8-Hydroxyguanine, an Oxidative DNA and RNA Modification

Hiroshi Kasai and Kazuaki Kawai

Contents

Abstract Reactive oxygen species (ROS), produced by ionizing radiation and many other environmental agents, damage DNA and RNA. They are also endogenously generated in cells by oxygen metabolism. 8-Hydroxy-2′-deoxyguanine (8-OHdG) was first reported in 1983, as a major form of oxidative DNA damage produced by heated sugar, Fenton-type reagents, and ionizing radiation in vitro. 8-OHdG has been detected in cellular DNA by HPLC-ECD and LC/MS/MS methods in many laboratories. The increase in the 8-OHdG level in cellular DNA, detected by these chromatographic methods, is supported by its immunochemical detection and enhanced repair activity. Its analysis in human leukocyte DNA, and in urine and saliva, is a promising approach toward the assessment of an individual's oxidative stress level. The ribonucleoside 8-hydroxyguanosine (8-OHGuo), in tissue RNA and urine, is also a good marker of oxidative stress

H. Kasai (✉) • K. Kawai
Department of Environmental Oncology, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, Japan, Fukuoka, Japan
e-mail: h-kasai@med.uoeh-u.ac.jp; kkawai@med.uoeh-u.ac.jp

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in vivo. The free 8-hydroxyguanine (8-OHGua) base is also detectable in biological samples, such as urine, serum, and saliva. In this chapter, the validity of the general use of 8-OHdG, 8-OHGuo, and 8-OHGua as markers of cellular oxidative stress is discussed.

Keywords Reactive oxygen species • 8-OHdG • 8-oxodG • 8-OHGuo • 8-OHGua • DNA damage • Oxidative stress • Biomarker

Abbreviations

8-OHdG	8-Hydroxy-2′-deoxyguanosine
8-OHGuo	8-Hydroxyguanosine
8-OHGua	8-Hydroxyguanine
ROS	Reactive oxygen species
HPLC-ECD	High performance liquid chromatography equipped with an electrochemical detector
ELISA	Enzyme-linked immunosorbent assay

1 Introduction

Many mutagens and carcinogens react with DNA and induce mutations in cancer-related genes. 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. A major form of oxidative DNA damage, 8-hydroxydeoxyguanosine (8-OHdG, 7,8-dihydro-8-oxodeoxyguanosine), was discovered in Japan in 1983, during a study of DNA modifications generated by heated glucose and ROS-forming agents (Kasai and Nishimura 1983; Kasai et al. 1984a) in vitro (Fig. 1). Since then, various aspects of this type of oxidative DNA damage, such as the mechanisms of its formation, its mutagenic effects, and its repair, have been studied worldwide, clarifying its biological significance. Floyd et al. first developed a sensitive method to analyze 8-OHdG, using an electrochemical detector with high performance liquid chromatography (HPLC-ECD) (Floyd et al. 1986). This method revealed that various ROS-forming carcinogens induce increased levels of 8-OHdG in cellular DNA (Kasai 1997). Ames and his collaborators were the first to detect 8-OHdG in animal and human urine samples by HPLC-ECD (Shigenaga et al. 1989). These discoveries triggered further studies on the analysis of 8-OHdG as a biomarker for risk assessment, the molecular epidemiology of ROS-related diseases, and aging. Patients with various diseases, such as cancer, diabetes, and Alzheimer's disease (urine), showed higher levels of 8-OHdG. In contrast, the consumption of antioxidants, vegetables, fruits, green tea, etc. was

