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Forum Editorial

Oxidative DNA Damage: Mechanisms and Significance in Health and Disease

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Reactive oxygen species (ROS) are implicated as a cause of cancer and lifestyle-related diseases. Ionizing radiation and many environmental chemicals generate ROS and damage DNA. ROS are also produced endogenously as a by-product of oxygen metabolism. Therefore, ROS may also be involved in the aging process. 8-Hydroxydeoxyguanosine (8-OH-dG, 7,8-dihydro-8-oxodeoxyguanosine) was discovered in 1983 during an *in vitro* study of DNA modifications caused by mutagens produced by heating carbohydrates, which were being used as a model of cooked foods (9–11). In 1986, Floyd *et al*. developed a sensitive method to analyze 8-OH-dG using an electrochemical detector with high performance liquid chromatography (HPLC–ECD) (4). This method revealed that various ROS-forming carcinogens induce an increase of 8-OH-dG in cellular DNA (12, 13). Ames and his collaborators were the first to detect 8-OH-dG in animal and human urine samples by HPLC–ECD (24, 26). These discoveries triggered further studies on mutagenesis, oxidative DNA damage repair enzymes, and the molecular epidemiology of various ROS-related diseases. Patients with cancer (urine), chronic hepatitis (urine), diabetes (urine, leukocyte DNA), heart disease (leukocyte DNA), Alzheimer's disease (urine), Parkinson's disease (urine), atopic dermatitis (urine), as well as premature babies (urine), showed higher levels of 8-OH-dG (3, 7, 16, 18, 19, 21, 25, 28, 30, 31). In contrast, the consumption of vitamins E and C, lutein, β-cryptoxanthin, vegetables, fruit, green tea, and tomato sauce was correlated with a reduction in the amount of 8-OH-dG in urine or leukocyte DNA (1, 5, 6, 8, 15, 29). Therefore, 8-OH-dG is a useful marker for monitoring cellular oxidative stress involved in the induction of cancer and lifestyle-related diseases and their prevention by antioxidants. During the last 2 decades, publications on 8-OH-dG have increased as shown in Fig. 1. In parallel, publications on urinary 8-OH-dG (Fig. 2) and the inhibition of 8-OH-dG by antioxidants (Fig. 3) also increased.

In this forum, we show that the urinary 8-OH-Gua free base is a better marker than 8-OH-dG for oxidative stress in relation to the maximum lifespan (MLSP) of various animals, as analyzed by the HPLC–ECD method (27). Olinski *et al*. (23) provide exact measurements of the oxidatively damaged products, 8-OH-Gua (8-oxoGua), 8-OH-dG, and 5-hydroxylmethyluracil in urine, by an isotope dilution method with GC/MS. Loft and Moller (17) point out the importance of cohort study to establish a link between oxidative DNA damage and human cancer, by reviewing many published reports on oxidative DNA damage and repair activity, including genetic polymorphisms.

The excess production of oxides of nitrogen may be a risk factor for cancer development in patients infected with hepatic parasites, as well as in hepatitis and other chronic inflammation-related diseases. Therefore, DNA damage induced by reactive nitrogen species may also be an important mechanism of carcinogenesis. Ohshima *et al*. (22) and Kawanishi and Hiraku (14) recently performed a study on oxidative and nitrative DNA damage and carcinogenesis, particularly focusing on the formation of 8-nitroguanine.

Increases in reactive oxygen and nitrogen species due to inflammation induce lipid peroxidation. Various reactive electrophilic compounds can be formed by lipid peroxidation, and some of them react readily with protein and DNA. For example, α,β-unsaturated aldehydes, such as 4-hydroxy-2-nonenal and crotonaldehyde, react with DNA to form 1,N2-propano-dG derivatives and etheno-type adducts via 2,3-epoxy derivatives (2). Matsuda and his collaborators (unpublished observations) successfully detected a crotonaldehyde-dG adduct (CdG) and other endogenous adducts in DNA isolated from healthy human blood with high sensitivity by an LC/MS/MS technique by monitoring the MS/MS transitions corresponding to the loss of deoxyribose from the molecular ion. Using an ultrasensitive immunoaffinity-^{32}P-postlabeling method, Bartsch and his collaborators (20) observed increases in etheno-dA and etheno-dC in tissues from patients affected by the cancer-prone chronic inflammatory diseases, chronic pancreatitis, Crohn's disease, and ulcerative colitis, where oxidative stress and lipid peroxidation are implicated in the disease progression.

