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Cancer

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Abbreviations:
ANOVA, analysis of variance.
AT, 3-amino-1,2,4-triazole.
BSO, buthionine sulfoximine.
BCNU, 1,3-*bis*(2-chloroethyl)-1-nitrosourea
CuSOD, Copper zinc superoxide dismutase.
CAT, catalase.
DHEA, dehydroepiandrosterone.
DCFH-DA, 2',7'-dichlorodihydro-fluorescein diacetate
GSSG, glutathione disulfide.
GSH, glutathione.
GR, glutathione reductase.
GS, glutathione synthetase.
G-6-PD, glucose-6-phosphate dehydrogenase.
GPx, Glutathione peroxidase.
H_2O_2, hydrogen peroxide.
$HO^{\bullet}$, hydroxyl radical.
MnSOD, manganese-containing superoxide dismutase
O_2, ground state oxygen.
$O_2^{\bullet -}$, superoxide.
O_2^1, singlet oxygen.
SOD, superoxide dismutase.
ROS, reactive oxygen species.

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Abstract

Cancer is one of the major causes of death in human carcinogenesis. Reactive oxygen species (ROS) containing molecules that have a higher reactivity than ground-state oxygen (O_2), and free radicals, molecules that contain at least one unpaired electron, are postulated to be involved in this development of cancer, especially in the stage of initiation and promotion. Mitochondria is believed to be a major site of ROS production. Cells contain a large number of antioxidants to repair the damage caused by ROS, such as superoxide dismutase (SOD), catalase (CAT), and peroxidase. Each antioxidant enzyme has its own function. MnSOD is the only known enzyme that scavenges $O_2^{\cdot -}$ in mitochondria. Mitochondrial defects can increase the production of ROS resulting in carcinogenesis. Antioxidant treatments for cancers are currently being examined. Some potential experiments related to cancer therapy will be designed.

Introduction

Cancer is a major public health problem. More than 1.6 million Americans develop cancer each year. The outlook for Americans with cancer has improved steadily since the beginning of the 20th century, when few cancer victims survived for very long. By the 1930s, only one out of five cancer patients survived 5 or more years after treatment and was considered "cured." Since then, the cure rate has climbed in almost every decade. During the 1940s, the 5-year survival improved to one out of four; in the 1960s, it was one out of three; and in the 1970s, 38 percent of cancer patients were cured. Today, 51 percent of cancer patients survive for 5 years or more, and the American Cancer Society estimates that an additional 25 percent to 30 percent of cancer deaths could be prevented with earlier diagnosis and treatment [1].

The development of cancer is generally divided into three stages: initiation, promotion, and progression [2]. Reactive oxygen species (ROS), oxygen containing molecules that have a higher reactivity than ground-state oxygen (O_2), and free radicals, molecules that contain at least one unpaired electron, are postulated to be involved in this process, especially in the stage of initiation and promotion [2]. Even though many therapies are being applied to treat various cancers, such as radiation, chemotherapy and surgical treatment, numerous scientists are still seeking a new therapy related to antioxidants which distribute to the inhibition of cancer cell growth. In this paper, we will focus on the key role of ROS in cancer and anticancer effects of antioxidants. Some potential experiments related to cancer therapy will be also discussed.

Reactive Species and Cancer

Reactive oxygen species (ROS) are the side-products generated endogenously by all aerobic cells as a result of the metabolism of oxygen. They are oxygen-containing molecules that have higher chemical reactivity than ground–state molecular oxygen. ROS include not only oxygen-centered radicals such as superoxide oxygen anion ($O_2^{\cdot -}$) and hydroxyl radical ($HO^{\cdot}$), but also molecules such as singlet oxygen ($^1O_2$) and hydrogen peroxide (H_2O_2) [3]. ROS are generated during normal aerobic metabolism, and increased amounts of these species are produced during various forms of oxidative stress [4]. ROS are known to react with various intracellular targets, including lipids, proteins, and DNA. ROS-induced damage can result in cell death, mutations, chromosomal aberrations or carcinogenesis [5]. Mitochondria are believed to be a major site of ROS production according to an endogenous and continuous physiological process under aerobic conditions [6]. Figure 1 shows the formation and the fate of superoxide ions.

