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Kertas Asli/*Original Articles*

Reactive Oxygen Species (ROS) in Cancer and Cancer Stem Cells

Spesies Oksigen Reaktif (ROS) dalam Kanser dan Kanser Stem Sel (CSC)

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ABSTRACT

Reactive Oxygen Species (ROS) are aerobic metabolic byproducts, mainly produced by mitochondria. Most types of cancer contain high amounts of ROS. An increase in endogenous ROS triggers adaptive changes, induces oxidative stress and cytotoxic. Oxidative stress can lead to cancer. But on the other hand, the radiotherapy treatment method induces the formation of ROS in the process of cell death. Resistance therapy in cancer cells is associated with high antioxidant enzymes that neutralize ROS in cancer cells. In addition, therapeutic resistance and recurrence are also associated with the presence of cancer stem cells (CSCs). Several studies have shown that ROS levels are found to be low in CSCs. Low levels of ROS are likely to play a role in the survival of CSCs. Therefore, modulation of ROS levels in CSCs can be used as an alternative therapy.

Keywords: ROS; CSCs; therapy

ABSTRAK

Spesies Oksigen Reaktif (ROS) adalah produk sampingan metabolisma aerobik, yang dihasilkan oleh mitokondria. Sebilangan besar jenis kanser mengandungi jumlah ROS yang tinggi. Peningkatan ROS endogenus mempunyai potensi mengakibatkan perubahan adaptif, mendorong tekanan oksidatif dan sitotoksik. Tekanan oksidatif boleh menyebabkan kanser. Tetapi, kaedah rawatan radioterapi membawa kepada pembentukan ROS dalam proses kematian sel. Terapi ketahanan pada sel kanser dikaitkan dengan enzim antioksidan tinggi yang meneutralkan ROS pada sel kanser. Selain itu, rintangan dan pengulangan terapeutik juga dikaitkan dengan kehadiran Sel Dasar Kanse (Cancer Stem Cell, CSC). Beberapa kajian menunjukkan bahawa tahap ROS didapati rendah pada CSC. Tahap ROS yang rendah cenderung memainkan peranan dalam kelangsungan CSC. Oleh itu, modulasi tahap ROS dalam CSC dapat digunakan sebagai terapi alternatif.

Kata kunci: ROS; CSC; terapi

INTRODUCTION

Cancer is a major problem both in developed and developing countries. Cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths or one in six deaths in 2018. World Health Organization (WHO) estimates that in 2030 cancer is one of the increasing causes of death (WHO 2020). Cancer starts from the transformation of normal cells that accumulates called a tumor. Cancer cells grow abnormally and uncontrollably, invade surrounding tissues and are able to migrate to other organs through the blood circulation or lymphatic system. The ability to migrate is known as metastasis (Almeida & Barry 2010).

Cancer is caused by many factors, one of which is reactive oxygen species (ROS). ROS is a compound that contains reactive oxygen. Low levels of ROS function to activate and modulate signal transduction pathways, modulate the activity of redox sensitive transcription factors and regulate cell defenses (Halliwell & Gutteridge 2007; Zhang et al. 2016). Conversely, high levels of ROS are toxic to cells and induce oxidative stress. Oxidative stress can induce damage to various components in cells such as protein, carbohydrates, fats and DNA. DNA damage triggers cancer. ROS plays an important role in the initiation, progression and defense of cancer cells. But on the other hand, the radiotherapy treatment method induces the formation of ROS in the process of cell death. Cancer cell resistance is associated with high ROS antidote antioxidant enzymes in cancer cells. Besides therapeutic resistance and recurrence are also associated with the

presence of cancer stem cells (CSCs) (Liou & Storz 2010; Yang et al. 2018).

CSCs are small populations of cancers that have the ability to self-renewal and differentiate to produce cancer cells. In addition, CSCs are responsible for progression, metastasis, therapeutic resistance and recurrence (Tower 2012). While non-CSCs or progeny cells loses growth activity as a consequence of differentiation and aging (Reya et al, 2001). Several studies have shown that ROS levels in CSCs lower than non-CSCs (Diehn et al. 2009; Kim et al. 2012). But on other hand, the radiotherapy treatment method induced the formation of ROS in the process of cell death. Therefore, this article will explore how the role of ROS in cancer stem cells (CSCs) (Liou & Storz 2010; Yang et al. 2018).

