Review Article/บทฟื้นฟูวิชาการ

Oxidative Stress in Pediatric Patients with Acute Lymphoblastic Leukemia.

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Abstract

Oxidative stress is associated with cancers via many mechanisms including lipid peroxidation and DNA damage. The interest in research on the role of free radicals in cancer pathogenesis is increasing. Acute lymphoblastic leukemia (ALL), the most common childhood cancer, is the primary cause of cancer-related mortality in children. Many components given to treat leukemia are associated with free radical production. In addition, the properties of antioxidant compounds for protection and alleviation of side effects of chemotherapy have been reported. However, there are a few reports on oxidative stress and antioxidant status in children with ALL. Therefore, we reviewed this topic for scientific knowledge and future research.

Keywords: Oxidative stress, Antioxidant, Cancer, Acute lymphoblastic leukemia, Pediatric patients

Abbreviations: ALL, Acute lymphoblastic leukemia; CAT, Catalase; GPx, Glutathione peroxidase; H_2O_2, Hydrogen peroxide; $OH^{\bullet}$, Hydroxyl radical; 8-OHdG, 8-Hydroxy-2´-deoxyguanosine; MDA, Malondialdehyde; ROS, Reactive oxygen species; RNS, Reactive nitrogen species; GSH, Reduced glutathione; SOD, Superoxide dismutase; $O_2^{\bullet-}$, Superoxide radical; VC, Vitamin C; VE, Vitamin E

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Oxidative stress

Oxidative stress is a biochemical condition that is characterized by the imbalance between relatively high levels of toxic reactive species, principally consisting of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS), and the defense systems.[1-3]

ROS and RNS are either organic or inorganic molecules formed in vivo via oxidation-reduction reactions and are very reactive. ROS includes both free radicals, including hydroxyl radical ($OH^{\bullet}$) and superoxide radicals ($O_2^{\bullet -}$), and non-radicals, including hydrogen peroxide (H_2O_2) and singlet oxygen.[4] While oxygen is an important substrate in oxidative metabolism in the human body, it can also be partially reduced to form ROS.[4] ROS are essential for life because of their roles in many vital processes such as signal transduction and bactericidal activity of phagocytes.[5]

Oxidative stress in cancer

The biological functions of oxidative stress and its potential role in cancer development and progression have been investigated for several decades. Mantovani et al.[6] demonstrated that ROS levels were significantly higher in cancer patients than controls; moreover, glutathione peroxidase (GPx) and superoxide dismutase (SOD) activities were significantly higher in cancer patients.

There is evidence suggesting that cancer cells are under the increased oxidative stress in association with oncogen-induced transformation, increased metabolic activity, mitochondrial malfunction, and increased generation of ROS compared to normal cells.[7-9] Abnormal growing cell are often infiltrated with inflammatory phagocytes, which can generate large amounts of ROS.[10] In addition, cancer cells are metabolically active; thus, they require a high level of ATP supply for uncontrolled cell growth and proliferation. The demand for high energy produced from the mitochondrial respiration chain contributes to increased ROS generation.[11] Other mechanisms that may lead to the increased oxidative stress in cancer patients include altered energy metabolism due to malnutrition, an excessive production of proinflammatory cytokines, and the use of antineoplastic drugs.[12]

Oxidative damage

A life requires keeping potentially harmful molecules at the lowest toxic level by balancing the production and the scavenging as well as the destruction of those molecules. An imbalance may occur due to the overproduction of free radicals or the decrease in the capacity of the physiological defense systems. Such imbalance leads to oxidative damage, cellular injury, and eventually, diseases. The targets of oxidative damage include biomolecules such as lipids, DNA, and proteins.[13]

Lipid peroxidation

Lipid peroxidation is a free radical chain reaction, causing cell damage through a pathway, which a hydrogen atom is removed from an unsaturated fatty acid. Such removal results in the formation of a lipid radical. Malondialdehyde (MDA) is a product of lipid peroxidation. MDA can also form cross-linking reaction with RNA and DNA. Such cross-links produce DNA-protein cross-links in nucleoproteins, DNA strand breaks, and base pair damage, resulting in mutation.[14]

Oxidative DNA damage

DNA damage, or oxidative DNA damage, caused by ROS is the type of injury that aerobic cells mostly encounter. Numerous DNA lesions have been identified in cells and tissues at steady-state levels and upon exposure to free radical-generating systems.[15] Such damage can produce a multiplicity of modifications in DNA including base and sugar lesions, strand breaks, DNA-protein cross-links, and base-free sites. Accurate

measurement of these modifications is essential for understanding mechanisms of oxidative DNA damage and its biological effects.

