MINI-REVIEW

Roles of Oxidative Stress in the Development and Progression of Breast Cancer

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Abstract

Oxidative stress is caused by an imbalance in the redox status of the body. In such a state, increase of free radicals in the body can lead to tissue damage. One of the most important species of free radicals is reactive oxygen species (ROS) produced by various metabolic pathways, including aerobic metabolism in the mitochondrial respiratory chain. It plays a critical role in the initiation and progression of various types of cancers. ROS affects different signaling pathways, including growth factors and mitogenic pathways, and controls many cellular processes, including cell proliferation, and thus stimulates the uncontrolled growth of cells which encourages the development of tumors and begins the process of carcinogenesis. Increased oxidative stress caused by reactive species can reduce the body's antioxidant defense against angiogenesis and metastasis in cancer cells. These processes are main factors in the development of cancer. Bimolecular reactions cause free radicals in which create such compounds as malondialdehyde (MDA) and hydroxyguanosine. These substances can be used as indicators of cancer. In this review, free radicals as oxidizing agents, antioxidants as the immune system, and the role of oxidative stress in cancer, particularly breast cancer, have been investigated in the hope that better identification of the factors involved in the occurrence and spread of cancer will improve the identification of treatment goals.

Keywords: Oxidative stress - breast cancer - free radicals - reactive oxygen species (ROS)

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Introduction

Today cancer is a major health problem and a common cause of death worldwide. Cancer results from uncontrolled cell growth and proliferation caused by mutations in DNA by the carcinogenesis process, or carcinogenic (drugs and chemicals), biological (viruses), or physical (radiation) agents. Mutations in DNA convert proto-oncogenes into oncogenes; then oncogene expression changes, cell proliferation is increased, and ultimately normal cells are transformed into malignant neoplastic cells. The characteristics of cancer cells include loss of contact inhibition, resistance to apoptosis, and insensitivity to cell growth arrest signals. Angiogenesis is a chief characteristic of cancer cells (Visvader and Lindeman, 2008; Klaunig et al., 2010; Fiaschi and Chiarugi, 2012; Siegel et al., 2013).

Among cancers, breast cancer is the most common cancer in women and has the highest mortality rate in the world (Park et al., 2014). Every year 502,000 women die from this disease. The etiology of breast cancer is multi factorial, its major risk factors being age, early menarche, delayed menopause, use of contraceptives or oral medications, hormone therapy, family history, history of benign breast disease, obesity, and having excess weight. The mentioned risk factors show their effects through oxidative stress (Gönenç et al., 2006; Nelson, 2006; Izquierdo et al., 2008; Badid et al., 2010; Gupta et al., 2012).

Damage caused by oxidative stress is involved in many types of diseases, including neurological diseases (Alzheimer's and Parkinson's), diabetes, atherosclerosis, arthritis, inflammation, and, most importantly, broader types of cancer including breast cancer (Gonenc et al., 2005; Aldini et al., 2010; Kruk and Duchnik, 2014).

Oxidative stress is an imbalance in the ratio between oxidants (free radicals) and antioxidants, a condition in which the body's redox and oxidation reactions - resuscitation problems arise. Disorders are caused by the increasing of the imbalance between production and removal of free radicals and reactive species in the body (Chandra et al., 2000; Tandon et al., 2005; Dayem et al., 2010; Omar et al.,2011). Many cellular processes, including cell metabolism, signaling pathways, pathways regulating gene expression, cell proliferation, and apoptosis (programmed cell death), are affected by oxidative stress (Chandra et al., 2000; Poli et al., 2004; Kim et al., 2013). Increasing the free radicals changes the structure and functions of the main bimolecular body,

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including changes in proteins, lipids, and nucleic acids, and can lead to tissue damage. Products derived from this injury are used as biomarkers of oxidative stress in the assessment and diagnosis of all cancers. Especially breast cancer (Gonenc et al., 2005; Dayem et al., 2010; Sosa et al., 2013).