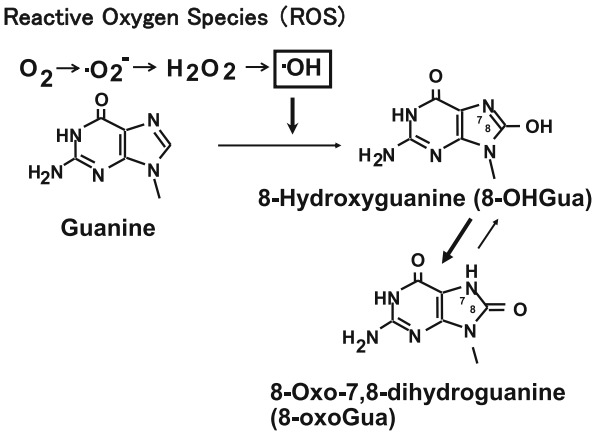

Fig. 1 Formation of 8-OHGua and its tautomeric change

correlated with a reduction in the amounts of 8-OHdG in urine, serum, and tissue DNA. Therefore, 8-OHdG seems to be a useful marker for monitoring the cellular oxidative stress involved in the induction of cancer and in lifestyle-related diseases and their prevention by antioxidants. In addition, the ribonucleoside 8-hydroxyguanosine (8-OHGuo), in tissue RNA and urine, is a good marker of oxidative stress in vivo. The free 8-hydroxyguanine base (8-OHGua) has also been detected in biological samples, such as urine, serum, and saliva. In this chapter, we summarize the studies on 8-OHdG and its related derivatives, reported over the past 32 years, with a particular focus on their usefulness as biomarkers.

2 Discovery of 8-OHdG and Mechanisms of Formation

The formation of 8-OHdG was first detected during a study on DNA modifications caused in vitro by mutagenic heated carbohydrates, which were being used as a model of cooked foods (Kasai et al. 1984a). Methylreductic acid and hydroxymethylreductic acid were later isolated and identified from heated carbohydrates as major ROS-forming mutagenic compounds (Kasai et al. 1989). Various ROS-forming agents, such as Fenton-type reagents (Kasai and Nishimura 1984b), ionizing radiation (Kasai et al. 1984b), metals (Kasai and Nishimura 1984c), cigarette smoke condensate (Kasai and Nishimura 1991), and asbestos (Kasai and Nishimura 1984a), also effectively promoted the formation of 8-OHdG in DNA in vitro. A hydroxyl radical ($^{\bullet}$OH) is involved in these reactions. The formation of 8-OHGua in vitro was most efficient with the monomer nucleoside, as compared to that in RNA and DNA polymers (described later in detail). A preliminary account of these results was reported in 1983 (Kasai and Nishimura 1983). Floyd and his collaborators found that methylene blue plus visible light specifically induces 8-OHdG in DNA without a strand break, suggesting the involvement of singlet oxygen in that reaction (Schneider et al. 1990). In collaboration with Cadet's group,

Kasai et al. found that riboflavin plus visible light induces 8-OHdG in DNA by a non-singlet oxygen mechanism; namely, via a guanine radical cation followed by a hydration reaction (Kasai et al. 1992). As an interesting example, Barton and his collaborators demonstrated that photoactivated metallointercalators induced 8-OHdG in DNA at sites 34–200 Å (10–60 base pairs) away from their binding sites, by long-range electron transfer along the DNA chain (Nunez et al. 1999). Kohda et al. reported that 8-OHdG is produced in cellular DNA by a treatment with the carcinogen 4-nitroquinoline 1-oxide, via N7-arylaminated dG followed by hydrolytic rearrangement (Kohda et al. 1986). Together, these results revealed that 8-OHdG is produced by a variety of mechanisms.

3 Nomenclature

8-OHdG is considered to exist mainly as the 8-oxo-form in aqueous solutions, because its UV spectrum resembles that of 7-methyl-8-oxoguanosine (Culp et al. 1989; Rizkalla et al. 1969), (Fig. 1). An X-ray crystallographic study of 8-OH-9-ethylguanine actually revealed the 8-oxo-structure (Kasai et al. 1987). In DNA, its 8-oxo-form mispairs with adenine and induces GC to TA transversion mutations (Shibutani et al. 1991) (Fig. 2). A repair enzyme that removes 8-OHGua in DNA was identified in mammalian cells and named oxoguanine glycosylase 1 (OGG1) (Lu et al. 1997). Therefore, many researchers, especially those studying the mutagenic effects and the repair enzymes, use the name 8-oxodG, rather than 8-OHdG. In fact, Cooke et al. recommended using the 8-oxodG nomenclature (Cooke et al. 2010). However, a drawback is that the correct name of 8-oxodG is rather complicated, as it is 7,8-dihydro-8-oxo-dG or 8-oxo-7,8-dihydro-dG, etc. The 7,8-double bond of the guanine skeleton must be saturated before the 8-oxo is added to the guanine name, in the systematic nomenclature rules used by Chemical Abstracts, IUPAC, etc. Surprisingly, the incorrect name, 8-oxodeoxyguanosine, is

