Review Article

Current research progress in the role of reactive oxygen species in esophageal adenocarcinoma

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Abstract: In the past few decades, the incidence of esophageal adenocarcinoma has increased by six-fold in western countries, as the proton pump inhibitor targeting the gastric acid reflux has failed to control the disease. It is currently suggested that deoxycholic acid reflux leads to esophageal adenocarcinoma. As an inflammation-related cancer, the formation and progression of esophageal adenocarcinoma are closely related to the concentration of reactive oxygen species (ROS). Meanwhile, the critical developmental stage of esophageal adenocarcinoma involves characteristic pathological changes in which the distal esophageal squamous epithelial cells are replaced by intestinal columnar epithelial cells, suggesting the involvement of cancer stem cells. Thus, esophageal adenocarcinoma is a good model to study the interplay between ROS and stem cells in cancer. Until now, some important questions related to ROS in esophageal adenocarcinoma remain unanswered. For example, the molecular mechanism by which deoxycholic acid induces malignant transformation in esophageal adenocarcinoma remains unclear. In addition, whether ROS are involved in the induction of cancer stem cell formation by chemotherapeutic drugs and deoxycholic acid stimulation in esophageal adenocarcinoma remains to be further explored. This review summarizes current research progress on ROS and stemness activity, regulation of ROS by stanniocalcin-1 (STC1)/uncoupling protein 2 (UCP2), and inspiration for ROS in esophageal adenocarcinoma to guide further research and provide insight into the clinical treatment of esophageal adenocarcinoma.

Keywords: Reactive oxygen species (ROS); stanniocalcin-1/uncoupling protein 2 STC1/UCP2; esophageal adenocarcinoma; deoxycholic acid; cancer stem cells

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Introduction

The origin of reactive oxygen species (ROS)

ROS are defined as oxygen-containing substances that readily oxidize other molecules and include superoxide (O_2^-), hydroxyl (HO), and hydrogen peroxide (H_2O_2) molecules (1). ROS are produced in the mitochondria by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX). G-protein-coupled receptor 5 (TGR5), NOX1, and NOX2 are NADPH hydrogenases. Early studies have shown that acids and bile acids produce ROS by upregulating TGR5 (2,3). Recent studies have shown that bile acids also produce ROS by upregulating NOX1 and NOX2, causing DNA damage and the malignant progression of Barrett's esophagus. Meanwhile, NOX1 and NOX2 inhibition by siRNA interference can reduce ROS production and DNA damage (4). Both P16 and P53 are important tumor suppressor genes. Hong *et al*. (2) showed that ROS methylate P16DNA and downregulate P16mRNA expression, promote cell proliferation, and cause the malignant transformation of Barrett's esophagus into esophageal adenocarcinoma. Cardin *et al*. (5) showed that the accumulation of DNA oxidative damage activates telomerase and telomere lengthening occurs in the late stage, ultimately leading to *p53* gene mutation and adverse effects on cell growth, apoptosis, and DNA repair that promote cancer progression.

The relationship between ROS and esophageal adenocarcinoma

ROS do not only cause cancer by damaging DNA, but also by activating inflammatory pathways and producing inflammatory mediators, which further promote tumor microenvironment formation. These processes are related to apoptosis resistance, invasion, and metastasis. Nuclear factor kappa B (NF-κB) is an important inflammatory pathway in esophageal adenocarcinoma. Liu *et al*. (6) found that deoxycholic acid-mediated NF-κB-interleukin 8 (IL-8) pathway activation is related to ROS, and the activated NF-κB pathway also produces anti-apoptotic protein Bcl-2, rendering DNA-damaged cells resistant to apoptosis (7). Signal transducer and activation of transcription 3 (STAT3) is also an important inflammatory pathway in esophageal adenocarcinoma. Acid and bile acid reflux have been shown to activate the interleukin 6 (IL-6)–STAT3 pathway and increase expression of the anti-apoptotic protein Bcl-xL, leading to apoptosis resistance in cancer cells (8). STAT3 inhibitors significantly reduce the proliferation and migration of esophageal adenocarcinoma cells, suggesting that the STAT3 pathway is also associated with esophageal adenocarcinoma proliferation and metastasis (9). Studies have found that ROS activation promote malignant lung cancer progression by stimulating the Janus kinase (JAK)-STAT3 pathway. After UCP2 silencing, ROS levels increase, thus activating the STAT3 pathway. Rotenone or NOX inhibitor pretreatment reduces ROS and eliminates STAT3 pathway activation (10). In addition, studies on gastric cancer have found that *H. pylori* promotes the STAT3 pathway activation by increasing ROS production, further leading to Wnt pathway activation and excessive cancer cell proliferation, while antioxidants significantly inhibit STAT3 pathway activation and prevent malignant cancer progression (11). However, whether ROS can also activate the STAT3 pathway in esophageal adenocarcinoma has not been studied yet.