Free Radicals (oxidants)

Because of non-bonding electrons, free radicals have a tendency to react with other compounds and act as electron acceptors or oxidizing agents. The main oxidants include reactive oxygen species (ROS), nitrogen (RNS), chloride (RCS), and sulfur. The most important antioxidant and major cause of oxidative damage to the body's bimolecules is ROS. ROS also plays an important role in the formation of reactive species such as RNS (Yoshikawa and Naito, 2002; Gonenc et al., 2005; 2006; Sosa et al., 2013).

Internal sources of ROS include mitochondria, peroxisome, the inflammatory cells (neutrophils, eosinophils, and macrophages), flavin, adrenaline and dopamine, quinones, the enzyme complex cytochrome P450, NADPH oxidase, and xanthine oxidase. External sources of ROS can be environmental pollution, radiation, optical radiation, and chemical compounds including anti-cancer drugs, smoking, and alcohol (Valko et al., 2006; Aldini et al., 2010; Sosa et al.,2013). Reactive oxygen species include superoxide anion ($O2^-$), hydroxyl radical (OH), and hydrogen peroxide (H_2O_2) as the most reactive hydroxyl radicals, and ROS is generated from H_2O_2 and metals such as iron via the Fenton reaction (Noda et al., 2001; Barrera, 2006; Klaunig et al., 2010). The first and most important ROS in the body is superoxide anion, which is generated during oxidative phosphorylation reactions and electron transport along with a respiratory chain in the mitochondrial inner membrane (the main source of ROS). This active species reacts with other compounds to cause other types of reactive oxygen and nitrogen (Gonenc et al., 2005; Sosa et al., 2013). As noted earlier, the objectives of ROS, proteins, lipids, and nucleic acids, metabolites resulting from the injuries which are used as a biomarker of oxidative stress in various diseases and cancers, including breast cancer (Valko et al., 2006; Waris and Ahsan, 2006; Ananda et al., 2013).

Antioxidants

Antioxidants are the body's defense mechanisms against oxidants that maintain redox status and remove reactive species, and the balance of redox reactions plays an important role in the body (Gupta et al., 2013). The most important and frequent antioxidant enzymes, including catalase (CAT), glutathione peroxidase (GPX), superoxide dismutase (SOD), and non-enzymatic antioxidants including vitamin E, vitamin C (ascorbic acid), vitamin A, flavonoids, albumin, glutathione, thioredoxins, uric acid, metabolites of polyphenols, and metal ions shelators such as ferritin and transferrin are ceroplasmin (Gönenç et al., 2006; El-Hefny et al., 2009; Aldini et al.,2010; Omar et al., 2011; Sosa et al., 2013). The main forms of superoxide dismutase in the body include Zn/Cu-SOD and Mn-SOD in the cytoplasm, mitochondria, and lysosomes, which catalyse the dismutation of superoxide anion into hydrogen peroxide (Valko et al., 2006; Aldini et al., 2010). Catalase in the peroxisome is the most abundant antioxidant enzyme that causes hydrogen peroxide to degrade into water and oxygen. Glutathione peroxidase (GPX) by glutathione (GSH) causes hydrogen peroxide and lipid hydroperoxides to be reduced to water and alcohol related. During this process GSH is oxidized to GSSG with a disulfide bond, which eventually becomes revitalized by a glutathione reductase enzyme (El-Hefny., 2009; Aldini et al., 2010).