Data accumulated over many years clearly show that oxidative DNA damage plays an important role in a number of disease processes such as cancers. Therefore, biomarkers of oxidative DNA damage are used for identifying persons at risk from developing cancers. The measurements of DNA strand breaks have been employed for investigation of oxidative damage to DNA. Moreover, specific types of DNA damage produce DNA adduct.[15-16]

8-Hydroxy-2´-deoxyguanosine (8-OHdG) is one of major DNA adducts. It is a product of oxidative damage by $OH^{\bullet}$ at the C-8 position of guanine in DNA base pair, forming 8-hydroxyguanine. 8-Hydroxyguanine is promutagenic due to its tendency to preferentially pair with adenine over cytosine during DNA replication, leading to G:C to T:A transversion. Some of damaged DNA are repaired by endonuclease and glycosylase enzymes to form 8-OHdG and excreted into urine.[17] Since 8-OHdG has the capability of mutagenicity, it is used as a biomarker of oxidative stress and a potential marker for carcinogenesis.[18]

Antioxidant defense system

The cellular defense mechanisms involve antioxidants in scavenging ROS to protect the organism against oxidative stress. An antioxidant is defined as "any substance that significantly delays or prevents an oxidizable substrate."[13]

The antioxidant defenses can be classified, according to their mechanisms of action into 2 groups: enzymatic antioxidants and non-enzymatic antioxidants.

Enzymatic antioxidants

The free radical produced early from oxygen in aerobic organisms is the $O_2^{\bullet -}$. This primarily species causes proliferation of further radical species, leading to free radical-initiated and -mediated damage. Fortunately, aerobic organisms have evolved to produce enzymatic antioxidants at early levels of defensive mechanism to prevent cells against oxidative radical damage. These enzymatic antioxidants include superoxide dismutase, catalase, and glutathione peroxidase.

Superoxide dismutase (SOD) is a metalloenzyme that catalyzes the dismutation of $O^{\bullet -}$ into H_2O_2.[19] This dismutation is often called the primary defense.[20] There are 3 different SOD isozymes found in mammalian tissues: (1) Cu/Zn-SOD found in the cytoplasm of most cells, (2) a high molecular weight Cu/Zn-SOD found in extracellular fluid such as plasma, and (3) Mn-SOD present within the mitochondria compartment. These enzymes catalyze the same reaction, which is the conversion of 2 superoxide anions (and 2 protons) to O_2 and H_2O_2 as shown in the following reaction[13]:

$$2\ O^{\bullet -} + 2\ H^{+} \xrightarrow{SOD} O_2 + H_2O_2$$

In the above reaction, $O^{\bullet -}$ acts as both oxidant and reductant. One $O^{\bullet -}$ donates electron whereas another accepts electron to form H_2O_2.[21] The SOD activity is increased through enzyme induction by chemicals or conditions that increase the production of $O_2^{\bullet -}$.[13]

The body has a defense system including H_2O_2-removing enzymes to prevent the generation of the hydroxyl radical ($OH^{\bullet}$) from H_2O_2.[22,23] Catalase (CAT) is a heme protein, and an enzyme that is involved in H_2O_2 removal. It contains 4 protein subunits, each of which contains a heme group within the active site. CAT presents in most aerobic cells and principally locates in peroxisomes. However, it is found to a lesser extent in the cytoplasm. This may be because CAT removes H_2O_2 that is generated by oxidase enzymes located within the peroxisomes. In human tissues, there is a very high concentration of CAT in

liver and erythrocytes but relatively much less in brain, heart, and skeleton muscle.[22-24] The general reaction catalyzed by CAT is shown below:

$$2\ H_2O_2 \xrightarrow{\text{Catalase}} 2\ H_2O + O_2$$

CAT is able to use 1 molecule of H_2O_2 as a substrate electron donor and another molecule of H_2O_2 as an oxidant or electron receiver to form water and oxygen.[25]