Reflux of bile acid and ROS in esophageal adenocarcinoma

It is currently suggested that bile acid reflux is an important factor leading to the formation and progression of Barrett's esophagus and esophageal adenocarcinoma. Bile acids are structurally classified into two groups: free bile acids—including cholic acid, deoxycholic acid, goose deoxycholic acid, and a small amount of licholic acid—and the conjugated products of bile acid with glycine or taurine, termed the conjugated bile acid. Bile acid reflux in patients with Barrett's esophagus usually ranges from 3 to 820 μM, with a median of 180 μM (12), but may reach 6,400 μM (13). In the rat reflux model, it was found that gastric acid alone could not induce Barrett's esophagus formation; in contrast, bile acid alone could produce it (14). Shen *et al*. (15) successfully reprogramed deoxycholic acid-induced immortal esophageal squamous epithelial cell line Het-1a to express caudal-type homeobox gene 2 (CDX2) and mucin 2 (MUC2), which serve as intestinal epithelial cell markers. Huo *et al*. (7) treated Barrett's esophagus cell lines with deoxycholic acid and ursodeoxycholic acid and found that deoxycholic acid causes oxidative stress reaction and subsequent cell DNA damage, while hydrophobic ursodeoxycholic acid does not damage cell DNA. Esophageal adenocarcinoma is defined as an inflammation-related cancer in which excessive ROS is mediated by bile acid (deoxycholic acid) reflux (6). Therefore, unconjugated deoxycholic acid may be an important determinant in bile that causes carcinogenesis and the transformation

of esophageal squamous epithelial cells into Barrett's esophagus (16). Specifically, the molecular mechanism by which deoxycholic acid induces malignant transformation remains unclear.

ROS and cancer stem cells

Current conventional chemoradiotherapy kills most cancer cells by increasing ROS levels in the cells, but cancer stem cells survive due to their resistance to chemoradiotherapy and thus can induce relapse by differentiating into cancer cells at the appropriate timing. Cancer stem cells are a small number of self-renewing and differentiating cells in tumors, which are closely related to recurrence, metastasis, and chemoradiotherapy resistance. Cancer stem cells may be transformed from normal stem cells, as well as progenitor, tumor, or normal non-stem cells after dedifferentiation and reprogramming (17-19). Therefore, it is particularly important to understand cancer stem cell formation to subsequently perform targeted treatment to improve the efficacy of cancer treatment and improve the survival prognosis of patients.

This review focuses on the research progress of ROS specifically in esophageal adenocarcinoma, including the relationship between stemness activity and ROS, the regulation of ROS, and the inspiration for clinical treatment based on ROS levels.

ROS and stemness activity in esophageal adenocarcinoma

Markers of cancer stem cells in esophageal adenocarcinoma

The critical developmental stage of esophageal adenocarcinoma involves characteristic cellular morphological changes, which may suggest cancer stem cell involvement. Esophageal adenocarcinoma developed from the normal esophagus proceeds through several developmental stages, including Barrett's esophagus, low-grade dysplasia, high-grade dysplasia, and esophageal adenocarcinoma. The critical precancerous stage Barrett's esophagus has been marked by columnar epithelial cells replacing squamous epithelial cells in the distal esophagus (20), which strongly suggests the involvement of stem cell-related activities (21).