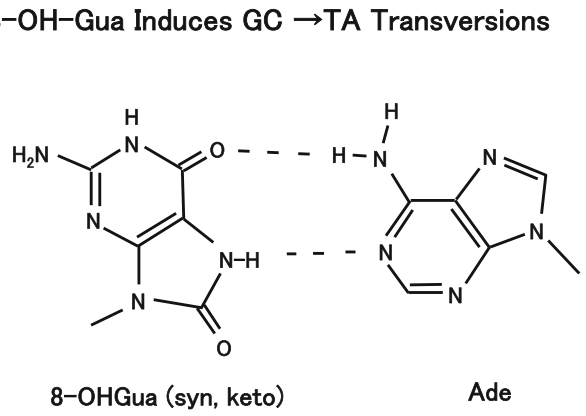

Fig. 2 Mismatched base pair caused by 8-OHGua

Table 1 The number of published reports with 8-OHdG in the title

Keywords	1983–2000[a]	2001–2010[b]	2011–2015[c]	Total[(a+b+c)]
8-Hydroxy-2′-deoxyguanosine (A)	120	215	107	442
8-Hydroxydeoxyguanosine (B)	156	140	44	340
8-OHdG (C)	16	87	58	161
8-OH-dG (D)	8	19	1	28
(A) or (B) or (C) or (D)	300	461	199*	960*
8-Oxo-7,8-dihydro-2-′-deoxyguanosine (E)	32	90	43	165
8-Oxo-7,8-dihydrodeoxyguanosine (F)	3	1	1	5
8-Oxo-2′-deoxyguanosine (G)	45	73	18	136
7,8-Dihydro-8-oxo-2-′-deoxyguanosine (H)	15	15	3	33
7,8-Dihydro-8-oxodeoxyguanosine (I)	0	7	1	8
8-Oxodeoxyguanosine (J)	17	23	1	41
8-oxodG (K)	7	22	15	44
8-oxo-dG (L)	4	16	11	31
(E) or (F) or (G) or (H) or (I) or (J) or (K) or (L)	123	247	93	463

*The numbers of these items are less than the sum of the above-described numbers, because some papers overlap

quite often used (Table 1). Therefore, the 8-oxo-type nomenclature is somewhat confusing. There are at least 6 different 8-oxo-type names, excluding abbreviations (Table 1). In contrast, 8-hydroxy-2′-deoxyguanosine is a simple, clear, and suitable name as a systematic nomenclature. In fact, 60–70 % of the published papers have consistently used 8-OHdG-type names in the titles throughout the past 32 years, as shown in Table 1. A major tautomeric structure in aqueous solution is not related to the systematic nomenclature of chemicals and is not always recommended as the nomenclature. For example, malondialdehyde (MDA, IUPAC name propanedial) is a widely used name, although it mainly exists in the 3-enol form in aqueous solution. However, the name 3-hydroxy-2-propenal (or ß-hydroxyacrolein) is not used for MDA (Marnett 2002).

4 Formation of 8-OHdG In Vivo

What kinds of carcinogenesis-related factors contribute to the generation of 8-OHdG? The relationship between well-known carcinogens and 8-OHdG generation in DNA has been investigated in animal experiments and human studies, to clarify the carcinogenic mechanism. The measured levels of 8-OHdG depend on the balance between its formation and repair, and thus the 8-hydroxyguanine

Table 2 The 8-OHdG levels are dependent on the balance between formation and repair

