*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