Three types of markers can be used for the recognition of cancer stem cells, including cell surface molecules, transcription factors, and molecules of signaling pathways. Cell surface molecules mainly include aldehyde dehydrogenase (ALDH), CD44, and CD133, while transcription factors include Octamer-binding transcription factor 4 (OCT4), homeobox protein (Nanog), and sex-determining region Y-box 2 (SOX2). The signaling pathways include Notch, JAK/STAT3, phosphatidylinositol 3-kinase/ protein kinase (PIK3/AKT), Wnt, etc. (19). In esophageal adenocarcinoma, researchers have found that cancer stem cells of esophageal adenocarcinoma express stem cell markers, such as ALDH (22), OCT4 (23), CD44 (21), and CD133 (21). Lynam-Lennon *et al*. (22) confirmed that ALDH expression was associated with cancer stem cells. Patients with esophageal adenocarcinoma and elevated ALDH expression were less responsive to chemoradiotherapy. In addition, studies have found that ALDH1+ cells, which can prevent ROS-induced apoptosis by reducing ROS production, are more resistant to oxidative stress than ALDH1– cells (24). ALDH expression inhibition target cancer stem cells in ovarian cancer, enhancing the sensitivity of ovarian cancer to chemotherapy from taxanes and platinum. These results suggest that cancer stem cells in esophageal adenocarcinoma may also develop resistance to radiotherapy and chemotherapy through ALDH expression to improve antioxidant capacity in cancer. OCT4, also known as OCT3, is an important transcription factor that maintains the pluripotency of stem cells. Studies have shown that OCT4 expression increases with the progression of Barrett's esophagus to esophageal adenocarcinoma, while the decrease in OCT4 expression reduces the invasiveness and cloning ability in esophageal adenocarcinoma cells, reducing cancer stem cell generation. This suggests that OCT4 might play an important role in the progression of Barrett's esophagus to esophageal adenocarcinoma by promoting cancer stem cell formation (23). Signaling pathways such as Notch have been proven to drive the formation of esophageal adenocarcinoma cancer stem cells, while inhibition of Notch signaling could reduce the number of cancer stem cells, increasing their sensitivity to chemoradiotherapeutic drugs (25). The JAK/STAT3 pathway is also recognized as an important signaling pathway regulating the formation of cancer stem cells. It has been found in lung cancer that STAT3 could regulate ALDH activity, which is essential for the maintenance of lung cancer stem cells (26,27). In cervical cancer, STAT3 affects the expression of OCT4 and Nanog transcription factors and regulates the biological characteristics of cervical cancer stem cells (28). It has also been found in esophageal adenocarcinoma that the JAK/STAT3 pathway is activated under the stimulation of

acid or deoxycholic acid to promote apoptosis resistance, proliferation, and metastasis (8,9). However, whether the STAT3 pathway in esophageal adenocarcinoma can regulate stem cell formation remains unclear, and further studies are needed.

ROS induces stemness activity in cancer

Studies have shown that low and medium ROS concentrations promote stemness formation in cancer cells (29). In fact, it is one of the reasons for cancer resistance to chemoradiotherapy and its recurrence after chemoradiotherapy. Chemoradiotherapy kills cancer cells by producing ROS; although high ROS concentrations kill cancer cells, playing a therapeutic role, low ROS concentrations act as signaling molecules in related signaling pathways, inducing cancer cells to transform into cancer stem cells and enhancing cancer malignancy (30,31). Both insufficient chemotherapeutic drugs or antioxidant system enhancement in cancer might have the opposite consequence to the desired therapeutic outcome.