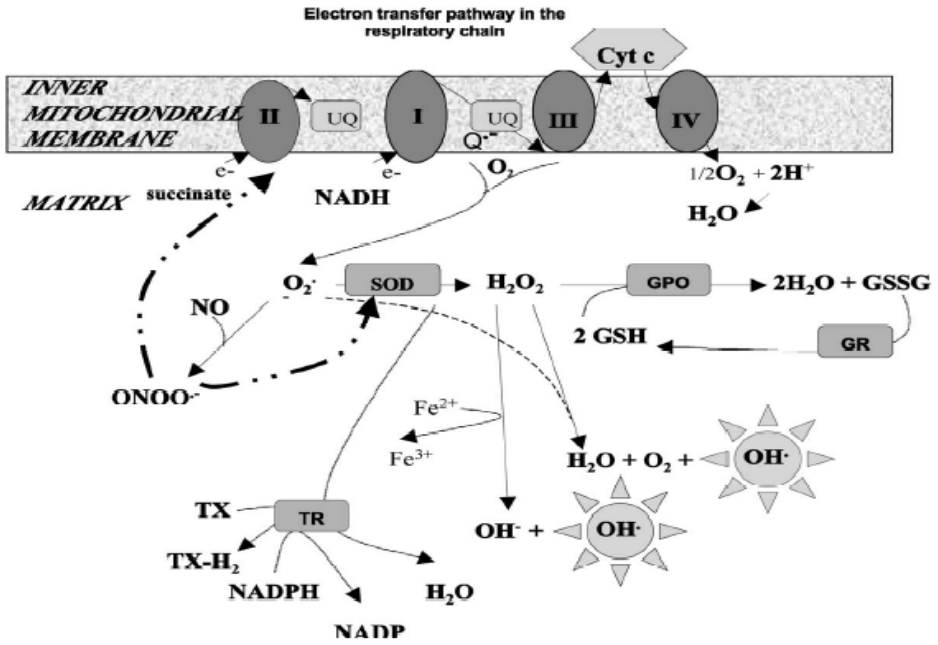

Figure 1. Schematic representation of the formation and the fate of superoxide ions ($O_2^{\bullet-}$) in mitochondria [6].

Superoxide

Superoxide is a reactive anion and free radical, formally $O_2^{\bullet-}$. It has an unpaired electron, is not particularly stable, and spontaneously decomposes into peroxide over time [7]. It is generated *in vivo* in a variety of ways. A major source is the electon transport chains in mitochondria and endoplasmic reticulum. Figure 1 shows that complex I and III are identified as primary components; they can leak electrons onto molecular oxygen and produce superoxide.

Hydroxyl Radical

Oxidative DNA damage from active oxygen species such as hydroxyl radical ($HO^{\bullet}$) has been hypothesized to play a critical role in diverse biological processes including mutagenesis, carcinogenesis, radiation damage, and cancer chemotherapy [8]. Since cellular metabolism generates superoxide ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2), $HO^{\bullet}$ may be produced by a Fenton-type mechanism in which iron reduced by superoxide decomposes H_2O_2. Hydroxyl radical is also

considered to be generated during the reaction of iron with reducing agents in the presence of oxygen.

Hydrogen Peroxide

Oxygen reactive species — H_2O_2, is one of the most powerful oxidizers known, stronger than chlorine, chlorine dioxide, and potassium permanganate [5]. As described above, MnSOD can convert superoxide to hydrogen peroxide which is further catalyzed by catalase and glutathine peroxidase to water. In recent years, much evidence has accumulated suggesting that H_2O_2 at high concentration are cytotoxic, whereas H_2O_2 at low concentration is involved in the regulation of several key physiological processes [3].

Mitochondria Defects in Cancer

Mitochondria plays important roles in cellular energy metabolism, free radical generation, and apoptosis. In general, therefore, inherited mitochondrial defects, whether nuclear- or mitochondrial-encoded, result in severe clinical sequelae that affect the entire organism, or at least affect the main organs, such as the central nervous system and the heart, which have the highest energy consumption [9]. Mitochondrial defects also have long been suspected to play an important role in the development and progression of cancer [4]. Figure 2 shows that the majority of the respiratory chain components are nuclear-encoded and imported into mitochondria after their translation in the cytosol. Thus, oxidative phosphorylation is a unique biochemical process achieved by a well-coordinated effort of the protein products from two separate genomes (nuclear and mitochondrial) working in concert within the same cells.