Glutathione peroxidase (GPx) is the other H_2O_2-removing enzyme. It is a selenium-containing enzyme with a selenocysteine residue present at the active site and essential for enzyme activity. In contrast to CAT, GPx reduces H_2O_2 to water using reduced glutathione (GSH), a tripeptide with a sulfhydryl group, as a substrate. The sulfhydryl group of GSH serves as an electron donor; then GSH is oxidized to glutathione disulfide (GSSG) as in the reaction shown below[13]:

$$2\ GSH + H_2O_2 \xrightarrow{GPx} GSSG + 2\ H_2O$$

Once GSSG is formed, it is reduced back to GSH by glutathione reductase (GR). GR requires NADPH as a source of electron donor. The reaction is shown below[13]:

$$GSSG + NADPH + H^+ \xrightarrow{GR} 2\ GSH + NADP^+$$

In case NADPH is decreased, GSH is depleted, leading to increased oxidative stress.

Non-enzymatic antioxidants

The radicals such as $OH^\bullet$, ROOH, and other substances in biological environments are produced through the interaction between $O_2^{\bullet-}$ and H_2O_2. They cannot be destroyed by the enzymatic antioxidants. Moreover, $OH^\bullet$ has extremely high reactivity and rapid consumption. In the human body, there are non-enzymatic antioxidants that scavenge those free radicals. The well-known non-enzymatic antioxidants include GSH, vitamin E (VE), vitamin C (VC), and β-carotene. VE, VC, and β-carotene are antioxidant vitamins, which cannot be synthesized by most mammals including human; therefore, the human body needs to get those compounds from dietary sources.[26]

Glutathione is a tripeptide consisting of glycine, cysteine, and glutamic acid. It is moved between reduced form (GSH) and oxidized form (GSSG), in which 2 tripeptides are linked by a disulfide bond. The levels of GSH are maintained in a high intracellular concentration by activities of glutathione synthetase and GR. GSH participates in a variety of detoxification, transport, and metabolic process. It involves in conjugation to drugs to make them more water-soluble, transport of amino acid across cell membranes, leukotriene biosynthesis, and rearrangement of protein disulfide bond. In addition, it plays a key role in detoxification of H_2O_2 and organic peroxides, which are the harmful byproducts for an aerobic life.[27]

In the presence of GPx, GSH is converted to GSSG as mentioned earlier. Then, GSSG can be reconverted to GSH by GR in coupling with NADPH + H^+. The NADPH is mainly produced in the pentose phosphate pathway. GSH is very important in maintaining stability of cell membranes including the erythrocyte membranes.[27]

Vitamin E is a lipid-soluble vitamin in humans. VE occurs naturally in 8 different forms: 4 tocopherols (α-, β-, γ-, and δ- tocopherols) and 4 tocotrienols (α-, β-, γ-, and δ- tocotrienols).[28] α-Tocopherol is the most active form of VE in humans. It is a powerful biological antioxidant for it is the major membrane bound antioxidant in the cell.[29] Generally, the term VE can be used interchangeably with α-tocopherol. Therefore, VE in this review means α-tocopherol.

α-Tocopherol (α-TocH) is mainly present in low density lipoprotein (LDL) particles and the membranes.[30] It functions *in vivo* as a free radical chain

breaker, especially for polyunsaturated fatty acids (PUFAs) at cell membranes and other sites of lipid accumulation.[20] The α-tocH interferes with the propagation step of lipid peroxidation in PUFAs by scavenging lipid peroxyl radicals (ROO() as shown in the reaction below[13]:

$$\alpha\text{-TocH} + ROO^{\bullet} \longrightarrow \alpha\text{-Toc}^{\bullet} + ROOH$$

When α-tocH reacts with ROO(, (-tocopheryl radical ((-toc() is formed and the chain reaction of lipid peroxidation is terminated. (-Toc(can react with another ROO(, producing a covalent adduct as shown in the reaction below:

$$\alpha\text{-Toc}^{\bullet} + ROO^{\bullet} \longrightarrow \alpha\text{-Toc-OOR}$$

Thus, each molecule of α-tocH can scavenge 2 molecules of ROO•. Alternatively, α-toc• can react with VC at the surface of membranes and lipoproteins to regenerate the α-tocH as shown in the diagram below:

$$\alpha\text{-Toc}^{\bullet} + \text{Ascorbate} \longrightarrow \alpha\text{-TocH} + \text{Ascorbate}^{\bullet}$$

(or semidehydroascorbate)

Several epidemiological trials demonstrated the effects of VE supplements on cancers. White et al.[31] reported a case control study involving 251 men and 193 women diagnosed with colorectal cancer in 1985-1989. Their results showed that patients who had the average the intake of VE at the dose of 200 IU/day over 10 years had the lower incidence of colorectal cancer compared with non-VE users.

