Review

Antioxidant Enzymes and Cancer

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ABSTRACT

Although oxidation is the most common biological and energy producing reaction, oxidative stress is harmful to cell, because the products of oxidation such as free radicals and peroxides damage the cellular components, causing several diseases. Damage in DNA is responsible for cancer formation and progression. However, several enzymes such as superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, glutathione S-transferase etc. act as antioxidants to influence oxidative stress. Polymorphisms in these enzymes are supposed to be associated with DNA damage and subsequently the individual's risk of cancer susceptibility. This review article aims to further elucidate the relationship between antioxidant enzymes and cancers by summarizing the findings of some of the important study concerning expression levels and genetic polymorphisms of antioxidant enzymes in cancer patients.

Keywords: Superoxide dismutase; Catalase; Glutathione peroxidase; Glutathione-S-Transferase; Cancer

INTRODUCTION

Oxidation occurs in over one-quarter of the known chemical reactions catalyzed by enzymes in living cells. In many cases, this is accomplished by the transfer of hydrogen atoms or electrons from one molecule to another. Metabolic reactions of this type are the major source of energy for life processes[1]. A paradox in metabolism is that although the vast majority of complex life on Earth requires oxygen for its existence, oxygen is a highly reactive molecule that damages living organisms by producing reactive oxygen species including hydrogen peroxide (H_2O_2), hypo- chlorous acid (HOCl) and free radicals such as the hydroxyl radical (·OH), the superoxide anion (O_2^-) and lipid peroxides[2]. Directly or indirectly, these chemical species of oxygen can transiently or permanently damage nucleic acids, lipids, and proteins. Oxidative damage to these cellular macromolecules is implicated in the genesis of several diseases, including cancer[3,4]. To protect themselves, body maintains complex systems of multiple types of antioxidants, such as glutathione, vitamin C and vitamin E as well as enzymes such as catalase(CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR) and glutathione-S-transferase (GST)[1,4]. These components or enzymes are involved in multiple biochemical reactions to prevent the harmful oxidative damage. Certainly, the genetic polymorphisms of these enzymes and their different expression levels are correlated to the individual's susceptibility to DNA damage and cancer risk.

Oxidative Damage to DNA and Cancer

Oxidative stress plays an important role in carcinogenesis because of induction of DNA damage and its effects on intracellular signal transduction pathways[5]. Reactive oxygen species (ROS) induce almost all forms of DNA damage, including base modifications, base-free (apurinic and apyrimidinic) sites, strand breakage and DNA- protein cross-links, but the specific spectrum of products depends on the reactive species involved. These types of mutation are

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reported in genes whose dysfunction is involved in the genesis of cancer[6]. ROS may also play a key role in cancer development by inducing and maintaining the oncogenic phenotypes of cancers[7]. The highly significant correlation between consumption of fats and oils and death rates from leukemia and malignant neoplasia of the breast, ovaries and rectum among persons over 55 years may be a reflection of greater lipid peroxidation[8].

Currently, oxidative stress has been increasingly postulated as a major contributor to carcinogenesis. The assessment of damage in various biological matrices, such as tissues and cells, is vital to understand the mechanisms of carcinogenesis and subsequently devising intervention strategies. Study on genetic polymorphisms, gain or loss of functions of several antioxidant enzymes such as SOD, CAT, GR, GPx and GST has become important way to understand the development of cancer and its therapies[9].