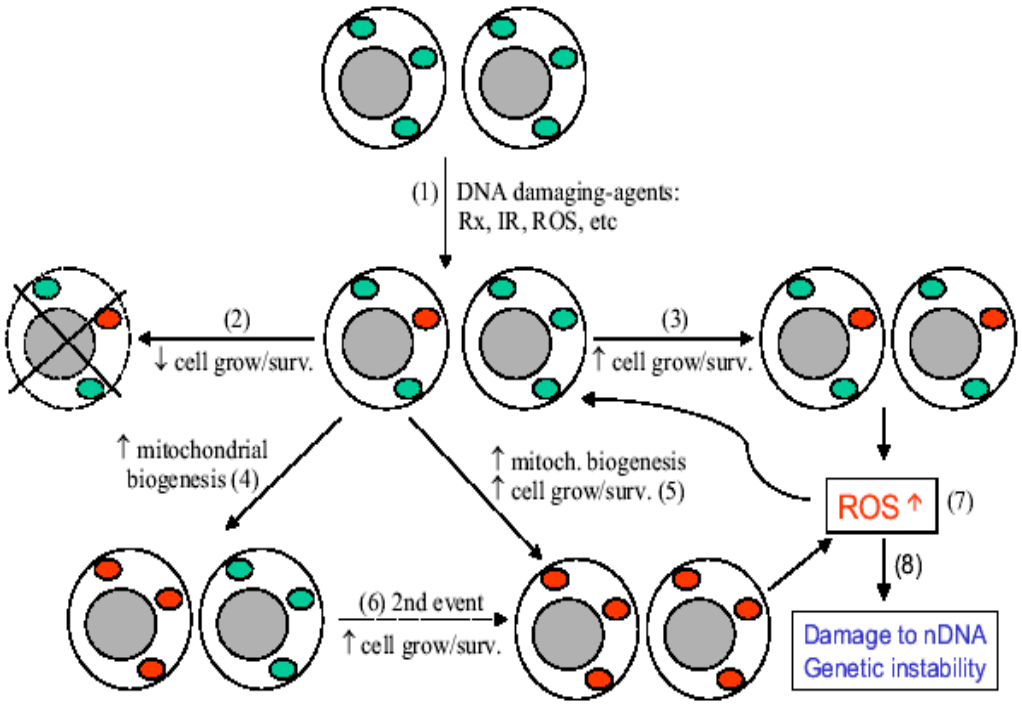

Figure 2. Schematic illustration of somatic mtDNA mutation. Mitochondrial DNA mutations can be induced by endogenous or exogenous DNA-damaging agents such as ROS, chemical agents, and radiation. The numbered arrows indicate possible outcomes of mtDNA mutations, including heteroplasmic and homoplasmic states [4].

It is important to note that as electrons are transported through the respiratory chain during mitochondrial respiration, some of the electrons may escape or leak from electron transport complexes and react with molecular oxygen to form superoxide radicals ($O_2^{\bullet -}$). This diversion of bifurcation of electron flow occurs mainly at complexes I and III [10.11]. It is reasonable to assume that certain mtDNA mutations may cause an alteration of the electron transport components that compromises the normal electron flow. This can lead to an increase of bifurcation and generation of superoxide radicals, which are subsequently converted into other reactive oxygen species (ROS).

Antioxidant Enzymes and Cancer

As described above, ROS are involved in initiation and promotion of cancer. To control the flux of ROS, cells have developed their own defense systems, the antioxidant system, which includes enzymatic and non-enzymatic components. The enzymatic antioxidant defense includes four major enzymes: manganese-containing superoxide dismutase (MnSOD), copper and zinc-containing superoxide dismutase (CuZnSOD), catalase (CAT), and glutathine peroxidase (GPx) [3]. Non-enzymatic antioxidant defense includes ascorbic acid (vitamin C), α-tocopherol (vitamin E), glutathione (GSH), β-carotene, and vitamin A [12]. Next, we will focus on some enzymatic antioxidants.

Manganese-containing superoxide dismutase (MnSOD)

MnSOD is a homotetramer (88 kDa) containing one manganese atom per subunit that cycles from Mn (III) to Mn (II) and back to Mn (III) during the two step dismutation of superoxide [12]. It mainly exists in mitochondria. In most cells, mitochondria consumes over 95% of the cell's oxygen. The mitochondria electron transport chain is believed to be a principal source of endogenous ROS generation. MnSOD is the only known enzyme that scavenges $O_2^{\cdot -}$ in the mitochondria (reaction 1) [3].

$$O_2^{\cdot -} + O_2^{\cdot -} + 2H^+ \xrightarrow{\text{SOD}} H_2O_2 + O_2 \quad (1)$$

Previous studies have shown that the lack of MnSOD gene in *Escherichia coli* and yeast leads to hypersensitivity and oxidative stress [13]. Homozygous mutant mice lacking MnSOD died within the first 10 days after birth and showed dilated cardiomyopathy, accumulation of lipid in liver and skeletal muscle, and metabolic acidosis. Furthermore, mice lacking MnSOD showed degenerative injury of the central nervous system, particularly in the basal ganglia and brain stem associated with damaged mitochondria [13].