		8-OHdG	Repair activity
		Level in DNA	(OGG1 type)
Cultured cell	γ-Rays	↗	↘
	Arsenite	↗	↘
Animal organ	Chromium (VI)	↗	↘
	Cadmium (GSH depletion)	↗	↘
	Diesel exhaust particles	↗	↘
	Ethanol (Nutrition-deficient)	↗	↗
	3′-Me-4-DAB	↗	↗
	Fe-NTA	↗	↗
	Asbestos	↗	↗
	$KBrO_3$	↗	↗
Human leukocyte	Cigarette smoking	↗	↗
	Physical exercise	↘	↗

(8-OHGua) repair activity (OGG1 type) should also be assayed in evaluations of the cellular oxidative stress (Table 2). For example, when ethanol (under nutrition-deficient conditions) (Asami et al. 2000), 3′-methyl-4-dimethylaminoazobenzene (Hirano et al. 2000), ferric nitrotriacetate (Fe-NTA) (Yamaguchi et al. 1996), potassium bromate ($KBrO_3$) (Lee et al. 1996), and asbestos (Yamaguchi et al. 1999) were administered to rats, increases in both the 8-OHdG level and the repair activity were observed in the target organs, esophagus, liver, kidney, and lung. Cigarette smoking also increased the levels of both 8-OHdG and its repair activity in human leukocytes (Asami et al. 1996). In contrast, cancer preventive physical exercise induced an increase in the repair activity and a decrease in the 8-OHdG level (Asami et al. 1998a). The administration of cadmium (Cd) to rats, under conditions of glutathione depletion, impaired the 8-OHGua repair activity in the target organ, testis, while the 8-OHdG levels in the DNA were increased (Hirano et al. 1997). When rats were exposed to diesel exhaust particles (DEP) by intratracheal administration (Tsurudome et al. 1999), or to a hexavalent chromium (Cr) mist by inhalation (Maeng et al. 2003), again the repair activity was decreased in the lungs, while the 8-OHdG levels in the DNA were increased. These potent carcinogens, Cd, Cr, and DEP, may enhance the accumulation of 8-OHdG by impairing the repair activity.

One of the mechanisms of asbestos fiber genotoxicity appears to be the generation of ROS, either from its surface by reactions involving catalytic iron or from its phagocytosis by frustrated phagocytes (Kamp and Weitzman 1999). For example, increased levels of 8-OHdG were observed in rat and hamster lung DNA after the intra-tracheal instillation of crocidolite asbestos (Yamaguchi et al. 1999). These results agreed well with our prediction and suggested that one of the mechanisms of asbestos-induced lung cancer or mesothelioma is 8-OHdG generation in DNA. A positive correlation between the 8-OHdG levels in leukocyte DNA and the grades of asbestosis at a Chinese asbestos plant (Takahashi et al. 1997) was also observed.

A German group conducted a large-scale study of asbestos-exposed workers, to determine whether asbestos induces the formation of 8-OHdG in white blood cells (Marczynski et al. 2000). The data from that study revealed a 1.7–2-fold increase in 8-OHdG due to asbestos exposure ($p < 0.001$). These data support the hypothesis that asbestos fibers damage cells through an oxidative mechanism. Based on these results, preventive and therapeutic approaches using antioxidants may be possible. The various chemicals and environmental factors that induced increases in 8-OHdG levels are listed in Table 3.

5 Ionizing Radiation

Oxidative DNA damage is one of the major causes of radiation injury. 8-OHdG and 8-OHGua are increased in a linear fashion by 20–300 mGy of gamma irradiation to aqueous solutions of dG and Gua, respectively (Li et al. 2013b). These markers are considered to have sufficient sensitivity for detecting oxidative damage by ionizing radiation. The adverse health effects of radiation doses around 100 mSv have been vigorously discussed, especially in terms of cancer induction. Meanwhile, we reported that the threshold radiation level for increasing the 8-OHdG level in mouse urine was about 100–200 mGy (Li et al. 2013b), which supports the threshold theory of some reliable epidemiological studies on atomic bomb survivors (Land 1980; Shimizu et al. 1992). However, in most reports, an increase in 8-OHdG could be detected after irradiation with doses greater than a few Gy. Furthermore, most of the human data were collected from patients undergoing radiotherapy, who usually get quite high doses of radiation. It is essential to collect lower dose data to clarify the contribution of oxidative damage to the adverse health effects and to develop protective measures. In addition, the radiation health effects change with the radiation dose rate (Gy/min) (Tanooka 2011). At present, the evidence for the effects of low dose rate radiation is insufficient, especially for the human population. In cells, low molecular weight antioxidants and ROS-scavenging enzymes may process some of the ROS generated by radiation and prevent cellular DNA and nucleotide damage. In addition, the higher 8-OHdG levels induced in tissue DNA may decrease as time passes. This is due to the cellular DNA repair systems, such as nucleotide excision repair, base excision repair, and damaged nucleotide sanitization. As a result, oxidized nucleosides and bases accumulate in the urine. Therefore, urinary 8-OHdG is a sensitive marker for radiation-induced oxidative damage in vivo. The published data on the increased formation of 8-OHdG by ionizing radiation are summarized in Table 4.

