Cancer and Oxidative Stress

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Abstract: Oxidative stress is closely related to all aspects of cancer, from carcinogenesis to the tumor-bearing state, from treatment to prevention. The human body is constantly under oxidative stress arising from exogenous origins (e.g., ultraviolet rays) and endogenous origins (at the cellular level where mitochondria are involved). When such oxidative stress exceeds the capacity of the oxidation-reduction system of the body, gene mutations may result or intracellular signal transduction and transcription factors may be affected directly or via antioxidants, leading to carcinogenesis. The tumor-bearing state is also said to be under oxidative stress associated with active oxygen production by tumor cells and abnormal oxidation-reduction control. One of the mechanisms by which anticancer agents and radiation therapy exert their effects is through apoptosis of cancer cells. Oxidative stress is also involved in the problem of resistance to these treatments. The efficacy of antioxidants in the prevention of carcinogenesis is currently under investigation. Issues to be addressed in the future include the establishment of easy, accurate methods of measurement and evaluation of the extent of oxidative stress in the body as well as the clinical application of experimentally obtained knowledge to the prevention and treatment of cancer.

Key words: Carcinogenesis; Anticancer drugs; Redox; Thioredoxin

Introduction

The terms "free radicals" and "active oxygen", having attracted the attention of large numbers of people, are now topics of daily conversation. This paper discusses cancer and oxidative stress in terms of the following five points: (1) Oxidative stress in the human body; (2) methods of evaluating oxidative stress; (3) the relation between oxidative stress and carcinogenesis; (4) the tumor-bearing state and oxidative stress; and (5) the application of experimental results to the treatment and prevention of cancer.

Oxidative Stress in the Human Body

Human beings are constantly bombarded by exogenous factors such as ultraviolet rays and

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tobacco smoke that cause oxidative stress. Such stress can also arise from drugs (including anticancer drugs) that are used in medical practice. In addition to those exogenous sources, endogenous sources of oxidative stress include those derived from activities of mitochondria or microsomes and peroxisomes in the electron transfer system and those from the enzyme NADPH present in macrophages and neutrophils as a mechanism of protection against infection. It is clear that injuries to cells by such stresses are too significant to be ignored.

Various reducing substances in the human body control the status of oxidation-reduction (redox), and a continuing imbalance in favor of oxidation causes various problems when it exceeds the capacity of such control.

Methods to Evaluate the Degree of Oxidative Stress

Possible methods by which to evaluate oxidative stress include (1) measurement of active oxygen species themselves, (2) detection of oxidized DNA and lipids, and (3) quantification of antioxidants. However, the actual measurement and evaluation of these agents involve various problems,[1] because a large number of substances are involved in the oxidation-reduction system. Moreover, these substances are intertwined in a complex manner through cross talk. Therefore, interpretation of the results requires consideration of the type of sample, sampling site, substance to be measured, and method of measurement. It may be difficult to achieve accurate measurement because the targets of measurement are often unstable substances and because the difference in their concentration compared with the background level is often very small.

A method for the detection of oxidized DNA, the 8-hydroxydeoxyguanosine assay, was reported in 1986.[2] This method is now widespread use because of its simplicity, which derives from the use of high performance liquid chromatography. Many substances, including other DNA oxides and lipid peroxides, have been proposed as markers of oxidative stress. As markers of the redox status in the body, measurements are also being carried out on antioxidants such as superoxide dismutase (SOD), catalase, vitamins E and C, β-carotene, uric acid, and glutathione.

The measurement of reliable markers of oxidative stress is indispensable for future clinical practice, for examining oxidative stress in relation to carcinogenesis, and for determining the effects of antioxidants on cancer. Free radicals and antioxidants can exert varying influences on cells according to their concentration, thus underlining the need for advances in studies pursuing easy, accurate quantitative procedures. It is also important to keep in mind which element of the entire redox mechanism is being examined when interpreting the results.

Relation between Oxidative Stress and Carcinogenesis

Active oxygen may be involved in carcinogenesis through two possible mechanisms: the induction of gene mutations that result from cell injury and (2) the effects on signal transduction and transcription factors. Which mechanism it follows depends on factors such as the type of active oxygen species involved and the intensity of stress.[3]

Cellular targets affected by oxidative stress include DNA, phospholipids, proteins, and carbohydrates on the cell membrane. Oxidized and injured DNA has the potential to induce genetic mutation. That some telomere genes are highly susceptible to mutation in the presence of free radicals, is now apparent and it is known that tumor suppressor genes such as p53 and cell cycle-related genes may suffer DNA damage. In addition, oxidized lipids react with metals to produce active substances (e.g., epoxides and aldehydes) or synthesize malondialdehyde, which has the potential to induce mutation.