Cancer cells are nearly always low in MnSOD [3]. Scientists elevate SOD in cancer cells by exposing cancer cells to superoxide, using liposomes and cDNA transfection [3]. Many studies demonstrated that overexpression of MnSOD can inhibit tumor cell growth. As can be seen from Figure 3, overespression of MnSOD decreases the tumor growth compared with the control.

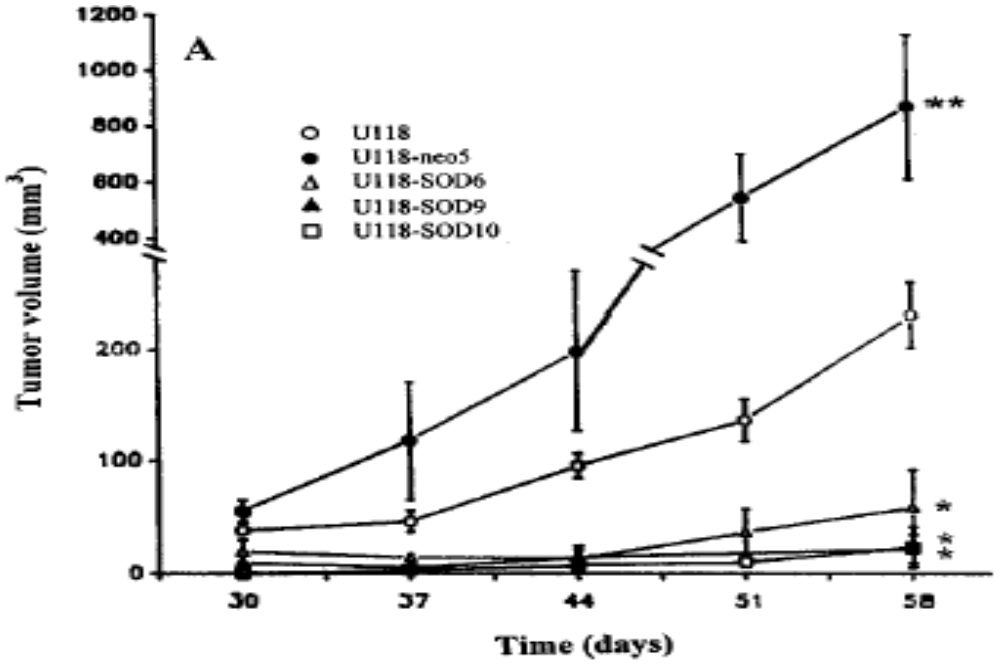

Figure 4. Effect of overexpression of MnSOD on tumorigenicity of U118 cells in nude mice. Neo5, vector. SOD6, SOD9 and SOD10 are MnSOD overexpression transfectants [13].

CuZnSOD

Copper zinc superoxide dismutase (CuZnSOD) is an essential primary antioxidant enzyme that converts superoxide radicals to hydrogen peroxide and molecular oxygen in the cytoplasm. It is a M_r 32,000 dimeric protein that is localized in the cytoplasm [14]. CuZnSOD in this location is thought to remove $O_2^{\bullet -}$ generated by endoplasmic reticulum and cytosolic as well as membrane oxidases. In tumor cells, the activity of CuZnSOD is usually low [3]. One study demonstrated that overexpression of CuZnSOD can inhibit tumor cell growth [15]. From figure 4, it can be

seen that plating efficiency was decreased in cells transduced with *Ad*CuZnSOD compared with wild type and vector control.