Biomarkers of Oxidative Stress

The best and most common method to measure free radicals and oxidative stress is to determine the products of the reaction of free radicals with bimolecules as a biomarker. The biomarkers of oxidative stress are very important clinically, and the evaluation of body tissue and fluids is used to diagnose pathological conditions, diseases, and cancer types. The polyunsaturated fatty acids (PUFA) in cell membranes are the primary targets of ROS, which are oxidized during the process of lipid peroxidation (LPO). The products of LPO, including metabolites such as malondialdehyde (MDA), 4 - hydroxynoneal (4-HNF), and acrolein that, through binding to proteins and functional changes, cause enzyme inhibition and receptor changes and consequently cell injury. Studies indicate that MDA, as an indicator of LPO and biomarker of oxidative stress, increases in various cancers, including breast cancer (Gonenc et al., 2005; Omar et al., 2011; Sreenivasa and Kumari, 2012). ROS also targets nucleic acids. Hydroxyl radicals react with DNA and induce cross-linking, causing changes in the deoxyribose. Metabolites resulting from oxidative damage to DNA are thymine glycol and 8-hydroxydeoxy guanosine (8-OHdG). One common product of oxidative damage to DNA and a main marker of oxidative stress is 8-hydroxyguanosine (8-OHdG), which accumulates in breast tumor cells. Therefore, it may be useful in clinical diagnoses and can be used as a tumor marker (Yoshikawa and Naito, 2002; Klaunig et al., 2010). Glutathione is an antioxidant and reducing compound in the body which exists in two forms: resuscitation (GSH) and oxidized (GSSG). In healthy individuals, the highest level of GSH is related to its reduced form (GSH). Therefore, an increase of GSSG in cells and tissue can be a marker of oxidative stress. Studies indicate that GSH decreases in the blood of patients with breast cancer, thus acting as a biomarker of oxidative stress (Martínez Sarrasague., 2006; Valko et al., 2007; Badjatia et al., 2010; Vieira et al., 2011; Delwar et al., 2011).

Oxidative Stress and Cancer

Previous studies have demonstrated that oxidative stress is associated with carcinogenesis and the incidence of cancer. During the carcinogenesis process, the level of reactive oxygen species in cancer cells increases and levels of antioxidants dwindle. ROS in these cells can increase under the influence of intrinsic or extrinsic

factors, resulting in induction gene mutations and changes in transcriptional processes as well as changes in signaling pathways and, ultimately, the occurrence of cancer (Gao et al., 2003; Hwang et al., 2007). Contributory factors in the increased production of ROS in cancer cells can be referred to as cancer-associated fibroblasts (CAFs), cancer-associated macrophages (CAMs), and hypoxia. CAMs produce ROS via NADPH oxidase in tumor cells. ROS derived from CAMs in tumor cells causes increased expression of the hypoxia-inducing factor (HIF-1α) and signaling proteins such as vascular endothelial growth factor (VEGF), which eventually leads to angiogenesis and tumor progression. CAFs within CAMs also contribute to increases of ROS in tumor cells, and thus, with the release of matrix metalloproteinases (MMPs), cytokines induce tumor metastasis and migration, which stimulates the growth of cancer cells. In addition, hypoxia through the impairment of complex III (cytochrome b oxidoreductase) of the mitochondrial respiratory chain and the activity of NADPH oxidase of macrophages play important roles in aggregate ROS and the intrinsic oxidative stress in tumors. Thus, the hypoxia participates in the induction of tumor angiogenesis and promotes cancer (Barrera, 2012; Fiaschi and Chiarugi, 2012; Sosa et al., 2013). Studies have shown that oxidative stress affects several signaling pathways associated with cell proliferation (Soliman et al., 2014). Among them the epidermal growth factor receptor signaling pathway (EGFR) can be mentioned, in which proteins such as the nuclear factor erythroid 2-related factor2 (Nrf2) and Raf are involved. Furthermore, the mitogen activated protein kinases (MAPKs), phosphatidyl inositol 3-kinase (PI3K), phospholipase C, and protein kinase C, are affected by oxidative stress. ROS also alters the expression of the p53 suppressor gene that is key in apoptosis. Thus, oxidative stress caused by changes in gene expression, cell proliferation, apoptosis, and angiogenesis plays a significant role in tumor initiation and progression (Matsuzawa and Ichijo, 2008; Nguyen et al., 2009; Wiemer, 2011; Barrera, 2012).