Active oxygen species act directly or indi-

rectly via DNA damage on gene expression (DNA binding of transcription factors) and signaling at the cellular level. Some antioxidants play a role in such signal transduction. Two examples are glutathione and thioredoxin, working in the mechanisms of redox regulation.[4)]

The aspect common to these substances is that thiol works as the major subject of redox control, implementing regulation of the activity of transcription factors and taking part in gene expression. It is also known that thioredoxin in the extracellular setting exerts a growth-promoting action and a cytokine-like action on certain cells. This contributes to the activation of protein kinase, the oncogenes Fos and Jun, and the transcription factor NF-κB.

Many studies on oxidative stress and carcinogenesis have been carried out in animal experiments and clinical practice. For instance, metals such as free iron and copper are known to produce free radicals and cause cell injury. Iron administered to post-esophagoduodenostomy rats is also reported to result in the deposition of iron in the esophagus, oxidation of DNA and lipids, and development of esophageal cancer.[5)] In the clinical setting, carcinogenesis related to infection from microorganisms (bacteria and viruses) or nonspecific inflammatory diseases, has been considered an example of the strong involvement of active oxygen in the carcinogenic process. The studies include the relationship between hepatitis B or hepatitis C and hepatocellular carcinoma, that between *Helicobacter pylori*-induced gastritis and gastric cancer, and that between ulcerative colitis and colon cancer.

For instance, *H. pylori* itself produces superoxide as it engages in the production of azo compounds and mutagenic active substances such as peroxynitrite through reaction with nitric monoxide in the gastric juice.[6)] Furthermore, it induces nitric monoxide production from macrophages, and the production of free radicals and secretion of cytokinesis from the gastric mucosal epithelium. As demonstrated by the relation between *H. pylori* and gastric cancer, it is apparent that various phenomena take place and have a role in oxidative stress.

Insufficient antioxidant activity in the body is also considered a risk factor for developing cancer. For example, it was reported that women who have Mn-SOD with amino acid mutation are at a higher risk of developing breast cancer.[7)]

Tumor-bearing State and Oxidative Stress

To determine the state of oxidative stress in cancer tissue and cancer patients, assays of 8-hydroxydeoxyguanosine and other oxidants and antioxidants have been performed locally as in the tissues of solid cancer and systemically as in the blood and urine.[8)] Factors considered to be involved in this condition of oxidative stress are the production of active oxygen by tumor cells themselves and by activated neutrophils and macrophages, and abnormality in antioxidants controlling the redox status.

One of the possible clinical applications of oxidative stress status in cancer is the use of oxidative stress markers as tumor markers. As an example, it has been suggested that the blood Mn-SOD level in ovarian cancer may be useful as a tumor marker.[9)]

Although thioredoxin, mentioned above, works as a redox-controlling agent, it is also involved in gene expression and exerts a growth-promoting effect on other cells in the extracellular environment. Therefore it is possible that its increase as a scavenger in oxidative stress in cancer may serve in turn, as a tumor growth promoter.[10)] Increased blood levels of thioredoxin have been reported in various types of cancer, including liver cancer.[11)] However, the details of how such increases actually operate in the body remain unclear.

The relationships between the various oxidation-reduction substances under cancer-derived oxidative stress are considered complex. The answers to the possibilities mentioned above may vary according to the type of tumor, its progression, and the condition of the indi-

vidual patient, such as whether antioxidants in the body under oxidative stress are increased by promoted expression or decreased by elimination, and whether treatment to reduce the active oxygen species or the oxidative stress promotes or inhibits tumor growth.

Oxidative Stress and the Treatment and Prevention of Cancer

1. Anticancer drug therapy and oxidative stress

In general, treatment with anticancer drugs and radiation creates a state of oxidative stress in the body, and active oxygen triggers apoptosis via p53 and cytochrome release from mitochondria. Anticancer drugs whose main mechanisms of action involve active oxygen include the anthracyclines (represented by adriamycin), bleomycin, mitomycin C, and cisplatin. Redox control is also involved in various issues related to anticancer drug therapy. It is possible that excessive antioxidation mechanisms take part in a tumor's acquisition of drug resistance. Thioredoxin and glutathione also play roles in the resistance to anticancer drugs. An attempt to improve the efficacy of anticancer drugs by decreasing thioredoxin expression in cisplatin-resistant cancer cells has been reported in the literature.[12)]

Secondary cancer associated with the use of anticancer drugs or radiotherapy is another area of investigation. A temporary decrease in antioxidants (vitamins C and E, uric acid, etc.) in the plasma of patients with osteosarcoma or testicular tumor after cisplatin-based chemotherapy has been reported.[13)] Although the main cause is considered to be the consumption of antioxidants to eliminate the oxidative state, persistent imbalance in the redox state in the body due to anticancer treatment may also be a cause in cases of secondary cancer associated with anticancer drugs or radiotherapy.

With regard to the side effects of anticancer drugs, if it is possible to ensure that tumor cells receive more damage than do normal cells, this may be useful for reducing both the therapeutic dose of anticancer drugs and their side effects.