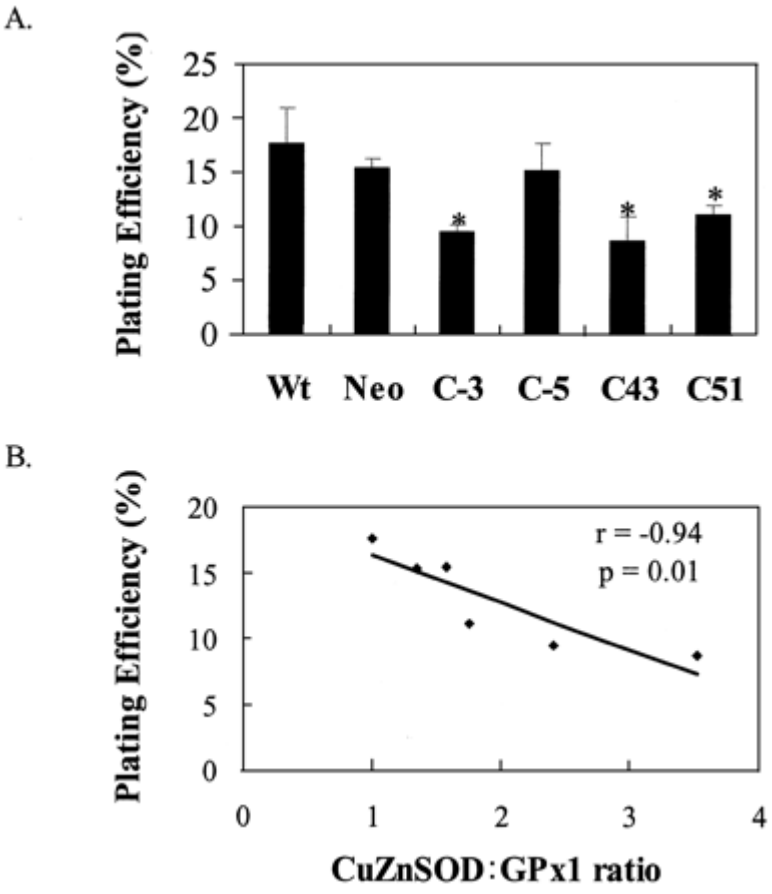

Fig. 4. CuZnSOD overexpression decreased cell plating efficiency; *A*, cell plating efficiency. Wt, wild type U118-9 cells; Neo, vector control; C-3, C-5, C43 and C51 are CuZnSOD overexpression transfectants. *B*, correlation analysis of plating efficiency *versus* CuZnSOD:GPx activity ratio [15].

CAT and GPx

CAT (EC 1.11.1.6) is a tetrameric enzyme consisting of four identical tetrahedrally arranged subunits of 60 kDa that contains a single ferriprotoporphyrin group per subunit, and has a molecular mass of about 240 kDa [16]. CAT reacts very efficiently with H_2O_2 to form water and molecular oxygen (shown as reaction 2).

$$2\,H_2O_2 \xrightarrow{CAT} 2\,H_2O + O_2 \quad (2)$$

In animals, hydrogen peroxide is detoxified by CAT and GPx. CAT protects cells from hydrogen peroxide generated within them. Even though CAT is not essential for some cell types under normal conditions, it plays an important role in the acquisition of tolerance to oxidative stress in the adaptive response of cells. Survival of rats exposed to 100% oxygen was increased when liposomes containing SOD and CAT were injected intravenously before and during the exposure [17]. The increased sensitivity of transfected CAT-enriched cells to some drugs and oxidants is attributed to the property of CAT in cells to prevent the drug-induced consumption of O_2 either for destroying H_2O_2 to oxygen or for direct interaction with the drug [18].

The selenium-containing peroxidase glutathione peroxidase (GPx) (EC 1.11.1.19) contains a single selenocysteine (Sec) residue in each of the four identical subunits, which is essential for enzyme activity. GPx (80 kDa) catalyses the reduction of hydroperoxides using GSH, thereby protecting mammalian cells against oxidative damage. In fact, glutathione metabolism is one of the most essential antioxidative defense mechanisms [12].

$$2GSH + H_2O_2 \xrightarrow{GPx} GSSG + 2H_2O \quad (3)$$

One study double overexpressed MnSOD and GPx1 into PU118-9 cells [2]. They found that overexpression of GPx1 rescues the growth suppression by MnSOD (Figure 5). This evidence indicates that GPX1 is a major antioxidant enzyme that protects cells against lethal oxidative stress.