Oxidative Stress and Breast Cancer

As mentioned before, destruction caused by oxidative stress has an impressive role in the occurrence and progression of breast cancer. Studies suggest that in this disease oxidative stress is increased. Many mechanisms are effective in enhancing oxidative stress, including genetic variations in antioxidant enzymes, estrogen therapy, and excess reactive oxygen species (Badid et al., 2010; Omar et al., 2011). Tumor cells produce more free radicals compared with normal cells; thus, they are influenced by oxidative stress. Because of that, markers of oxidative stress have been identified in samples of breast carcinoma. Numerous factors through different mechanisms are involved in increasing reactive oxygen species of breast tumor cells; some of them will be described in this section. Thymidine phosphorylase enzyme is highly expressed in most breast cell carcinoma and plays an important role in the production and enhancement of ROS in cancer cells. This enzyme causes the degradation of thymidine to thymine and 2 deoxi-D-ribose phosphate. A rise in gene expression of thymidine phosphorylase in breast tumor cells is the main cause of oxidative stress in these patients (Brown and Bicknell, 2001). Lactoperoxidase enzyme involved in the metabolism of estrogenic hormone is produced in the mammary gland via the oxidation of 17-estradiol panoxyl radicals, which causes oxidative stress in breast carcinoma (Sipe et al., 1994). Inflammation, a process in a variety of cancers, also takes place in breast cancer and involves immune cells, including macrophages and neutrophils, in the immune response. Therefore, breast tumors are susceptible to macrophage penetration. Macrophages through NADPH oxidase cause ROS to increase in these cells. These enzymes are regulated by the G-protein Rac-1. This G-protein is encoded by Ras proto-oncogene, Ras and Rac proteins with the domains of GTP-binding having GTPase activity and, by producing superoxide anion as a ROS, have essential roles in the distortion of cells, including fibroblasts (Brown and Bicknell, 2001; Ríos-Arrabal et al., 2013).

Rapid growth in breast tumors is associated with a lack of blood glucose and hypoxia. Glucose deficiency in MCF-7 cells is related to increased production of ROS and oxidative stress. The production of ROS affects various signaling pathways, including those of mitogen-activated protein kinase (MAPKs), so ROS can affect many cellular processes such as proliferation and differentiation, growth control, apoptosis and senescence, metastasis, and resistance against chemo- and radiation therapy. The MAPK family consists of p38α, ERK1 (extracellular-regulated kinase), and JNK (c-Jun N-terminal kinase). They have kinase activity and, via the phosphorylation of various proteins, play a role in controlling messages (Brown and Bicknell, 2001; Martindale and Holbrook, 2002; Erwin et al., 2009). The ERK pathway is activated by mitogenic stimuli, whereas p38 and JNK pathway activity is directly associated with oxidative stress. That is why these proteins are named SAPK (stress-activated protein kinase) (Martindale et al., 2002). AP-1 (activating protein 1) is one transcription factor that is made up of two subunits, Jun and Fos, under conditions of oxidative stress in cancer cells activated by protein kinases including MAPKs, and plays a vital role in cell proliferation and transformation. In other words, increased ROS in cancer cells leads to the activation of p38 and JNK, resulting in hyper-phosphorylation of c-Jun and c-Fos oncoproteins and ultimately AP-1 activation. Thus, many of the affected genes are activated by AP-1 to cell proliferation. Accordingly, the MAPKs pathway and AP-1 participate in cell growth and the occurrence of cancer under conditions of oxidative stress (Brown and Bicknell, 2001; Behrend et al., 2003; Valko et al., 2006). Addition, stimulation of AP-1 activity by the affection of EGF and PDGF causes cell transformation and creates cancer cells. AP-1 also has a role in the balance and regulation of gene expression through Per and anti-apoptotic genes and can act as an inhibitor of apoptosis (Vera-Ramirez et al., 2011). Following the activation of the p38 pathway under conditions of oxidative stress, the phosphorylation of Hsp-27 (heat shock protein) occurs. The phosphorylation of this protein is related to MDA-