REACTIVE OXYGEN SPECIES (ROS)

ROS are compounds that contain reactive oxygen so that it is easy to form new compounds with other molecules around it. In general, ROS is divided into two types, namely oxygen free radicals and non-radicals (Halliwell & Gutteridge 2007). ROS free radicals have one or more unpaired electrons in their outer orbitals, for example superoxide (O_2•-). Nonradical ROS do not have unpaired electrons but are reactive compounds that can be converted into ROS free radicals, for example peroxide (H_2O_2) is converted to hydroxyl radicals (H_O•). Some examples of ROS can be seen in Table 1. ROS can come from exogenous and endogenous. Exogenous ROS, such as pollutants, cigarette smoke, xenobiotics and radiation. Endogenous ROS is produced through many mechanisms, especially mitochondria, peroxisomes, endoplasmic reticulum and NADPH oxidase (NOX) complexes in cell membranes. Mitochondria as the main site producing endogenous ROS (Halliwell & Gutteridge 2007; Zhang et al. 2016).

Mitochondrial DNA encodes a protein that is important for energy formation pathways, namely oxidative phosphorylation that produces ATP, and ROS as a byproduct and initiates cell death. Therefore, because of its role, mitochondria are also called "power houses" for cells.

TABLE 1. Radical and nonradical ROS and antioxidant systems of enzymes and nonenzymes. The function of antioxidant, both enzymes and non-enzymes, is to neutralize free bonds of ROS. ROS and antioxidant are produced by the body. Howeever, if antioxidant levels are reduced, additional nutrients are added examples Vitamin A, C or E

ROS	Symbol	Antioxidant Systems	Symbol
Radical		Enzymes	
Superoxide	O_2•-	Superoxide dismutase	SOD
Hydroxyl radicals	HO•	Catalase	CAT
Nitric Oxide	NO•	Glutathione peroxidase	GPX
Peroxyl radicals	ROO•	Glutathione S-transferase	GST
Organic radicals	R•	Glutathione reductase	GR
NonRadical		Nonenzymes	
Hydrogen peroxide	H_2O_2	Glutathione	GSH
Singlet oxygen	$^1O_2$	Glutaredoxin	Grx
Ozone	O_3	Thioredoxin	Trx
Hypochloroic acid	HOCl	Sulfiredoksin	Srx
Peroxynitrite	ONOO-	Vitamins A, C, E	

Mitochondria where electron transport takes place which is the main source of ROS, specifically complex I and III. Electrons derived from NADH and ubiquinone (Q) can directly react with oxygen to form free radicals. During aerobic metabolism, most of the oxygen is converted to water and 1-5% in the form of superoxide (O_2•-) (Halliwell & Gutteridge 2007; Zhang et al. 2016).

Superoxide is a precursor for most ROS and mediators in the respiratory chain. Dismutation of superoxide anions, both spontaneously and reactions catalyzed by the enzyme superoxide dismutase (SOD), in the mitochondrial matrix by manganese superoxide dismutase (MnSOD) or in the cytoplasm by copper/zinc superoxide dismutase (Cu/ZnSOD), will produce hydrogen peroxide (H_2O_2). The peroxide is then completely reduced by catalase to water (H_2O) or partially reduced to hydroxyl radicals (OH•) which are highly reactive oxygen. The formation of hydroxyl radicals is catalyzed by a reduced transition metal, namely iron (Fe^{2+}) or copper (Cu^{2+}) (Halliwell & Gutteridge 2007; Zhang et al. 2016).

Physiologically, the body requires low levels of ROS. Low levels of ROS function to activate and modulate signal transduction pathways, modulate the activity of transcription-sensitive redox factors and regulate defense mechanisms. Given the function of ROS as a signaling molecule, ROS must be produced by cells when needed. Normal cells regulate intracellular ROS levels to nontoxic limits by maintaining a balance between the resulting ROS and those that are removed. The ROS removal system is

facilitated by antioxidants which can be enzymes or non-enzymes (Halliwell & Gutteridge 2007; Zhang et al. 2016).

REACTIVE OXYGEN SPECIES (ROS) CAUSES CANCER

Cancer is caused by many factors, one of which is ROS. High levels of ROS are toxic to cells and induce oxidative stress. Oxidative stress is the amount of free radicals in the body that exceeds the body's capacity to neutralize it. Oxidative stress can induce damage to various components in cells such as protein, carbohydrates, fats and DNA. The situation ultimately triggers a cell death program through an increase in the apoptotic pathway (Liou & Storz 2010; Nourazarian et al. 2014).

