD1 function(s) is probably involved such as aforementioned transcriptional regulation. Consistently, ATN-224-induced elevation of H_2O_2 leads to activation of p38 mitogen-activated protein kinase (MAPK), which decreases the level of the antiapoptotic factor Mcl1 and results in apoptotic cell death [39]. Together, these studies demonstrate that SOD1 is essential for growth and survival of malignant cells. Because some of the dyes can detect multiple ROS species, further characterization will be necessary to understand changes in ROS homeostasis caused by SOD1 inhibition.

It has been noted that certain estrogen derivatives such as 2-methoxyoestradiol (2-ME) (Fig. 4) selectively kill human leukemia cells but not normal lymphocytes [62]. It was further shown in the same study that 2-ME does not bind to the estrogen receptor but causes p53 accumulation. SOD1 was identified as a target of this compound. Treatment with 2-ME causes elevated cellular O_2^- damage to mitochondrial membranes, and release of cytochrome c from mitochondria and apoptotic death of the cancer cells [62]. However, 2-ME has not been shown to bind to SOD1 directly and a follow-up study suggests that the effect is not due to SOD inhibition [63]. Instead, it is due to interference of the *in vitro* assay itself [63]. Based on its chemical structure, it may act indirectly through a redox-reaction-mediated mechanism. 4,5-Dichloro-2-*m*-tolylpyridazin-3(2*H*)-one (LCS-1) (Fig. 4) is another small-molecule SOD1 inhibitor that was discovered from a high-throughput screen by Harold Varmus' group for compounds that preferentially inhibit the growth of lung adenocarcinoma cells with K-Ras or EGFR mutations [64]. Subsequent ligand-affinity

purification and *in vitro* assays identified that SOD1 is the biological target [42]. LCS-1 binds to SOD1 and inhibits SOD1 enzyme activity *in vitro*. The sensitivity of lung cancer cell lines to LCS-1 is closely correlated with SOD1 expression level, suggesting that SOD1 overexpression is a driver for LCS-1-sensitive lung cancer cells. So far no follow-up study has been reported. It is not clear whether the compound has favorable pharmacological properties for further development.

Concluding remarks

Owing to aberrant metabolism, cancer cells accumulate excessive ROS that can cause severe cellular damage and induce apoptotic cell death. To ameliorate the cytotoxic effect, cancer cells are under selection pressure to develop a powerful antioxidant system [65]. Late-stage cancer cells are crucially reliant on a highly active antioxidant system to sustain rapid proliferation and survival. Indeed, a large body of evidence indicates that it is indeed the case for SOD1 and SOD2, two intracellular SODs crucial for dismutating O_2^- free radicals. This key characteristic of cancer makes disrupting the antioxidant defense system a useful strategy to target malignant cells selectively. To date, several compounds targeting SODs have been identified that show promising anticancer activity in preclinical studies, demonstrating the feasibility of this approach. Looking forward, it will be important to improve the pharmacological profiles of the existing compounds and understand their mechanism-of-action in different human cancers, which will lay a foundation for targeting SODs in appropriate cancer types. Another area to explore is combination with other therapies such as drug, immunological and radiation therapies that may be enhanced by modulation of tumor cell ROS levels, improving overall treatment outcomes.

Conflicts of interest
The authors declare no conflict of interest.

Acknowledgments

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