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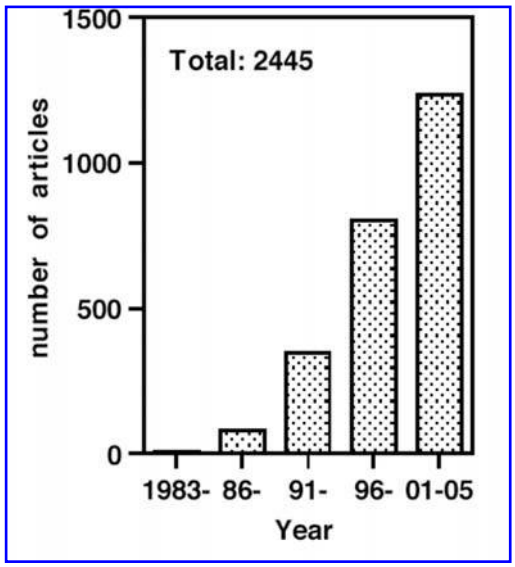

FIG. 1. Publications on 8-OH-dG.

Many authorities in this field have submitted up-to-date manuscripts about oxidative DNA damage and human health. In this forum, representative researchers, mostly employing chemistry-based approaches toward oxidative DNA damage analysis, were selected. Of course, this forum cannot cover all of the active research groups, due to the space limitations. We reconfirmed the importance of DNA protection from oxidative damage for human health. There is a lot of strong circumstantial evidence for a correlation between oxidative DNA damage and human disease. To apply the results of these studies to human health promotion, further experimentation may be required to define the mechanism. The accuracy and sensitivity of oxidative DNA damage detection are still growing, and will facilitate further studies. We hope this forum will contribute toward the establishment of a theoretical basis for health promotion by the control of oxidative damage.

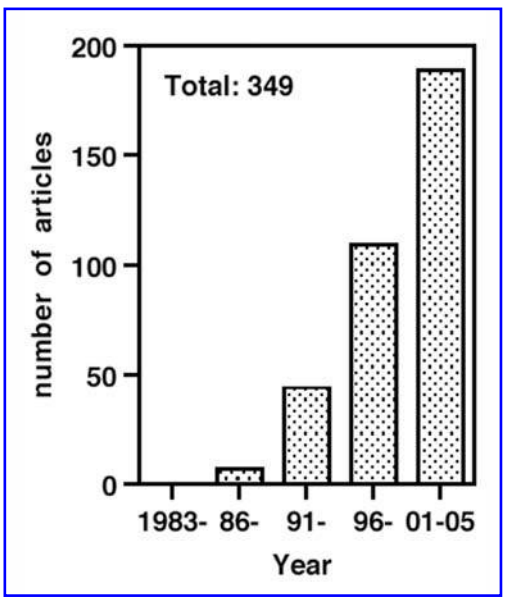

FIG. 2. Publications on urinary 8-OH-dG.

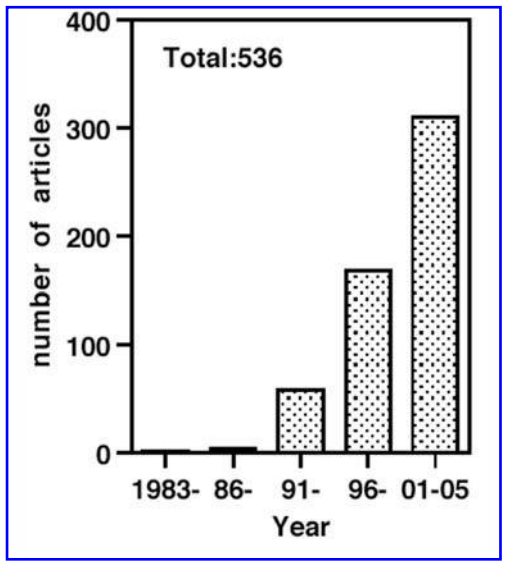

FIG. 3. Publications on inhibition of 8-OH-dG formation by antioxidants.

ABBREVIATIONS

CdG, crotonaldehyde-dG; 8-OH-dG, 8-Hydroxydeoxyguanosine; ROS, reactive oxygen species.

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