Expression of Superoxide Dismutase in Cancer

SOD is a class of enzymes that catalyze the dismutation of superoxide into hydrogen peroxide and oxygen. As such, they are important antioxidant defense in nearly all cells exposed to oxygen. A defect in SOD is experimentally proved to be associated with several types of cancer such as hepatocellular carcinoma. Mice deficient in Cu/Zn-SOD showed no overt abnormalities during development and early adulthood, but had a reduced lifespan and increased incidence of neoplastic changes in the liver, and increased cell proliferation in the presence of persistent oxidative damage to macromolecules likely contributes to hepatocarcinogenesis later in life[10]. SOD-2 acts as a downstream mediator of the senescence-associated tumor suppression effect of mac25/insulin-like growth factor binding-protein related protein-1 (IGFBP-rP1) in the suppression of tumor formation and its growth in human breast and prostate epithelial cell lines[11]. Diminished SOD was observed in all brain tumor patients compared to control[12]. It was implicated that SOD has the potential to induce apoptosis through the generation of H_2O_2[13]. Unfortunately high levels of SOD and H_2O_2 are also associated with some cancers. Inflammation in the lung contributing high level of Mn-SOD was supposed to lead to increase H_2O_2 intracellularly and create an intracellular environment favorable to DNA damage and the promotion of cancer[14]. However, the orally active SOD derivative prevented tumor progression promoted by inflammation, which is thought to be through the scavenging inflammatory cell-derived superoxide anion[15]. Er et al[16] reported the differential expression of SOD in patients with breast cancer in Taiwan. They showed that there was no significant difference in Cu/Zn-SOD expression level between neoplastic and tumor-free breast tissues but a significant increase of Mn-SOD expression level in breast cancer tissues. The authors speculated that up-regulation of Mn-SOD expression induced by oxidative stress or local inflammation may contribute a selective growth advantage to tumor cells compared to their normal counterparts. In a recent study, in laryngeal carcinoma, SOD was found in higher amounts in tumor tissue; however, CAT and GPx were lower[17].

Expression of Catalase in Cancer

CAT is a very important enzyme of all living organisms which catalyzes the decomposition of hydrogen peroxide to water and oxygen, while the complete mechanism of CAT is not currently known. In 1960, Mason et al[18] reported that cancer patients had a 22% lower liver CAT activity than cancer-free people. After few years, human liver CAT was found depressed in the epidermis of patients with advanced cancer[19]. Later it was confirmed that hepatic CAT activity is decreased in patients with malignant disease[20].

Decreased CAT activity due to the inflammation in lung was supposed to lead to increase hydrogen peroxide intracellularly and create an intracellular environment favorable to DNA damage and the promotion of cancer[14]. Surapaneni and Sadagopan[21] suggested that there was higher oxygen free radical production and decreased CAT activity, supporting the oxidative stress in breast cancer. Ahn et al[22] evaluated the potential relationship between a functional polymorphism in CAT and breast cancer risk. According to their study, the high-activity CAT CC genotype was associated with an overall 17% reduction in risk of breast cancer compared with having at least one variant allele. The decrease in CAT level and the accumulation of H_2O_2 are significant events for monocyte/macrophage differentiation by TPA (12-O-tetradecanoylphorbol-13-acetate) and the treatment of U937 cells with CAT inhibited the enhancement of ROS generation induced by TPA, and blocked the TPA-induced differentiation of U937 cells[23]. Therapy against breast cancer was also proved effective by increasing CAT activity[24].

Expression of Glutathione Peroxidase in Cancer

GPx and GR act antioxidatively. Reduced glutathione (GSH) present in most cells, can

chemically detoxify H_2O_2 and forms oxidized glutathione (GSSG), catalyzed by GPx. GR reduces glutathione disulfide (GSSG) to the sulfhydryl form GSH and thus regenerate the antioxidative agent again[1,25,26].

Several studies implicated the association of dysfunctional GPx and GR and cancer risk. Loss of heterozygosity of cytosolic GPx1 gene was implicated in lung cancer patients by Moscow et al[27] in 1994. Ratnasinghe et al[28] investigated the association between the proline to leucine polymorphism at codon 198 of hGPx1 (human cellular GPx1) and lung cancer risk. They suggested that due to its high prevalence, the hGPx1 variant may contribute significantly to lung cancer risk among the Caucasians but not among the ethnic Chinese who do not exhibit this polymorphism.