Table 3 Occupational, environmental exposure and 8-OHdG

Chemicals or occupation	Ratio to control	Species	Sample	Method	Reference
Asbestos	1.31	Human	Urine	HPLC-ECD	Tagesson et al. (1993)
	1.45	Human	Urine	HPLC-ECD	Takahashi et al. (1997)
	1.37–1.64	Hamster, rat	Lung	HPLC-ECD	Yamaguchi et al. (1999)
	1.7	Human	White blood cell DNA		Marczynski et al. (2000)
PAHs	↗	Human	Urine	LC-MS/MS	Li et al. (2015)
	1.19	Human	Urine	HPLC-ECD	Harri et al. (2005)
	1.63	Human	White blood cell DNA	HPLC-ECD	Marczynski et al. (2009)
Refractory materials	1.54	Human	White blood cell DNA	HPLC-ECD	ibid.
Carbon electrodes	3.23	Human	White blood cell DNA	HPLC-ECD	ibid.
Converter workers	1.26	Human	White blood cell DNA	HPLC-ECD	ibid.
PAH, anthraquinone	↗	Human	Urine	ELISA	Wei et al. (2010)
DEP PM2.5	2.14	Human	Urine	ELISA	Lee et al. (2010)
PM 2.5	1.15	Human	Urine	ELISA	Kim et al. (2004)
	↗	Human	Urine	ELISA	Lee et al. (2012)
	>3	Human	Urine	ELISA	Wei et al. (2009)
	↗	Human	Urine	HPLC-ECD	Neophytou et al. (2013)
Coke oven worker	↗	Human	Urine		Guo et al. (2014)
	Top 1.20 Side 1.53	Human	Urine	HPLC-ECD	Nguyen et al. (2014)
	↗	Human	Urine	LC-MS/MS	Chao et al. (2008)
Coke production	1.4	Human	White blood cell DNA	HPLC-ECD	Marczynski et al. (2009)

(continued)

Table 3 (continued)

Chemicals or occupation	Ratio to control	Species	Sample	Method	Reference
Coke plant, policeman, taxi driver	↗	Human	Urine	Capillary electrophorasis-ECD	Zhang et al. (2013)
Bottom ash treatment plant, fly ash treatment plant	1.46	Human	Urine	ELISA	Liu et al. (2008)
Diesel exhaust emission inspector	>3	Human	Urine	ELISA	Wei et al. (2009)
Bus driver	1.3	Human	Urine	HPLC-ECD	Loft et al. (1999)
	1.27–1.45	Human	Urine	ELISA	Rossner et al. (2008)
Bus drivers, garagemen	2.59	Human	Urine	HPLC-ECD	Bagryantseva et al. (2010)
Long distance bus driver	Adjusted OR = 9.4	Human	Urine	ELISA	Han et al. (2010)
Traffic policeman	↗	Human	Leukocyte DNA	HPLC-ECD	Arayasiri et al. (2010)
Subway workers	1.07 ($p = 0.038$)	Human	Urine	ELISA	Mehrdad et al. (2015)
Foundry workers	2.72	Human	Urine	ELISA	Liu et al., (2009)
Toner-exposed	1.03	Human	Urine	HPLC-ECD	Kitamura et al. (2009)
Wildland firefighter	↗	Human	Urine	ELISA	Gaughan et al. (2014)
Temple workers, incense smoke	↗	Human	Leukocyte DNA	HPLC-ECD	Navasumrit et al. (2008)
Benzene	↗ 8-OHdG, 8-OHGuo, 8-OHGua	Human	Urine	LC-MS/MS	Manini et al. (2010)
	1.25–8.00	Human	Leukocyte DNA	HPLC-ECD	Liu et al. (1996)
	↗	Human	Urine	HPLC-ECD	Nilsson et al. (1996)
	↗ 8-OHdG, 8-OHGuo	Human	Urine	MS	Andreoli et al. (2012)
Styrene exposed workers	1.03–1.23	Human	Urine	LC-MS/MS	Manini et al. (2009)
Styrene	1.47	Human	Peripheral blood DNA	HPLC-ECD	Marczynski et al. (1997)
Gas station attendant, taxi driver	↗	Human	Urine	ELISA	Goeethel et al. (2014)