If the apoptosis program fails due to mitochondrial DNA damage, it will lead to cancer. Mitochondrial DNA is more susceptible to oxidative damage due to the absence of protective histone proteins. Strong hydroxyl radicals (HO•) are very selective to get out of the mitochondrial membrane. Consequently, if these radicals form, hydroxyl radicals can oxidize guanine (G) or thymine (T). A small amount of DNA damage due to oxidation can be repaired through the DNA repair system by the DNA glycosylase enzyme. If ROS levels are very high, the DNA repair system is not functioning enough to change DNA and cancer develops (Matés & Sánchez-Jiménez 2000; Nourazarian et al. 2014).

DNA damage by ROS is one of the main causes of cancer. Patients with diseases associated with cancer risk, indicated an increase in the rate of DNA oxidative damage or lack of DNA repair systems (Dayem et al. 2010). The damage will continue to the stages of carcinogenesis. Carcinogenesis is a gradual mechanism of cancer, consisting of three stages of initiation, promotion and progression. Initiation is the initial stage in which normal cells turn into premalignant. Carcinogens react with DNA causing continued mutations in gene amplification. In the initiation process, it is enough to be exposed to once a carcinogen, such as radiation, which is an initiator, causing a permanent and irreversible state (Dayem et al. 2010). Initiation does not change gene expression. Promotion by promoters, non-mutagenic substances, which can increase carcinogenic reactions and can cause gene amplification (Dayem et al. 2010). The nature of the promoter is to follow the work of the initiator, it requires repeated exposure and the situation can be reversible. Promotion can change gene expression, enzyme induction and differentiation. Progression occur, activation, mutation or loss of genes. In progression, changes occur in benign to premalignant and malignant (Dayem et al. 2010).

Research on cancer states that high levels of ROS play a role in causing cancer (Shi et al. 2012). On the other hand, if ROS levels increase to some extent which does not allow cells to survive, ROS has a very cytotoxic effect that causes cancer cell death thereby inhibiting cancer growth. It can be assumed that ROS is involved in cancer initiation, promotion and progression. ROS can also activate transcription factors that can control gene expression, including proliferation and death of cancer cells themselves (Shi et al. 2012; Sena & Chandel 2012).

REACTIVE OXYGEN SPECIES (ROS) TRIGGERING CELL DEATH

The high number of ROS can trigger cell death, both by apoptosis and necrosis (Gupta et al. 2012). Apoptosis controls cell death and can be initiated by death receptors (extrinsic pathways) or mitochondria (intrinsic pathways), both dependent on ROS. In the extrinsic pathway of apoptosis, ROS are generated by FAS ligand. FAS phosphorylation at the tyrosine residue, which is a signal for subsequent recruitment of Fas-associated protein with death domain and caspase 8 for apoptosis induction. In contrast, the intrinsic pathway is preceded by mithocondrial permeability transition (MPT) which causes loss of mitochondrial membrane potential. ROS can open pores by activating pore-destabilizing proteins and inhibiting pore-stabilizing proteins (Bcl-2 and Bcl-xL). Mitochondrial membrane depolarization causes the release of apoptosis inducing factor (AIF) and cytochrome c to the cytoplasm which is regulated by Bax and Bad. When both are released, the caspase pathway is activated. Cytochrome c interacts with Apaf-1 and procaspase-9 cofactors to form apoptosome, to activate caspase-9. Caspase-9 will activate procaspase-3 as caspase-3, the effector implementing apoptosis. Caspase breaks down proteins causing the nucleus to break and cells undergo apoptosis (Gupta et al. 2012).

Although an excess amount of ROS can induce apoptosis, a larger number of ROS can trigger necrosis of cell death. In some cases, ROS can induce apoptosis and necrosis in cancer cells. For example, in Jurkat T lymphocytes, H_2O_2 is found in two effects. Low H_2O_2 concentration causes cells to undergo apoptosis through caspase activation. High H_2O_2 concentrations, caspase activity is not detected and cells undergo necrosis then die (Gupta et al. 2012).

MECHANISMS OF PROLIFERATION AND CANCER DEFENSE

ROS can stimulate cell proliferation and activate defense pathways through several signaling mechanisms. DNA damage due to ROS is a major cause of cancer. Several

signaling pathways and transcription factors control ROS in cancer development, such as MAPKs and NF-κB.