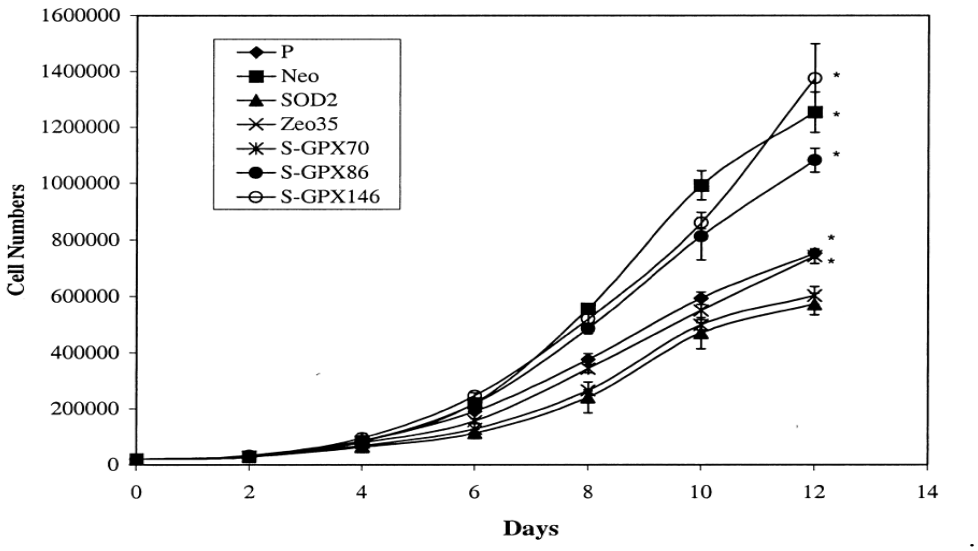

Fig. 5. Effect of GPx1 overexpression on cell growth *in vitro*. P, wild type PU118-9 cells; Neo, vector control; SOD2, MnSOD overexpression transfectant; Zeo35, vector control; S-GPxs, MnSOD-GPx1 double transfectants [2].

Therapy of Cancer

Cancer therapy falls into two major categories: treatment intended to control the primary tumor (surgery or radiation), and treatment intended to kill cells that have escaped from the primary tumor (drug therapy). Drugs that are used to kill or control tumor cells include chemotherapy and biologicals (hormones, interferons, interleukins, and growth factors) [19]. Surgery to remove the primary tumor and surrounding tissue is necessary to cure most tumors. About 25 percent of cancers are curable with surgery alone. Radiation therapy by itself can cure an additional 20 percent of cancers such as lymphoma, cervical cancer, and some forms of testicular cancer [20]. Cancer is increasingly being treated with combinations of treatments that produce both a higher cure rate and minimize adverse side effects. In this way, radiation therapy may be administered before surgery to reduce the size of a tumor or to decrease the amount of normal tissue that must be removed with the tumor, in some cases averting the need for

amputation of a limb. Similarly, anticancer drugs may be combined with surgery or radiation to increase the possibility of curing a cancer that has spread.

Besides the therapies described above, scientists are seeking other new therapies for cancer. Based on mechanisms of cancer and key role of ROS, scientists have found that elevation of antioxidant enzymes combined with anticancer drugs can inhibit tumor cell growth *in vitro* and *in vivo*. We hope that this promising antitumor combination will be applied to clinical trials in the future.

Potential Experiments Related to Cancer Therapy

According to what is discussed above, oxygen reactive species are being implicated in the pathogenesis of cancer. Some antioxidant enzymes distribute to inhibit the growth of tumor cells. Each antioxidant enzyme has its own function. Figure 6 shows us the antioxidant enzyme scheme.

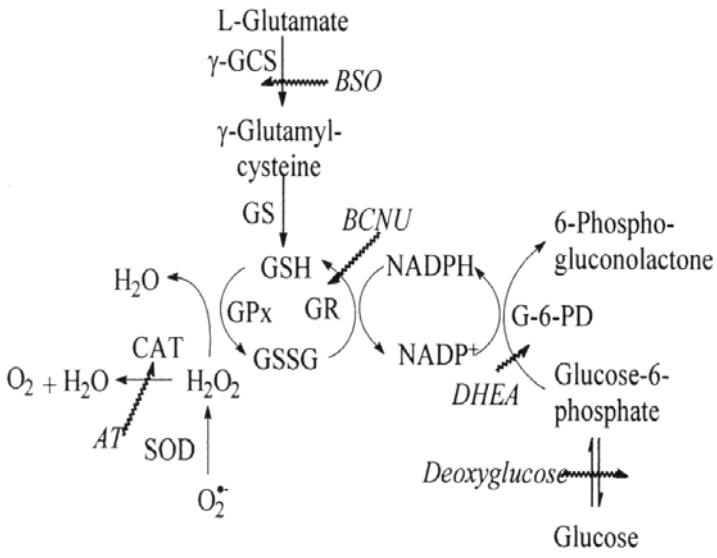

Figure 6. Antioxidant enzyme scheme. *g*-GCS, *g*-glutamylcysteine synthetase; G-6-PD, glucose-6-phosphate dehydrogenase; GR, glutathione reductase; GS, glutathione synthetase; GSH, glutathione; GSSG, glutathione disulfide; H_2O_2, hydrogen peroxide; $O_2^{\bullet-}$, superoxide. The inhibitors of the pathway are also shown: AT, 3-amino-1,2,4-triazole; BCNU, 1,3-*bis*(2-chloroethyl)-1-nitrosourea; BSO, buthionine sulfoximine; deoxyglucose, 2-deoxy-D-glucose; DHEA, dehydroepiandrosterone [3].