(continued)

Table 3 (continued)

Chemicals or occupation	Ratio to control	Species	Sample	Method	Reference
Ethylbenzene	4.21	Human	Urine	ELISA	Chang et al. (2011)
Di-(2-ethylhexyl) phthalate plastic recycling	1.27	Human	Urine	HPLC-ECD	Wang et al. (2011)
Smoker	2.15	Human	Urine	ELISA	Lu et al. (2014)
	1.5	Human	Urine	HPLC-ECD	Loft et al. (1992)
	1.43	Human	Lung	HPLC-ECD	Asami et al. (1997)
	2.13	Human	Leukocytes	HPLC-ECD	Lodovici et al. (2000)
Iron, smoking	↗	Human	Urine	LC-MS/MS	Hossain et al. (2014)
Environmental tobacco smoke	↗	Human	Plasma	LC-MS/MS	Chiang et al. (2012)
Hexavalent chromium electroplating worker	1.64	Human	Urine	ELISA	Zhang et al. (2011)
Chromium	1.57	Human	Urine	HPLC-ECD	Kuo et al. (2003)
Chromate	↗	Human	Urine	ELISA	Li et al. (2014)
Arsenic	4	Human	Saliva	LC-MS/MS	Hinhumpatch et al. (2013)
	1.12	Human	Urine	ELISA	Wong et al. (2005)
As, heavy metals	↗	Human	Serum	ELISA	Szymanska-Chabowska et al. (2009)
As, Cd	↗	Human	Urine	LC-MS/MS	Engstrom et al. (2010)
As, Cd, Ni, Se	↗	Human	Urine	ELISA	Lin et al. (2012)
Nickel-cadmium	1.05–2.55 8-OHGua	Human	Urine	HPLC-ECD	Yoshioka et al. (2008)
Manufacturing surgical instrument (nickel)	$r = 0.41$, $p < 0.0001$	Human	Urine	ELISA	Sughis et al. (2012)
Rubber	1.38	Human	Urine	HPLC-ECD	Tagesson et al. (1993)
Roofers	1.2	Human	Urine	HPLC-ECD	Toraason et al. (2001)

(continued)

Table 3 (continued)

Chemicals or occupation	Ratio to control	Species	Sample	Method	Reference
Azo-dye	1.79	Human	Urine	HPLC-ECD	Tagesson et al. (1993)
Cooking oil fume	1.46	Human	Urine	HPLC-ECD	Pan et al. (2008)
Cooking oil fume	↗	human	urine	HPLC-ECD	Ke et al. (2009)
Zinc oxide nanoparticle	↗	Rat	Blood		Chuang et al. (2014)
Nanoparticles from photocopiers	↗	Human	Urine		Khatri et al. (2013)
Metal nanoparticles	↗	Mouse	Urine, bone marrow, liver	HPLC-ECD	Song et al. (2012)
PCDD, dibenzofurans, etc.	3.84	Human	Urine	HPLC-ECD	Wen et al. (2008)
Aroclor 1254	>5	Mouse	Liver	HPLC-ECD	Faux et al. (1992)
TCDD	>20	Mouse	Urine	ELISA	Shertzer et al. (1998)
2,3,7,8-TCDD	↗	Human	Plasma	LC-MS/MS	Pelclova et al. (2011)
Trichloroethylene	↗	Human	Urine	LC-MS/MS	Abusoglu et al. (2014)
Agricultural worker	↗	Human	Urine	HPLC-ECD	Kisby et al. (2009)
Antineoplasic drugs	1.38	Human	Urine	ELISA	Huang et al. (2012)
VOCs*, hair salon	7.5	Human	Serum	ELISA	Ma et al. (2010)