ROS can directly activate Notch, STAT3, and other signaling pathways to induce cancer stem cell formation. Charles *et al*. (32) found that nitric oxide activates Notch signaling and promotes the stemness of glioma cells. Zhang *et al*. (29) found that during the treatment of pancreatic cancer, low-dose gemcitabine also induces pancreatic cancer stem cell formation by activating the STAT3 pathway through producing low and medium levels of ROS. However, the activated Notch or STAT3 signaling pathway upregulates ROS scavenger enzymes or increases anaerobic glycolysis through the phosphatidylinositol 3 kinase/protein kinase B (PIK3/AKT) pathway to control ROS levels (33), which helps to maintain a low level in cancer stem cells. In addition, transcription factors such as hypoxia-induced factor α (HIF-α) and NF-κB also promote the formation or maintenance of stemness in cancer. Researchers have found that ROS promotes cancer stem cell formation by regulating HIF-α expression and promoting NF-κB activation (34). Notably, ROS also induce mesenchymal transformation in tumor epithelial cells, promoting invasion and metastasis. As an E-cadherin inhibitor, Snail is the most important mesenchymal transformation transcriptional regulator. Studies have shown that ROS induce Snail expression, which could further activate Notch, PIK3/AKT, Wnt, and other signaling pathways to promote mesenchymal transformation in cancer (19). Mesenchymal transformation is closely related to cancer stem cell formation (35,36), possibly because mesenchymal transformation and cancer stem cells share common activation pathways, such as Notch, PIK3/AKT, Wnt, and others. Furthermore, it was found that mesenchymal transformation also activates cancer cells to obtain stemness through the Ras-mitogen-activated protein kinase pathway (37). In general, ROS induce cancer stem cell formation by directly activating the relevant signaling pathways or transcription factors of cancer stem cells, and also promote cancer stem cell generation by promoting the occurrence of cancer mesenchymal transformation. However, in esophageal adenocarcinoma, the relationship between ROS and cancer stem cells is still not clear. Studies have found that chemotherapeutic drugs also induce the formation of esophageal adenocarcinoma cancer stem cells (38). Bile acid stimulation upregulates esophageal adenocarcinoma stem cell markers and promotes cancer stem cell formation (23). It is known that both chemotherapeutic drug use and deoxycholic acid stimulation promote ROS generation. However, whether the induction of cancer stem cell formation by chemotherapeutic drugs and deoxycholic acid stimulation in esophageal adenocarcinoma is related to ROS remains to be further explored.

ROS uncoupling protein 2 (UCP2) and stanniocalcin-1 (STC1)

Proton leak, a significant biological energy phenomenon that greatly reduces the yield of ROS and adenosine triphosphate (ATP), is one of the important accomplices of drug resistance in cancer cells. Significantly high proton leak-mediated bioelectricity is one of the primary characteristics of cancer, rendering cancer cells different from normal cells (39,40). Although proton leak has not been directly studied in relation to cancer treatment, it plays a key role in cancer treatment strategies because proton leak determines the level of ROS. The up-regulated UCP2 expression in the UCP2-mediated proton leak in cancer cells is responsible for drug resistance. Reducing UCP2-mediated proton leak increased the level of ROS and chemical sensitivity to cisplatin therapy in cancer cells (40).

Studies have found that deoxycholic acid could reduce the expression of UCP2 and enhance the ability of cloning, proliferation, invasion, and metastasis in esophageal adenocarcinoma cells (41). UCP2 was found to be widely distributed in the liver, brain, pancreas, adipose tissue, immune cells, spleen, kidney, and central nervous system. Several studies have focused on UCP2 (42), which can pump protons between the inner and outer mitochondrial

membranes into the mitochondrial matrix. Proton transport bypasses ATP synthase and reduces the proton gradient of the mitochondrial inner membrane, leaving the oxidative complex of the electron transport chain in the mitochondrial inner membrane idle. This leads to a decrease in the mitochondrial inner membrane potential, electron leakage in the electron transport chain, and ROS production. Functionally, UCP2 is involved in insulin secretion, immune response regulation, and cell energy metabolism, which enhance glycolysis (43).

In recent years, studies have identified a key role of UCP2 in oncogenesis and progression. It is generally believed that UCP2 is inhibited in the early stage of carcinogenesis, during which intracellular ROS accumulation leads to genomic instability and induces cancer formation. In the subsequent stages of cancer development, UCP2 is activated or overexpressed in cancer cells compared to in normal tissue cells by reducing intracellular ROS levels, thereby increasing resistance to chemotherapeutic drugs in cancer cells, improving their invasiveness, and protecting cancer cells (42,44,45). Therefore, UCP2 and cancer might have a dual relationship. Proton leak determines the ROS level, which plays an important role in cancer treatment strategies. Reduction of mitochondrial oxidative metabolism is a hallmark biological energy feature of malignant tumors, and may have an adaptive effect on cancer occurrence. Targeting mitochondria is a promising new approach for cancer prevention and treatment (20). UCP2 is often overexpressed in drug-resistant cancer cells, where it controls the ROS level and limits drug toxicity.