MB231 cell migration (Rust et al., 1999; Lee et al., 2009; Schramek et al., 2011). JNK is important in controlling the expression of tumor suppressor genes such as p53. This gene is a tumor suppressor and is significantly involved in programmed cell death (apoptosis), preventing oncogenic changes and regulating antioxidant gene expression. The increase of free radicals in tumor cells is associated with an augmented expression of p53, DNA damage, and ultimately apoptosis. Thus, in response to the increase of ROS in breast cancer cells, JNK activation causes the phosphorylation of p53 and stimulation of apoptosis. However, a steady increase in ROS and oxidative stability in cancer cells cause the inhibition of JNK and induce apoptosis. Hence, the activity of the JNK pathway plays an important management role in apoptosis. Some studies indicate that the inhibition of JNK also causes changes in the cell aging process and correspondingly increases the production of free radicals in mitochondria and causes oxidative damage to DNA in MCF-7 breast cancer cells (Martindale and Holbrook, 2002; Schramek et al., 2011; Fiaschi and Chiarugi, 2012; Raj et al., 2012). P66sch proteins also persuade ROS production by inducing the expression of prolin oxidase. That is why P66sch plays a significant role in p53 activation and apoptosis. Moreover, increased free radicals mutilate the DNA in cancer cells and inactivates the genes that encode p53, ultimately leading to these cells resisting apoptosis (Halliwell, 2007; Vera-Ramirez et al., 2011). Continuous oxidative stress is a result of high levels of reactive oxygen species residue oxidation (Akram et al., 2006). Among oncogenes that are affected by ROS and activated in breast cancer cells, Raf-1 can be named that encoding the serine/threonine kinase involved in cell proliferation signals. An increase of hydroxyl radicals in these cells causes mutations in the Raf-1 gene and protein expression lacking regulatory domain. In this case, division continues without controlled cell proliferation, resulting in the construction of cell mass and cancer development. Growth factors, cytokines, interferons, and interleukins (IL) are other elements that produce active oxygen species (Vera-Ramirez et al., 2011). Consistent with study results, reactive oxygen species derive from interleukin-1-beta (IL-1β) by creating mitogenic signals in MCF-7 breast cancer cells, improving cell proliferation, and consequently increasing the risk of malignancy in patients (Roy, 2006). Growth stimulation factors including PDGF, EGF, IGF and VEGF cause increases in ROS rates in breast cancer cells. Hydrogen peroxide derived from growth factors induces the activation of the AKT pathway in order to improve the proliferation and survival of cells. Therefore, AKT is activated by H_2O_2 stimulus and acts as an anti apoptotic (Brown and Bicknel, 2001; Vera-Ramirez et al., 2011). IGF under conditions of oxidative stress induces the ROS-dependent MAPK activation in MCF-7 breast cancer cells in order for them to proliferate. Therefore, IGF plays a major role in carcinogenesis and tumor creation (Lin et al., 2007). One of the main characteristic of cancer cells is angiogenesis. Blood vessel growth in breast cancer is associated with metastasis and the involvement of other tissue. Vascular endothelial growth factor (VEGF) has a main role in angiogenesis. Hypoxia and oxidative stress together increase the stimulation of VEGF and angiogenesis of breast carcinoma. In other words, they stimulate the quick growth of breast cancer cells and increase the blood current in them, leading to hypoxia within the tumor. Inadequate oxygen in these cells is associated with DNA damage and necrosis. Re-oxygenation of the tumor cells after hypoxia causes increased ROS production. Moreover, hypoxia increases the expression of HIF-1α (hypoxia-inducing factor), that is a Pre-angiogenic factor which, by stimulating VEGF, plays a main role in angiogenesis. VEGF also causes the inhibition of apoptosis and stimulates the activity of free radicals, including the increased activity of nitric oxide synthase (NOS) that is involved in breast cancer. It can be stated that the hypoxia caused by tumor growth increases reactive oxygen species, consequently increasing the expression of HIF-1; then VEGF over-expression is the most significant factor in the initiation and progression of breast cancer. Nuclear factor NF-kB is a transcription factor involved in breast cancer that increases in response to oxidative stress and the peroxide resulting from re-oxygenation. During hypoxia in tumor cells, it activates and stimulates the expression of many genes, including growth factors involved in angiogenesis, such as VEGF and anti-apoptotic proteins like Bcl. Therefore, through increased angiogenesis and inhibition of apoptosis, NF-kB plays a major role in the progression of breast cancer (Brown and Bicknel, 2001; Takada et al., 2003; Storz, 2005; Kimbro and Simons, 2006). With the existing proof, we can conclude that the occurrence of oxidative stress and reduced antioxidant VEGF levels are increased in patients with breast cancer (Brown and Bicknel, 2001; Pande et al., 2011). Redox status and oxidative stress conditions affect the activity of many transcription factors such as Nrf-2. Oxidative stress can activate kinases proteins such as MAPKs, PI3K (phosphatidyl inositol kinase), and PKC (protein kinase C). NRF-2 is activated by these kinases, and thus it is transported from the cytoplasm to the nucleus. In the nucleus Nrf-2 is connected to anti-oxidant response elements (ARE) and elements that promote antioxidant and detoxification genes such as SOD, GPX, and GTS (glutathione-S-transferase) (Surh et al., 2008). According to study results, the absence of NRF-2 in the body leads to a defect in the detoxification process of chemical compounds and increases tumor formation induced by chemical agents (Ramos-Gomez et al., 2003; Kwak et al., 2004). However, NRF-2 plays an important role in the induction of defense factors, such as antioxidants, because it can cause resistance in cancer cells to chemotherapeutic drugs (Wang et al., 2008). In other words, Nrf-2 has a dual function: it causes the prevention of cancer through the induction of antioxidants, and it leads to treatment resistance in cancer cells through the coordinated expression of antioxidant proteins and transport proteins involved in multidrug resistance. In fact, under the influence of NRF-2, the chemical does not accumulate in normal cells but increases the survival of cancer cells resistant to chemotherapy (Meijerman et al., 2008). Phosphatases are the enzymes involved in programmed cell death which affect their activity by oxidative stress. Superoxide dismutase is an antioxidant