*VOCs: volatile organic compounds

6 Diseases

Oxidative stress leads to many kinds of diseases. Examinations of the oxidative damage in connection with diseases are quite important for their treatment and prevention. In epidemiological studies, chronic oxidative stress is a cancer risk factor. For example, higher levels of 8-OHdG were observed in the stomach tissues of children (Baik et al. 1996) and cancer patients with *Helicobacter pylori* infection. Increased levels of 8-OHdG have been reported in various types of cancer. Oxidative stress engenders vascular complications and pancreatic beta cell damage, which induces insulin resistance and diabetes. In these patients, the 8-OHdG and 8-OHGua levels in urine or plasma were higher than those in the control group. In addition to patients with hypertension or cardiac infarcts, those with Alzheimer's or

Table 4 Ionizing radiation studies on 8-OHdG

Type of radiation	Dose rate	Total dose	8-OHdG induced ratio to control	Sample	Method	Reference
X-ray	0.5 Gy/min	1 Gy	1.62	Mouse liver	HPLC-ECD	Li et al. (2013b)
	0.5 Gy/min	0.5 Gy	1.61	Mouse urine	HPLC-ECD	Li et al. (2013b)
	0.59 Gy/min	3.9 Gy	2	Rat mammary gland	HPLC-ECD	Haegele et al. (1998)
	0.4 Gy/min	3 Gy	3.07	Rat bone marrow	HPLC-ECD	Umegaki et al. (2001)
	0.55 Gy/min	6 Gy	1.77	Mouse serum	ELISA	Manda et al. (2007)
		0.5 Gy	2.75	MT-I/II null mouse serum	ELISA	Shibuya et al. (2008)
		0.5 Gy	3.12	MT-I/II null mouse urine	ELISA	Shibuya et al. (2008)
γ-ray	2.4 mGy/min	0.3 Gy	2.62	F1 medaka muscle	HPLC-ECD	Grygoryev et al. (2013)
		3 Gy	1.3	Rat urine	ELISA	Inano and Onoda (2002)
	1 Gy/min	5 Gy	1.7–2.7	Rat liver	HPLC-ECD	Kaneko et al. (2003)
	0.7 Gy/min	3 Gy	2.5	Mouse bone marrow	ELISA	Rithidech et al. (2012)
	0.7 Gy/min	4 Gy	6.28	Mouse intestine	ELISA	Qian et al. (2010)

Radiotherapy, 6 MeV photons	2 Gy/d, 5 d/w	70 Gy	1.6 (8-OHGua)	Human urine	HPLC-ECD	Roszkowski et al. (2008)
		70 Gy	2.42	Human urine	HPLC-ECD	Roszkowski et al. (2008)
High LET ^{56}Fe beam, 500 MeV/nucleon	0.89 Gy/min	2 Gy	1.7	Mouse serum	ELISA	Manda et al. (2008)
Radiochemotherapy		12 Gy	>2.34	Human urine	HPLC-ECD	Bergman et al. (2004)

Parkinson's disease also have higher levels of 8-OHdG. Interestingly, patients with mental disorders, such as schizophrenia, bipolar disorder, and autism, also have higher levels of 8-OHdG and 8-OHGuo. Examples of recent publications describing increased 8-OHdG levels in various diseases are provided in Table 5.