STC1 is a blood calcium and phosphorus metabolic balancing regulating protein expressed in various tissues and organs in the human body. In addition, it is involved in calcium and phosphorus transport and plays an important role in the formation and progression of cancer. Studies have shown that STC1 is overexpressed in multiple malignant tumors, such as laryngeal cancer, glioma, esophageal cancer, gastric cancer, colorectal cancer, thyroid cancer, kidney cancer, and breast cancer. STC1 promotes cell proliferation by regulating cell cycle protein expression (46). In kidney cancer, STC1 accelerates transformation from G1 phase to S phase, thereby shortening the cell cycle and increasing the proliferation rate of cancer cells (47). STC1 improves the anti-apoptosis effect in cancer, mainly by activating the ERK and JNK signaling pathways, promoting the expression of anti-apoptotic proteins Bcl-2 and Bcl-xL, and inhibiting the pro-apoptotic proteins Bax, Bak, and Bid (48). Moreover, STC1 also promotes blood vessel formation through the vascular endothelial growth factor/vascular endothelial growth factor receptor (VEGF/VEGFR2)-related signaling pathway (49). Therefore, the high expression of STC1 improves the malignant ability of the cancer and is a predictive marker of cancer progression. Wang *et al.* (50) showed that STC1 induces UCP2 expression in macrophages, which is an important factor that weakens the oxidative stress response in cells. Ono *et al.* (51) reported that large STC1 quantity mediates UCP2, reduces alveolar epithelial cell ROS production, and inhibits pulmonary fibrosis. These findings verify the existence of an association between STC1 and UCP2 in normal cells. Recent studies have found that STC1 is highly expressed in cancer, accompanied by a decrease in intracellular ROS (52). Considering the involvement of UCP2 in regulating cellular ROS production, it is speculated that the reduction of STC1 to ROS depends on the expression of UCP2 in related cancers.

ROS on the prevention and treatment of esophageal adenocarcinoma

Prevention of cancer (ROS lowering anticancer therapy)

It is known that deoxycholic acid stimulates the production of ROS, and the increased ROS triggers a series of malignant events. ROS can promote HIF-2a generation (53) and NF-κB activation (54) by damaging DNA (55) and interfering with the expression of tumor suppressor genes (2,5,56), thus inducing anticancer immune tolerance and promoting the expression of anti-apoptotic proteins (53), which together promote esophageal adenocarcinoma occurrence. On one hand, oxidative stress plays an important role in esophageal adenocarcinoma occurrence; therefore, antioxidant therapy may be effective in the prevention and treatment of esophageal adenocarcinoma, specifically by inhibiting ROS production and increasing ROS clearance. For example, NADPH oxidase is the key enzyme for peroxisomal ROS production. Studies have shown that inhibiting NADPH oxidase ROS species production and DNA damage, which may be an effective target for preventing tumorigenesis (4). On the other hand, an obstacle to the antioxidant system leads to an increase in ROS due to limited clearance. Studies have found decreased levels of superoxide dismutase (SOD) in Barrett's esophagus and esophageal adenocarcinoma, where SOD supplementation reduces oxidative damage to

the esophageal epithelium and prevents the progression of esophageal epithelium from Barrett's esophagus to esophageal adenocarcinoma (57). In addition, some antioxidants may be effective in the prevention of esophageal adenocarcinoma. Bhardwaj *et al.* (58) found that a natural antioxidant, oleandine, which may be used to prevent the occurrence of esophageal adenocarcinoma, inhibits ROS production, prevents DNA damage in Barrett's esophagus cells, and enhances DNA repair. Diallyl disulfide is a natural organic sulfur compound derived from garlic. Studies have shown that diallyl disulfide, which may be a good candidate for Barrett's esophagus or esophageal adenocarcinoma chemoprophylactic and therapeutic therapies, inhibits deoxycholic acid-induced ROS production, thereby inhibiting NF-κB activation and inflammatory cytokine and anti-apoptotic protein production (59). In addition, Jenkins *et al.* (60) confirmed that vitamin C blocks the genetic toxicity of esophageal mucosal epithelium caused by bile acids by clearing ROS, thus supporting the idea that antioxidants may be an effective chemical protectant. In short, ROS promotes the occurrence of esophageal adenocarcinoma through a variety of mechanisms. Therefore, lowering the ROS level in the body might contribute to the prevention of esophageal adenocarcinoma. Specifically, these measures could be achieved by inhibiting key enzymes involved in ROS production, enhancing the body antioxidant system, or using some antioxidants to reduce ROS levels in the body. However, effectiveness still needs to be confirmed using sufficient evidence. It is worth noting that antioxidant therapy may be effective for the prevention of cancer, but for malignant developed cancer, especially advanced cancer, antioxidant therapy is not helpful and may reduce the survival rate of tumor patients. This may be due to the elimination of ROS as well as the ROS-mediated apoptosis, leading to the survival of cancer cells. Therefore, it is necessary to increase the level of ROS to induce apoptosis in an advanced situation.