The role of allelic variation within the gene for GPx1 in the risk or etiology of breast cancer was investigated by Hu and Diamond[29]. By analyzing the frequency of a polymorphism within the GPx1 gene resulting in a leucine or proline at codon 198, it was determined that the leucine-containing allele was more frequently associated with breast cancer than the proline-containing allele.

Many studies have shown that selenium increases hGPx1 expression and activity[30,31]. It is generally assumed that selenium increases the antioxidant capacity of a cell, consequently reducing intracellular oxidative stress. The association between prospectively collected serum selenium and lung cancer has been reported in some studies. Most of these studies found that selenium concentration was slightly lower in the lung cancer cases than that in controls[28,32,33]. Epidemiological data have also supported a protective effect for selenium in humans with regard to the prevention of prostate cancer[34,35].

Expression of Glutathione S-transferase in Cancer

Another series of glutathione related important enzyme family is GST. GST family catalyzes the conjugation of reduced glutathione via a sulfhydryl group to electrophilic centers on a wide variety of substrates. This activity detoxifies endogenous compounds such as peroxidized lipids[36].

GSTM1 has been extensively studied as a cancer risk factor. Houlstone[37] reported that GSTM1 status has no effect on the risk of lung cancer. Also, the results of another study indicated that GSTM1 genetic polymorphisms are not associated with breast cancer risk, even in an environment low in antioxidant defenses[38]. The GSTM1 null genotype has also been reported as showing no association with breast cancer by Curran et al[39]. Smith et al[40] found no association of GSTZ1 variant and reported that GSTZ1 does not appear to play a significant role in the development of sporadic breast cancer. However, the GSTM1 null genotype was reported as showing significant association in breast cancer risk by Park et al[41]. A potential effect of the GSTP1 Ile105Val polymorphism genotype on smoking and the risk of prostate cancer was reported by Mao et al[42]. Nomani et al[43] suggested GST measurement as a marker in colorectal cancer, as they found plasma GSTs activity significantly higher in colorectal cancer patients than those obtained from normal individuals. According to Prabhu and Bhat[44], alterations in serum total GST level may have a role in cancer progression.

Expression of All Antioxidant Enzymes Is Not Similar in Different Cancers

In some studies, alterations of different antioxidant enzymes have been also proved to be associated with cancer. The serum levels of SOD, GPx and CAT and vitamin C and E were significantly declined in patients with multiple myeloma whereas malondialdehyde levels were elevated as compared with controls studied recently[45]. A comparative study of the systemic antioxidant activities in red blood cell lysate from subjects with non-small cell lung carcinoma (NSCLC) and healthy control subjects was conducted[46]. In this study, in subjects with lung cancer, there was similar CAT activity, lower SOD activity and higher GPx activity compared with controls.

A significant decrease in CAT and Cu/Zn-SOD activity in adenocarcinoma was proved while Mn-SOD activity was increased[47]. But lower activities of all enzymes i.e., GPx, CAT and Cu/Zn-SOD were found in erythrocytes of prostate cancer patients[48]. A significant alteration in SOD, CAT, GPx, GR activity in blood of prostate cancer patients was also revealed in another study[49]. The SOD and CAT levels were found significantly reduced in tissue samples of oral squamous cell carcinoma (OSCC) patients than that in the control group while in the erythrocytes, CAT level was significantly reduced and the SOD level was higher in OSCC group in comparison with the healthy controls[50].

Rajaraman et al[51] studied nine single nucleotide polymorphisms from seven genes involved in oxidative stress responsers including CAT, GPx1, NOS3, PON1, SOD1, SOD2, and SOD3 and observed increased risk of glioma and meningioma with the C variant of SOD3 rs699473. There was also indication of increased acoustic neuroma risk with the SOD2 rs4880 C(Ala) variant and decreased acoustic neuroma risk with the CAT rs1001179 T allele variant

suggesting that common variants in the SOD2, SOD3, and CAT genes may influence brain tumor risk.

Whole blood CAT and SOD activities were found in reduced level with increased plasmatic thiobarbituric acid reactive substances(TBARS) in acute lymphoblastic leukemia(ALL) patients, indicating a possible link between decreased antioxidants and increased cell alterations due to oxidative damage, supporting the idea that there is a persistence of oxidative stress in ALL[52].