Vitamin C is a water-soluble antioxidant, which efficiently scavenges OH•, peroxyl radicals (ROO•), and $O_2^{\bullet -}$. VC is found in the cytoplasm and extracellular fluid.[26] Donation of 1 electron by ascorbate to ROS gives the non-reactive substance and the semi-dehydroascorbate radical, which undergoes further oxidation by another ROS, giving the dehydro-ascorbate. Dehydroascorbate is unstable; therefore, it is irreversible changed by a complex series of reactions to oxalic and threonic acid. In human, there is dehydroascorbate reductase, the glutathione-dependent enzyme, which is responsible for the conversion of dehydroascorbate back to ascorbic acid.[32] Alternatively, the semidehydroascorbate may be directly reduced to ascorbate by the enzyme NADH-semidehydroascorbate reductase.

VC has been shown to scavenge aqueous superoxide and hydroxyl radicals.[33] VC indirectly protects lipid membranes by regenerating the active form of membrane-bound VE.[34] The high levels of VC in neutrophils are shown to provide to cellular and host tissue protection during the respiratory burst, in which free radicals are produced.[34]

The majority of evidence relating VC to cancers is from epidemiologic studies. Many studies demon-strated that the decrease in cancer incidence in the population was associated with increased dietary intake or tissue levels of VC.[35]

Oxidative damage in ALL

The results from several studies have shown that there is abnormality in oxidative-antioxidative balance in children with ALL. Compared to healthy children, increased lipid peroxidation and higher endogenous level of OH(-induced DNA products are found in patients with ALL.[36,37]

Pongrapeeporn et al.[38] showed that 20 adult patients, newly diagnosed ALL, had significantly higher levels of MDA in plasma as well as erythrocytes of adult patients with ALL compared to controls. The authors assessed the activities of creatine kinase (CK) and lactate dehydrogenase (LDH), indices of tissue membrane damage. They found that the activity of total CK in plasma of patients was not significantly

different from that in controls. However, the activity of total LDH was significantly higher in patients, indicating that erythrocytes and other tissues were damage by ROS.[38]

Singh et al.[39] showed that a significant increase in MDA levels was observed in 15 pediatric patients with different stages of ALL (aged 9-14 years) compared to controls. According to Brown et al.[40], the source of lipoperoxides is most likely the circulating lymphoblast. Furthermore, they investigated the possible role of concentrations of products from lipid peroxidation as a marker of disease activity in ALL. In that study, an increase in MDA levels during the active phase of disease was found. In contrast, MDA levels were significantly decreased in remission; although the patients in remission were still undergoing chemotherapy known to enhance lipid peroxidation. Miyuki et al.[41] reported that urinary 8-OHdG concentration was significantly elevated in pediatric patients with ALL compared to controls.

Antioxidant status in ALL

Yamanaka et al.[42] found that L1210 leukemic cell line and human leukemic cells had reduced activity of Mn-SOD, which could lead to increased accumulation of $O_2^{\bullet-}$. Pongrapeeporn et al.[38] showed that 20 adult patients who were newly diagnosed ALL had significantly lower concentration of VC, VE, and β-carotene compared to controls.

Concerning the antioxidant status of pediatric patients with ALL, few reports have been found. Devi et al.[5] reported that 16 pediatric patients with ALL (aged 1-12 years) had a significant increase in the amount of $O_2^{\bullet-}$, generated by the leukocytes, as well as the activities of erythrocyte SOD and GPx compared to the controls. They also demonstrated an apparent increase in H_2O_2 with no statistical significance. Senturker et al.[43] conducted a study in 9 pediatric patients with ALL and 10 children without disease to determine the activities of SOD, CAT, and GPx in lymphocytes. They found that the activities of SOD, CAT, and GPx in lymphocytes of patients with ALL were significantly decreased compared to those in children without the disease.

Since patients with ALL receive a combination of chemotherapy, which may increase the free radical load, they are vulnerable to damage caused by the increased free radical production. Kennedy et al.[44] found a significant decrease in Oxygen Radical Absorbance Capacity (ORAC), concentration of plasma VE and total carotenoids in pediatric patients with ALL after chemotherapy. They also demonstrated that low concentration of plasma total carotenoids was a prediction of an increased risk of chemotherapy-related side effects during the first 6 months of treatment.