As can be seen from figure 6, besides the different function of antioxidant, there are five chemical agents which can inhibit the different antioxidant activities. Here, we will just focus on 3-amino-1,2,4-triazole (AT) and 1,3-*bis*(2-chloroethyl)-1-nitrosourea (BCNU) which can inhibit CAT and GR. We hypothesize that Ad*MnSOD* or Ad*CuZnSOD* combine 3-amino-1,2,4-triazole (AT) and 1,3-*bis*(2-chloroethyl)-1-nitrosourea (BCNU) will cause accumulation of hydrogen peroxide and decrease tumor cell growth.

Determination of different levels of antioxidant enzymes

Even though MnSOD, CAT and CuZnSOD activities are usually low in most cancer cells [3], testing the level of different antioxidant enzymes and their activities in a certain tumor cell line is an important step. Western blot can be down to see the expressions of different antioxidant enzymes in tumor cell line compared with that in a normal cell line. Activity gel and activity assay both can be used to test activities of antioxidant enzymes in cells.

Effect of increasing SOD on cancer phenotype

If antioxidant enzymes are important in cancer, then normalization of the levels of these enzymes should result in reversal of at least part of the cancer cell phenotype [3]. Based on this theory, we can increase MnSOD and CuZnSO by adnovirus tranduction of MnSOD cDNA or CuZnSOD cDNA into a tumor cell line in which the SOD is low. To determine if expression and activity of SOD are increased by cDNA transfection, western blot and activity gel are the common methods. Growth curve and clonogenic assay will be a necessary step to see inhibition effect in cancer cells.

Accumulation of hydrogen peroxide

We have known that SOD can convert superoxide to hydrogen peroxide which can further be removed by CAT and GPx. If we combine SOD, AT and BCNU, CAT and GPx can not function

to remove hydrogen peroxide. There should be an accumulation of hydrogen peroxide which will inhibit cancer cell growth. There are two methods to test hydrogen peroxide.

(1) The production of ROS can be assessed using the fluorescent probe specific for H_2O_2, 2',7'-dichlorodihydro-fluorescein diacetate (DCFH-DA), at a concentration of 5 μM. The fluorescent intensity will be evaluated by flow-cytometric analysis. We can use this method to test if H_2O_2 accumulates or decreases in tumor cells after different treatments.

(2) We also can double transduce Ad*MnSOD* and Ad*CAT* or Ad*MnSOD* and Ad*GPx* to tumor cells, and then do a growth curve. We will find that the tumor cell growth increases compared with Ad*MnSOD* alone. This evidence will indicate that MnSOD inhibits tumor cell growth due to hydrogen peroxide cytotoxicity, and can be coverted to harmless product such as water by CAT or GPx.

Therapy combinations used to inhibit tumor growth *in vitro* and *in vivo*

In order to get better anticancer effect *in vitro* and *in vivo*, avoid the cancer cells proliferating again, we expect that the combination of Ad*MnSOD* or Ad*CuZnSOD* with AT, BCNU will lead to a greater increase in the killing of human cancer cells. First of all, tumor cells can be treated with either of them or combination of them, then we do clonogenic assay to see if plating efficiency decreases in combination compared with either of them alone. Trypan blue is also an important method to compare cell killing (%) with different treatments.

Once our hypothesis is demonstrated *in vitro*, animal experiments should be started. Tumor cells will be injected subcutaneously into the flank region of female nude mice, four animals per group, with a 1 cc tuberculin syringe equipped with a 25 gauge needle. Tumors will be allowed to grow until they reach approximately 70 mm^3 ($5 \times 5 \times 5$ mm^3) calculated from the following equation: $TV\ (mm^3) = (L \times W^2)/2$, where TV = tumor volume, L = length, and W = width. Then tumors will be injected Ad*MnSOD* of Ad*CuZnSOD* or combination with AT and BCNU. Tumors

will be subsequently measured every 2 to 3 d using a vernier caliper prior to animal sacrifice. Finally, a curve will be drawn to show the trend of tumor growth with the function of time.

Statistical analysis

Analysis of variance (ANOVA) will be performed for multiple comparison of each dependent variable. P value < 0.05 is considered to be statistically significant. All data is presented as mean $\pm$ SD.

Summary

Cancer is one of the major causes of death in human carcinogenesis. Reactive oxygen species (ROS), oxygen containing molecules that have a higher reactivity than ground-state oxygen (O_2), and free radicals, molecules that contain at least one unpaired electron, are postulated to be involved in this development of cancer, especially in the stage of initiation and promotion. Mitochondria are believed to be a major site of ROS production. Mitochondrial defects can increase the production of ROS resulting in carcinogenesis. Each antioxidant enzyme has its own function. Antioxidant treatments are thoroughly examined.