enzyme that converts superoxide anions to hydrogen peroxide. SOD actually has a dual role. First, it acts as an antioxidant because it eliminates superoxide anion, and secondly it acts as a prooxidan, because it produces hydrogen peroxide. Thus, H_2O_2, through its effects on protein tyrosine phosphatase (PTPs) and the oxidation of cysteine residues at the active site of these enzymes, leads to inhibition and causes change in the signaling pathway. Thus, the inhibition of SOD on one hand causes the activation of phosphatases and stimulates the process of apoptosis, and on the other hand leads to the inhibition of MAPKs in tumor cells. Tyrosine kinases are enzymes involved in processes such as cell growth and proliferation and are inhibited by tyrosine phosphatase. Thus, the inhibition of PTPs by ROS causes the activation of the tyrosine kinase cascade pathway in cell proliferation and tumorigenesis progression (Vera-Ramirez et al., 2011).

Matrix metalloproteinase (MMPs) have zinc (Zn) in their active site and participate in the metastases of cancer cells (Yadav et al., 2014). Oxidative stress in breast tumor cells, by stimulating metalloproteinase and inhibition anti-proteases, provides an appropriate niche for cell migration and metastasis. Metalloproteinase-1 (MMP-1) is collagen involved in the angiogenesis that is secreted by the effects of oxidative stress and increases the stimulation of growth in tumor blood vessels. MMP-2 is another member of the metalloproteinase family that is activated by the reaction of the thiol group with ROS; it has an important role in the metastasis of breast cancer cells (Rajagopalan et al., 1996; Brown et al., 2000; Artacho-Cordon et al., 2012). Another metalloproteinase is MMP-3 protein. Its expression in cancer cells results in the conversion of Rac-1 to the active form of Rac-1b and increases the production of ROS in cancer cells; subsequently, it causes damage to DNA and chromosomal instability (Colotta et al., 2009). Protease inhibitor proteins play an important role in decreasing migration and tumor cell movement. Free radicals within the tumor environment, by reacting with catalytic groups in the active site of inhibitors, cause their inactivation, the activation of proteases, and the subsequent increases metastases in cancer cells. Some inhibitors can be noted such as proease-1α and plasminogen activator proteins that become inactive via the oxidation of oxidants (Rajagopalan et al., 1996; Swaim et al., 1998). Figure 1 show the relationship between reactive oxygen species with various cellular processes in breast cancer cells.