1. Mitogen-Activated Protein Kinase (MAPKs)

Mitogen-Activated Protein Kinases (MAPKs) belong to the serine/threonine kinase group involved in various cellular processes, including energy metabolism, regulation of gene expression and cell proliferation. The implication of the MAPKs pathway in cell proliferation is confirmed in the observation of cascade kinase deregulation which results in cells transforming into cancer. ROS has the ability to activate various signaling pathways, including the cascade of phosphorylation of MAPKs. The cascade includes extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 MAPK (Kurata 2000; Kennedy et al. 2007; Dayem et al. 2010).

High levels of ROS in the environment of cancer cells, activates cascade signaling, triggering activation and phosphorylation of MAPKs including ERK. As a result, NF-κB and AP-1 transcription factors are activated. The activation triggers c-jun and c-fos gene responses that play a role in inflammation, inhibits apoptosis, triggers cell proliferation, transformation and differentiation. Conversely, low ROS level in environment of CSCs, selectively activate p38 MAPK and trigger abnormal cell cycle progressions. ROS activates the p38 MAPK pathway causing quiescent CSCs to cycle more frequently and eventually become exhausted (G0 phase) (Puar et al. 2018; Kurata 2000; Dayem et al. 2010).

ERK, JNK and p38 MAPK maintains redox balance. The balance of activating ERK and JNK functions as a defense system. A decrease in ERK and increase in JNK are important to indicate apoptosis. The ERK pathway mainly controls the process of cell proliferation and defense, whereas the JNK pathway promotes proliferation or apoptosis. Activation of both can trigger increased proliferation and defense, although loss of JNK in some cases can trigger tumorigenesis. On the other hand, p38 MAPK is activated by ROS and can inhibit the proliferation or promotion of apoptosis. p38 MAPK selectively functions as a ROS sensor during tumorigenesis initiation (Kurata 2000; Dayem et al. 2010).

2. Nuclear Factor Kappa B (NF-κB)

Nuclear Factor Kappa B (NF-κB) is a transcription factor which when activated can significantly modulate redox. NF-κB plays a role in regulating several genes involved in immunity, inflammation,antiapoptotic response, cell transformation, proliferation and metastasis. NF-κB play a role in controlling the defense response to ROS. NF-κB activation is related to carcinogenesis because of its role in cell growth and differentiation and inflammation. NF-κB which induces the expression of IL-6, a cytokine that plays a role in immune and inflammatory responses. NF-κB normally passes through the Iκ-Bα inhibitor protein in the cytoplasm. ROS activates NF-κB through phosphorylation, ubiquinone and proteasomal degradation of Iκ-Bα protein inhibitors rapidly. The translocation of NF-κB to the nucleus activates transcription genes, including bcl-2, bcl-xL, TRAF 1, TRAF 2, SOD and A20, which promote cell defense inhibits the apoptotic pathway. NF-κB is a transcription factor that plays an important role in the expression of several genes whose products can suppress tumor cell death, stimulate tumor cycle progression, increase the epithelial transition to mesenchymal which is important in tumor invasion and produce tumors with a micro-inflammatory environment. The environment supports progression, invasion and tissue metastasis. (Puar et al. 2018; Dayem et al. 2010).

Based on the explanation above, ROS can activate signaling pathways that inhibit the death of cancer cells themselves by activating the phosphorylation cascade of MAPKs and NF-κB (Dayem et al. 2010). Other than that, NF-κB upregulated Inducible Nitric Oxide Synthase (iNOS). We mention because nitric oxide (NO) is often produced where superoxide ROS leading to formation of the highly reactive peroxynitrite, cause cellular damage and can activate cell death pathways (Morgan & Liu 2011). But on the other hand, the radiotherapy treatment method induces the formation of ROS in the process of cell death. Cancer cell resistance is associated with high ROS antidote antioxidant enzymes. In addition, lately therapeutic resistance and recurrence have also been linked to CSCs (Kurata 2000; Tower 2012; Dayem et al. 2010).