Recently, we conducted a study to determine oxidative stress and antioxidant status in pediatric patients with ALL at the time of diagnosis and during chemotherapy. Our preliminary results showed that, at the time of diagnosis, pediatric patients with ALL had higher activities of SOD, GPx, CAT as well as higher levels of MDA and 8-OHdG than normal subjects. Moreover, we found that patients had lower level of GSH, plasma VE and VC than healthy counterparts. During chemotherapy, patients in our study had decreased plasma VE and VC. Moreover, their levels of MDA and 8-OHdG remained high at 6 months after treatment. In addition, amount of their dietary VE and VC intakes also decreased during treatments.

A number of studies suggests that the supplementation of antioxidant vitamins ameliorates damage, which is caused by free radical during cancer therapy, to adjacent normal cells in patients with malignancy at various sites.[45] Kennedy et al.[46] showed the beneficial effect of a combination of VE and VC supplementation for 1 year in 20 patients with prostatic or gynecological malignancy. Their results demonstrated that cancer patients with chronic radiation

proctitis had a significant improvement in the symptom index. Weijl et al.[45] conducted a randomized, double-blind, placebo-controlled trial in 44 cancerous patients to investigate the effects of VC, VE, and selenium supplemented for 1 year on episodes of nephrotoxicity and ototoxicity induced by cisplatin. Their results showed that loss of high-tone hearing was significantly decreased in patients with the highest plasma concentration of 3 antioxidant micronutrients.

Currently, we have conducted a study of anti-oxidant vitamin supplementation in pediatric patients with ALL to determine the effects of those vitamins on oxidative stress and clinical outcomes. The study is ongoing.

Conclusion

There is a body of evidence indicating that patients with ALL have the persistence of oxidative stress. In addition, they suggest that low antioxidant status may be associated with neoplastic activity and subsequently poor health.

The results from observational studies indicate that childhood ALL is related to increased plasma MDA levels, increased DNA damage, and decreased activities of antioxidant enzymes. In addition, cancer treatments enhance oxidative stress by reduced plasma antioxidants levels and increasing free radical production and lipid peroxidation. The results of our ongoing study about the supplementation of anti-oxidant vitamins in childhood ALL may throw new light on the treatment outcomes.

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Review Article/บทฟื้นฟูวิชาการ

ภาวะ oxidative stress ในผู้ป่วยเด็กโรคมะเร็งเม็ดโลหิตขาวลิมโฟบลาสชนิดเฉียบพลัน

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บทคัดย่อ

ภาวะ oxidative stress มีความเกี่ยวข้องกับการเกิดโรคมะเร็งผ่านหลายกลไก รวมถึงการออกซิเดชั่นของไขมันและการทำลาย DNA ด้วย ปัจจุบันมีงานวิจัยที่น่าสนใจเกี่ยวกับบทบาทของอนุมูลอิสระในกระบวนการเกิดมะเร็งมากขึ้น โรคมะเร็งในเด็กที่พบบ่อยที่สุดคือ โรคมะเร็งเม็ดโลหิตขาวลิมโฟบลาสชนิดเฉียบพลัน (ALL; Acute lymphoblastic leukemia) ซึ่งพบว่าเป็นสาเหตุการเสียชีวิตอันดับหนึ่งของผู้ป่วยเด็กที่เป็นมะเร็ง นอกจากตัวโรคเองแล้ว การรักษาโรคนี้ด้วยวิธีต่างๆมีผลทำให้อนุมูลอิสระเพิ่มขึ้น มีรายงานเกี่ยวกับการให้สารต้านอนุมูลอิสระเพื่อช่วยป้องกันและลดผลข้างเคียงของการรักษาโรคมะเร็งชนิดนี้ อย่างไรก็ตามการศึกษาเกี่ยวกับสภาวะ oxidative stress และสารต้านอนุมูลอิสระในผู้ป่วยเด็กโรคมะเร็งเม็ดโลหิตขาวลิมโฟบลาสชนิดเฉียบพลันยังมีน้อย ดังนั้นผู้เขียนจึงได้ทบทวนบทความเรื่องนี้เพื่อเป็นความรู้และนำไปประยุกต์ใช้สำหรับงานวิจัยต่อไป