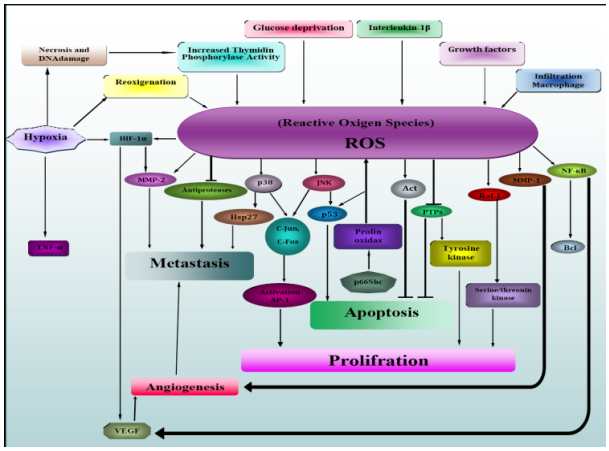

Figure 1. The Mechanisms of ROS in Development and Progression of Breast Cancer

Oxidative stress in cancer cells diminishes tumor cell adhesion to the basement membrane and facilitates their detachment from fibronectin and laminin and their entry into the bloodstream. Cadherin junctions can be noted from connections between cells, and changes in them are associated with rupture of cancer cells and metastases (Thiery, 2002; Wang and Shang, 2012). Free radicals are derived from some estrogen hormones such as the radical Panoxyl of beta – estradiol (Rahman et al., 2010).

In addition to the increase in free radicals, antioxidant changes are related to breast cancer risk. Studies have shown that levels of superoxide dismutase (SOD) and glutathione peroxidase (GPX) are higher in the blood of breast cancer patients than that of normal people. In other words, the active species is responsible for the increased expression of antioxidant elements (ARE), and the outcome arises in GPX and SOD. Increases in SOD are due to a growth in superoxide anion radicals in breast cancer patients (Zhang et al., 2008; El-Hefny et al., 2009; Sreenivasa Rao and Sarala Kumari, 2012).

Studies have shown that SOD activity was augmented in the early stages of the disease; therefore, it can be used as a marker for the diagnosis of breast cancer (Bogdanović et al., 2008).

Glutathione peroxidase (GPX) and catalase (CAT) are enzymes that cause the inactivation of MMP-2 and decrease mass migration of breast cancer cells which are associated with MMPs through the reduction and elimination of hydrogen peroxide (Zhang et al., 2002).

Studies on some patients have indicated that the GPX activity in the blood of breast cancer patients is related to progression of the disease and augments tumor masses. In other words, the improved activity of this enzyme could be a sign of cell proliferation (Sreenivasa Rao and Sarala Kumari, 2012).

Discussion

Carcinogenesis is caused by mutations resulting from damage to DNA. During this process, the expression of genes is altered. So many cellular processes, including cell proliferation and the differentiation process are disrupted. The main cause of damage to DNA is oxidative stress which increases the number of free radicals. Increases in free radicals in tumor cells occur under the influence of various factors such as increased expression of cellular enzymes, the activity of some cell-dependent tumor cells such as CAFs and CAMs, or the metabolism of estrogen. Reactive oxygen species (ROS) are some of the most important free radicals that cause major oxidative damage in the body. These free radicals affect intracellular signaling pathways including MAPKs pathways and several transcription factors such as AP-1. The results of this process, i.e. the creation of non-controlling signaling cascades, increased expression of certain genes, and thus uncontrolled cell proliferation and induced tumor masses, may lead to cancer. Moreover, increased ROS in the tumor environment plays an important role in cancer progression

by altering the expression of suppressor genes involved in apoptosis, increasing the expression of cytokines involved in angiogenesis, creates changes in the connections between cells and their effects on the metalloproteinase activity of proteinase involved in metastasis. In other words, an increase in cell proliferation leading to tumor mass requires a constant blood supply. Hypoxic tumor cells are affected. Hypoxia leads to increased free radicals, stimulates the expression of HIF-1α, VEGF expression, and angiogenesis in the tumor environment. Furthermore, increased ROS leads to a reduction in intercellular adhesion and the activation of metalloproteinases involved in metastasis. This process facilitates the migration of cancer cells to other parts of the body. Thus, increases in free radicals and oxidative stress both play important roles in the development of cancer.

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