The expressions of CAT and SOD were significantly lower in cancer tissue than that in normal bladder tissue but GPx expression was not significantly different. CAT and SOD expression was also significantly lower in invasive transitional cell carcinomas than that in superficial transitional cell carcinomas but again GPx expression was not significantly different indicating that down-regulation of the antioxidant enzyme system, as indicated by the expression of CAT and SOD, appears to be related to carcinogenesis and progression in bladder cancer[53]. It was showed that total SOD activity was increased, CAT activity decreased and glutathione and GPx were similar in lung tumors compared with tumor-free lung tissues. Alterations in antioxidant activities were attributable to increased Mn-SOD and decreased CAT protein and mRNA expression in tumors. Immunohistochemical localization of CAT in the lung revealed decreased or no expression in the tumor cells, although healthy adjacent airway epithelial cells were strongly positive for CAT. Parallel changes in antioxidant activities, protein, and mRNA expression were noted in lung carcinoma cell line A549 cells when exposed to cytokines (tumor necrosis factor-α, interleukin-1ß, and interferon-γ). Thus, inflammation in the lung may contribute to high levels of Mn-SOD and decreased CAT, which together may lead to increased H_2O_2 intracellularly and create an intracellular environment favorable to DNA damage and the promotion of cancer[14].

Antioxidant Enzymes against Cancer

The well established role of antioxidant enzymes against cancer is to prevent oxidative DNA damage. However, some newly understood mechanisms also exist. For example, over-expression of CAT has been found to delay G_0/G_1 to S-phase transition during cell cycle progression in mouse aortic endothelial cells[54]. CAT transduction made $CD4^+$ T cells less sensitive to H_2O_2-induced loss-of-function, measured by their cytokine production and ability to expand *in vitro* following anti-CD3 stimulation and may also enhanced the resistance to oxidative stress-induce cell death after co-culture with activated granulocytes and exposure to oxidized lipid 4-hydroxynonenal or H_2O_2. Expression of CAT by cytomegalovirus (CMV)-specific $CD8^+$ T cells saves cells from cell death and improved their capacity to recognize CMV peptide-loaded target cells when exposed to H_2O_2. This study indicated that CAT-transduced T cells are more efficacious for the immunotherapy of patients with advanced cancer or chronic viral infections[55].

Much more attempts have been taken by the researchers in cancer therapies. Some attempts include antioxidant therapies among which some were successfully acted against cancer. In a study using animal model, gene therapy with either GPx or Mn-SOD alone slowed tumor growth by 51% and 54% respectively, while the combination of these two suppressed tumor growth by 81% and increased animal survival[56].

Resveratrol is now proved suppressive of colorectal cancer in rats by preventing oxidative stress. Experimental results[9] showed that supplementation with resveratrol (entire-period) treatment regimen significantly increased the enzymatic (SOD, CAT, GR, GPx and GST) and non-enzymatic (reduced glutathione, vitamin C, vitamin E and beta-carotene) antioxidant status with a corresponding decrease in the extent of lipid peroxidation markers.

Taurine increases the expressions of SOD, GPx and CAT genes and thus effective against melanoma [57]. The anticancer activity of Ginkgo biloba extract is supposed to be due to the increasing activity of antioxidant enzymes, including SOD and CAT[58].

These findings encourage the researchers to do future works with antioxidant enzyme therapy and related studies to control cancer.

CONCLUSION

Over the last decades, a considerable number of studies have been done to find out the correlation between cancer susceptibility and the polymorphisms or different expression levels of antioxidant enzymes. Most of the works confirmed the relationship in both similar and different ways. As cancer is one of the most complicated diseases and its pathogenic mechanism is diverse, new studies about genetic polymorphisms and expression levels of several antioxidative enzymes will open new possibilities to understand the pathogenesis of cancers and therapies.

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