2. Preventive and therapeutic efficacy of antioxidants

Given the relation between oxidative stress and cancer, it has been assumed that ingestion of antioxidants such as vitamins E and C and β-carotene is useful in preventing carcinogenesis, and various related investigations have been implemented.[14)] Inhibition of inflammation using antioxidants has also been studied in relation to the risk of carcinogenesis, as in the nonspecific inflammatory disease mentioned above.[15)] This approach is expected to become useful for the prevention of cancer in the long run. However, it is possible that antioxidants may play a role as prooxidants, as has been suggested for vitamin C.[16)] Which antioxidants and the amount to ingest to obtain a preventive effect remain under investigation. The benefit of antioxidant ingestion after cancer has also yet to be demonstrated.

Conclusion

Oxidative stress causes injury to cells, induces gene mutation, and is involved in carcinogenesis by influencing intracellular signal transduction and transcription factors directly or indirectly via antioxidants. Easy, accurate methods of measuring oxidative stress in the human body are indispensable for investigating the relationship between it and disease and for applying the results of such research to clinical practice. Methods of measurements also still require improvement in terms of technology and interpretation of the results. The state of oxidative stress in carcinogenesis and tumor-bearing conditions is an intricate one in which various substances are involved in complex interactions. Further investigations are expected before application can be made to the prevention and treatment of cancer in the clinical setting.

REFERENCES

1) Halliwell, B.: Can oxidative DNA damage be used as a biomarker of cancer risk in humans? Problems, resolutions and preliminary results from nutritional supplementation studies. *Free Radic Res* 1998; 29: 469–486.
2) Floyd, R.A., Watson, J.J., Wong, P.K. *et al.*: Hydroxyl free radical adduct of deoxyguanosine: sensitive detection and mechanisms of formation. *Free Radic Res Commun* 1986; 1: 163–172.
3) Mates, J.M., Perez-Gomez, C. and Nunez de Castro, I.: Antioxidant enzymes and human diseases. *Clin Biochem* 1999; 32: 595–603.
4) Arrigo, A.P.: Gene expression and the thiol redox state. *Free Radic Biol Med* 1999; 27: 936–944.
5) Chen, X., Ding, Y.W., Yang, Gy. *et al.*: Oxidative damage in an esophageal adenocarcinoma model with rats. *Carcinogenesis* 2000; 21: 257–263.
6) Pignatelli, B., Bancel, B., Esteve, J. *et al.*: Inducible nitric oxide synthase, anti-oxidant enzymes and Helicobacter pylori infection in gastritis and gastric precancerous lesions in humans. *Eur J Cancer Prev* 1998; 7: 439–447.
7) Ambrosone, C.B., Freudenheim, J.L., Thompson, P.A. *et al.*: Manganese superoxide dismutase (MnSOD) genetic polymorphisms, dietary antioxidants, and risk of breast cancer. *Cancer Res* 1999; 59: 602–606.
8) Kondo, S., Toyokuni, S., Iwasa, Y. *et al.*: Persistent oxidative stress in human colorectal carcinoma, but not in adenoma. *Free Radic Biol Med* 1999; 27: 401–410.
9) Ishikawa, M., Tamate, K. and Sengoku, K.: Free radicals and disease. Diseases in obstetrics and gynecology. *Gendai Iryo* 1999; 31: 2579–2585. (in Japanese)
10) Grogan, T.M., Fenoglio-Prieser, C., Zeheb, R. *et al.*: Thioredoxin, a putative oncogene product, is overexpressed in gastric carcinoma and associated with increased proliferation and increased cell survival. *Hum Pathol* 2000; 31: 475–481.
11) Miyazaki, E., Noda, N., Okada, S. *et al.*: Elevated serum level of thioredoxin in patients with hepatocellular carcinoma. *Biotherapy* 1998; 11: 277–288.
12) Yokomizo, A., Ono, M., Nanri, H. *et al.*: Cellular levels of thioredoxin associated with drug sensitivity to cisplatin, mitomycin C, doxorubicin, and etoposide. *Cancer Res* 1995; 55: 4293–4296.
13) Weijl, N.I., Hopman, G.D., Wipkink-Bakker, A. *et al.*: Cisplatin combination chemotherapy induces a fall in plasma antioxidants of cancer patients. *Ann Oncol* 1998; 9: 1331–1337.
14) Terry, P., Lagergren, J., Ye, W. *et al.*: Antioxidants and cancers of the esophagus and gastric cardia. *Int J Cancer* 2000; 87: 750–754.
15) Kimura, I., Kumamoto, T., Matsuda, A. *et al.*: Effects of BX 661 A, a new therapeutic agent for ulcerative colitis, on reactive oxygen species in comparison with salazosulfapyridine and its metabolite sulfapyridine. *Arzneimittelforschung* 1998; 48: 1007–1011.
16) Podmore, I.D., Griffiths, H.R., Herbert, K.E. *et al.*: Vitamin C exhibits pro-oxidant properties. *Nature* 1998; 392: 559.