Cancer therapy (an anticancer therapy that increases ROS)

There are still no strategies for the treatment of esophageal adenocarcinoma. At present, neoadjuvant chemoradiotherapy combined with surgery is utilized, but the response rate of tumor to chemoradiotherapy is 16% of the complete pathological responses (34). Researchers have found that the existence of esophageal adenocarcinoma cancer stem cell subsets is important for resistance to neoadjuvant chemoradiotherapy; therefore, targeted treatment of cancer stem cells may increase the sensitivity of chemoradiotherapy and improve clinical results (25). It is known that the concentration of ROS in cancer stem cells is also lower than that in ordinary cancer cells, because cancer stem cells are more sensitive to ROS. Medium and low concentrations of ROS can help the formation of cancer stem cells, while high concentrations can inhibit the expression of cancer stem cells and even kill them. Therefore, current chemoradiotherapeutic drugs kill cancer and cancer stem cells by producing a large amount of ROS. However, cancer stem cells can reduce the concentration of ROS in cells through a powerful antioxidant system or the transformation of energy metabolism. In terms of antioxidant systems, cancer stem cells can enhance antioxidant capacity by inducing the activation of antioxidant protein nuclear factor erythroid 2-related factor 2 (NRF2) (61), increasing the expression of antioxidant enzyme superoxide dismutase1 (62), and increasing the production of antioxidant glutathione (63), to control the ROS level and avoid damage to cancer cells. Therefore, ROS levels may be low in this case, which may induce the formation of cancer stem cells, which is also a cause of cancer chemoradiotherapy resistance. Thus, under the condition of ensuring sufficient ROS production by chemotherapy, drugs that inhibit cancer antioxidant system can be combined to significantly increase ROS levels in cancer to achieve therapeutic purpose. Studies have shown that a combination of cisplatin and salazosulfapyridine can reduce the *in vivo* glutathione effect, leading to significant ROS accumulation, thereby enhancing the sensitivity of colorectal cancer to cisplatin and inhibiting cancer cell proliferation (64). Another study found that reducing the antioxidant enzyme Mn-superoxide dismutase (Mn-SOD) expression through siRNA can increase the sensitivity of ovarian cancer cells to chemically induced apoptosis (65). In addition, ALDH expression also contributes to the clearance of ROS in cancer stem cells. High ALDH expression is related to chemotherapeutic cancer resistance, while siRNA ALDH enhances the cytotoxicity of taxane and platinum and targets ovarian cancer stem cells (66). In short, improving the ROS level in cancer may be effective for cancer treatment. Due to the enhanced antioxidant capacity of cancer stem cells, drugs used solely to promote ROS production may be ineffective. Therefore, ROS-generating drugs combined with antioxidant system drugs could effectively improve the ROS level in cancer cells to achieve therapeutic effects. However, at present, few studies have focused on these methods in

esophageal adenocarcinoma, which still need to be further explored.

Conclusions

Esophageal adenocarcinoma is an inflammatory cancer caused by the chronic reflux of gastric and bile acids. ROS not only causes cancer by damaging DNA, but also activates inflammatory pathways, produces inflammatory mediators, and further promotes cancer microenvironment formation. ROS levels are also related to apoptosis resistance, invasion, and metastasis, as well as potentially cancer stem cells, and thus may be a key driver of the growth and metastasis of this cancer type to initiate tumorigenesis, self-renewal, and differentiation of cancer cells. In addition, interactions among ROS, UCP2, and STC1 are noteworthy. It is important to recognize that esophageal adenocarcinoma can be prevented or treated by regulating the ROS level in the body. Since high ROS levels can kill cancer cells significantly, the combination of chemotherapeutic drugs along with drugs that exhibit antioxidant system characteristics might serve as an effective treatment strategy.

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Footnote

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