References

[1]. Gatrell AC, Harman JC, Francis BJ, Thomas C, Morris SM, McIllmurray M. (2003) Place of death: analysis of cancer deaths in part of North West England. *J Public Health Med.* **25:**53-58.

[2]. Li SJ, Yan T, Yang JQ, Oberley TD, Oberley LW. (2000) The role of cellular clutathine peroxidase redox regulation in suppression of tumor cell growth by manganese superoxide dismutase. *Cancer Res*. **60:**3927-3939.

[3]. Oberley LW. (2001) Anticancer therapy by overexpression of superoxide dismutase. *Antioxid Redox Signal*. **3:**46-472.

[4]. Carew JS, Huang P. (2002) Mitochondrial defects in cancer. *Mol Cancer*. **1:**9.

[5]. Benhar M, Engelberg D, Levitzki A. (2002) ROS, stress-activated kinases and stress signaling in cancer. *EMBO Rep*. **3:**420-425.

[6]. Fleury C, Mignotte B, Vayssiere JL. (2002) Mitochondrial reactive oxygen species in cell death signaling. *Biochimie*. **84:**131-141.

[7]. Das UN. (2002) A radical approach to cancer. *Med Sci Monit.* **8:**79-92.

[8]. Fang YZ, Yang S, Wu GY. (2002) Free radicals, antioxidants, and nutrition. *Nutrition*. **18:**872-879.

[9]. Eng C, Kiuru MJ, Fernandez MJ**,** Aaltonen LA. (2003) A role for mitochondrial enzymes in ingerited neoplasia and beyond. *Nature Reviews Cancer.* **3**:193-202

[10]. Say Basili H, Yuksel M, Haklar G, Yalcin AS. (2001) Effect of mitochondrial electron transport inhibitors on superoxide radical generation in rat hippocampal and striatal slices. *Antioxid Redox signal.* **3:**1009-1104.

[11]. Staniek K, Gille L, Kozlov AV, Nohl H. (2002) Mitochondrial superoxide radical formation is controlled by electon bifur cation to the high and low potential pathways. *Free Radic Res*. **36:**381-387.

[12]. Mates JM, Perez-Gomez C, and Castro IND. Antioxidant enzymes and human diseases. *Clin Biochem*. **32:**595-603.

[13]. Takada Y, Hachiya M, Park SH, Osawa Y, Ozawa T, Akashi M. (2002) The Role of reactive oxygen species in cells overexpressing manganese superoxide dismutase: mechanism for induction of radioresistance. *Mol Cancer Res*. **1:**137-46.

[14]. Chang LY, Slot JW, Geuze HJ, Crapo JD. (1988) Molecular immunocytochemisty of the CuZn superoxide dismutase in rat hepatocytes. *J. Cell Biol*. **107:**2169-2179.

[15]. Zhang Y, Zhao WL, Zhang HJ, Doman FE, Oberley LW. (2002) Overexpression of copper zinc superoxide dismutase suppresses human glioma cell growth. *Cancer Res.* **62:**1205-1212.

[16]. Aebi HE. (1980) Enzymes 1: oxidoreductases, transferases. *Methods of enzymatic analysis*, **3:**273–82.

[17]. Turrens JF, Turrens, JD, Crapo, Freeman BA. (1984) Protection against oxygen toxicity by intravenous injection of liposome-entrapped catalase and superoxide dismutase. *J Clin Invest.* **73**:87–95.

[18]. Speranza MJ, Bagley AC, Lynch RE. (1993) Cells enriched for catalase are sensitized to the toxicities of bleomycin, adriamycin, and paraquat. *J Biol Chem.* **268**:19039–19043.

[19]. Eric M. Genden, Ferlito A, Scully C, Shaha AR, Higgins K, Rinaldo A. (2003) Current management of tonsillar cancer. *Oral Oncol.* **39:**337-342.

[20]. Dayananda PWA, Taylor JMG, Whiting DG. (2003) Prostate cancer: progression of prostate-specific antigen after external beam irradiation**.** *Mathematical Biosciences.* **182:**127-134.

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A ROLE FOR MITOCHONDRIAL ENZYMES IN INHERITED NEOPLASIA AND BEYOND

Charis Eng[1, 2], Maija Kiuru[3], Magali J. Fernandez[1] & Lauri A. Aaltonen[3] about the authors