ABILITY TO SELF RENEWAL AND DIFFERENTIATION OF CANCER STEM CELLS (CSC)

Stem cells have the ability to self-renewal and high differentiation, which aims to maintain the homeostasis of the stem cell pool system. Stem cells differentiate into terminal cells with varying morphology and functions. Most stem cells in tissues, such as bone marrow, are in the Go phase and hypoxic environment. The situation aims to protect cells from the accumulation of DNA replication errors, maintain homeostasis and regeneration. The situation in the Go phase with a slow cycle in stem cells, the possibility of increasing resistance to oxidative stress, chemical compounds or radiation. Therefore, ROS levels are a very important factor in regulating stem cells in the Go phase (Morrison & Kimble 2006; Tower 2012).

CSCs are small populations of cancers that have the

ability to renew and differentiate to produce tumor cells. In addition, cancer stem cells are responsible for progression, metastasis, resistance to therapy and recurrence of cancer cells. CSCs are thought to play a role in treatment resistance. There are three key observations defining cancer stem cells in the population. First, only minor cancer cell populations have the potential to become tumors when transplanted into immuno-deficient mice. Second, there are distinctive markers on each surface of cancer stem cells that can be distinguished from non-tumorigenic cells. Third, tumors consist of cancer stem cells and non-tumorigenic cells so that they provide a variety of phenotypes to the parent tumor (Shi et al. 2012; Tower 2012).

Research on stem cell leukemia uses a surface marker CD34+/ CD38- to separate tumorigenic and nontumorigenic cells. Cells that have a $CD34^{+}$/ $CD38^{-}$ marker on their surface can proliferate both in vitro and in vivo while others do not. Cancer stem cells can be enriched through various surface markers (Table 2). CD133 is believed to be a marker of cancer stem cells in various types of brain cancer. Cancer cells with $CD133^{+}$ markers can be enriched after radiation is performed on the glioma. The presence or absence of markers on the cell surface is known by means of flow cytometry, a method for isolating cancer stem cells. Cancer stem cells can be stained by fluorescent substances due to the binding of ATP transporters. The research shows that cancer stem cells have the ability to pluripotence (Gupta et al. 2012).

In addition to pluripotency, cancer stem cells are also able to differentiate. Several studies have shown that cancer stem cells have endothelial and adipotic potential. Majority of endothelial cells in glioblastoma carry the same mutations as cancer cells. The results concluded that cancer stem cells might contribute to vascular endothelium in tumors. These cells are able to differentiate into vascular

TABLE 2 Cell surface phenotypes of CSCs identified in human cancer

Cancer Type	CSCs Phenotype
AML	$CD34^{+}/CD38^{-}$, $CD44^{+}$, $CD34^{+}/CD123^{+}$, $CD47^{+}$
ALL	$CD34^{+}/CD10^{-}$, $CD34^{+}/CD19^{-}$
Breast cancer	$CD44^{+}/ESA^{+}/CD24^{-}/Lin^{-}$, $ALDH1^{low}$
Brain cancer	$CD133^{+}$, $CD15^{+}$
Melanoma	$ABCB5^{+}$, $CD271^{+}$, $JARIDIB^{+}$, $CD133^{+}$, $CD20^{+}$
Lung cancer	$CD133^{+}$, $CD133^{+}/EpCAM^{+}$
Heart cancer	$CD13^{+}$, $CD90^{+}/CD44^{-}$, $CD133^{+}$, $CD24^{+}$
Skin cancer	$CD34^{+}$, Integrin $\alpha_5\beta_1^{high}$
Prostate cancer	$CD44^{+}$/Integrin $\alpha_2\beta_1^{high}/CD133^{+}$

Note: AML (acute myeloid leukemia); ALL (acute lymphoblastic leukemia); ESA (special epithelial antigen); ALDH1 (aldehyde dehydrogenase-1); JARIDIB (H3K4 dematilase); EpCAM (epithelial cell adhesion molecule)

cells or vascular mimicry forms. CSCs have the ability to initiate and retain growth that is important for cancer progression and recurrence. Cancer stem cells can differentiate into cancer cells at different stages when maturation is an indirect process. The presence of signals in certain microenvironment makes the changes that occur to be balanced between cancer stem cells with non-tumorigenic (Gupta et al. 2012).

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THE ROLE OF REACTIVE OXYGEN SPECIES (ROS) IN CANCER STEM CELLS (CSCS)

The ability to renew itself and differentiate and survive in a hypoxic environment, makes cancer stem cells have a high resistance to stress. It is suspected that there are regulators that regulate resistance and prevent differentiation. The state of hypoxia is able to induce ROS and stabilize the hypoxia inducible factor 1α (HIF-1α) which plays a role in cell defense (Shi et al. 2012).

CSCs contain intracellular ROS in lower levels compared to non-tumorigenic cells, as well as an increase in antioxidant expression. CD44 is an adhesion molecule

expressed in various types of cancer stem cells. CD44v (CD44 isomer variant) in gastrointestinal cancer stem cells can trigger the amount of intracellular glutathione antioxidant (GSH) through xCT stabilization, the bright chain subunit of the glutamate-cystine exchange transporter in the plasma membrane. The function of xCT on cell surfaces is to increase the sharpness of cystine which is a substrate for GSH synthesis. xCT is very important in controlling intracellular redox status. CD44v removal inhibits xCT activity and results in an increase in the number of ROS and activates p38MAPK. This is shown in the observation of the number of ROS detected by DCFH-DA staining in $CD44^{low}$ or CD44-cancer cells which is more than CD44high cancer cells. The silencing of CD44 through interferent RNA triggers an increase in the amount of ROS. The target of CD44v therapy can interfere with ROS defenses that might kill these CSCs (Shi et al. 2012).

Research on breast CSCs with $CD44^{+}$/ $CD24^{-}$ markers shows an increase in the cell's defense system against ROS through overexpression of antioxidant enzymes, compared to non-tumorigenic cells. Antioxidants neutralize abundant ROS causing low ROS levels and increase the amount of CSCs. Therefore, a low amount of ROS is associated with tumorigenicity and radiation resistance. Therefore, to reduce clonagenicity and sensitivity to radiotherapy, an increase in the amount of ROS in cancer stem cells can be carried out (Diehn et al. 2009). Kim et al. (2012) also showed that increased CD13 expression could reduce ROS and increase the defense of liver CSCs through the process of transforming growth factors and inducing epithelial transitions into mesenchymal. CD13 is also associated with an increased amount of antioxidants in human liver cancer stem cells. Glutamate-cystine ligase catalyzes the synthesis stage of GSH, which overexpresses on $CD13^{+}$/ $CD90^{-}$ and $CD13^{+}$. These cells have lower ROS levels than $CD13^{-}$. CD13 can be suppressed using $CD13^{-}$ neutralizing antibodies or ubenimex. These specific compounds block CD13 through the zinc site antagonist process of aminopeptidase-N-domains, resulting in a significantly increased amount of ROS in $CD13^{+}$ cells., This mechanism can be used in cancer therapy with the aim of killing the root cause, namely CSCs (Kim et al. 2012).

ROS levels in cancer stem cells are lower than non-tumorigenic and maintain ROS^{low} cells in the overall population. Research on this matter is still very limited. Ramaswamy et al. found that breast cancer cell proliferation produced "Go-like" progeny through asymmetric division. Go-stage cells showed lower intracellular ROS counts and decreased Akt. Inhibition of the Akt signaling pathway in cancer cell proliferation results in an increase in the ratio of asymmetric division and the production of large numbers of ROS^{low} cells with slow growth. The stimulator dynamically modulates the turn of Akt signaling, symmetric cleavage to asymmetric in order to obtain an equilibrium between the number of cancer and nontumorigenic stem cells activity (Shi et al. 2012; Dey-Guha et al. 2011).

This explains, that the production of cancer cells with the characteristics of stem cells and ROS^{low} cells during proliferation, aims to protect new CSCs. The population protects the "tumor seed" from DNA damage which facilitates tumor propagation. ROS^{low} cells can be enriched after chemotherapy in breast cancer patients. ROS^{low} cells can be targeted during cancer therapy. Increasing the amount of ROS exogenously can kill cancer stem cells. Niclosamide is a potential agent that increases the amount of ROS selectively kills AML $CD34^{+}/CD38^{-}$ stem cells which are minimal cytotoxicity against progenitor cells in normal bone marrow cells from healthy individuals. The antineoplasmic mechanism of niclosamide is likely to inactivate the NF-κB pathway (Shi et al. 2012; Jin et al. 2010).

CONCLUSION

ROS basically is produced by the body to maintain homeostasis and maintain the life of beings. High levels of ROS trigger cancer. An exogenous increase in the number of ROS shows it can kill cancer cells selectively. Low ROS levels are associated with the stemness of CSCs. CSCs play a role in the proliferation and defense system of cancer against oxidative stress. Therefore, modulation of ROS levels in CSCs by administering ROS triggering agents at certain levels or inhibiting antioxidants, can be used as an alternative cancer therapy.

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