7 Lifestyle

Lifestyle factors are closely related to the individual oxidative status. Epidemiological studies have suggested that lifestyle improvements can lead to the prevention of cancers and lifestyle-related diseases, such as diabetes. A well-balanced diet rich in vegetables and fruits reduced the 8-OHdG levels in the body, as an oxidative stress marker. In contrast, alcohol consumption and job stress increased the oxidative stress. Interestingly, the BMI of smokers showed an inverse correlation between the 8-OHdG level (Mizoue et al. 2006), which partly supports the U-shaped relation between BMI and cancer risk, concluded from epidemiological studies (Inoue et al. 2004). Namely, cancer risk increases with a very low BMI, especially in smokers (Kabat and Wynder 1992). A very thin state may induce oxidative stress, due to a high metabolic rate (Shah et al. 1988). Smoking seems to be one of the worst factors for inducing oxidative damage. Moderate exercise reduced the 8-OHdG levels in leukocyte DNA, by the induction of either ROS-scavenging enzymes (SOD, catalase, and glutathione peroxidase) (Mena et al. 1991) or repair enzymes [OGG1 and MTH1 (Sato et al. 2003)]. Representative references describing the effects of lifestyle factors on 8-OHdG levels are provided in Table 6.

8 Antioxidants

Antioxidants help to keep the body healthy. There are several methods for evaluating antioxidant activity. Among them, the measurement of 8-OHdG as an oxidative damage marker is the most widely used method for in vivo experiments, including human studies. The 8-OHdG reducing effects of typical antioxidants on induced oxidative stress are shown in Table 7. Vitamin C intake significantly decreased the 8-OHdG levels induced by periodontitis, ischemia, and chronic hemodialysis. Alpha-tocopherol reduced the increased 8-OHdG levels caused by heavy athletic training or iron therapy. The combined effects of alpha-tocopherol, ascorbic acid, beta-carotene, acetylsalicylic acid, and sesamin were reported. Many components in fruits or vegetables, such as astaxanthin (Aoi et al. 2003), lycopene (Devaraj et al. 2008), resveratrol (Sirerol et al. 2015), green tea polyphenols (Luo et al. 2006), quercetin (Ozyurt et al. 2014), and curcumin (Okada et al. 2001), were also reported to reduce 8-OHdG levels.

Table 5 Diseases and 8-OHdG

Disease	8-OHdG levels case to control	Note	Sample	Method	Reference
Cancer					
Stomach	5.3	H. pylori	Human stomach	Immunohistochemistry	Raza et al. (2014)
	2.1		Human stomach	HPLC-ECD	Borrego et al. (2013)
	7.5		Human urine	HPLC-ECD	Borrego et al. (2013)
	2.08		Human stomach	HPLC-ECD	Farinati et al. (2008)
	1.43		Human leukocyte	HPLC-ECD	Siomek et al. (2006)
	1.29		Human urine	HPLC-GC/MS	Siomek et al. (2006)
	1.32	8-OHGua	Human urine	HPLC-GC/MS	Siomek et al. (2006)
Intestine, colon	↗		Human urine	LC-MS/MS	Hsu et al. (2009)
	1.44		Human lymphocyte	HPLC-ECD	Gackowski et al. (2002)
Liver	2.7	8-OHGuo	Human urine	LC-MS/MS	Broedbaek et al. (2009)
	7.3		Human liver	HPLC-ECD	Kato et al. (2001)
Bladder	1.96		Human urine	ELISA	Chiou et al. (2003)
Prostate	1.63		Human urine	ELISA	Chiou et al. (2003)
Breast	↗ IRR* 1.08		Human urine	HPLC-ECD	Loft et al. (2013)
	↗		Human urine	LC-MS/MS	Cho et al. (2006)
Lung	↗ IRR* 9.94	Men, never-smoker	Human urine	HPLC-ECD	Loft et al. (2012)
	1.41		Human lung	HPLC-ECD	Inoue et al. (1998)

(continued)

Table 5 (continued)

Disease	8-OHdG levels case to control	Note	Sample	Method	Reference
Diabetes	2		Human plasma	LC-MS/MS	Waris et al. (2015)
	2.6	8-OHGua	Mouse urine	HPLC-ECD	Li et al. (2013a)
	2	8-OHGua	Mouse serum	HPLC-ECD	Li et al. (2013a)
	↗ Hazard ratio 1.72	8-OHGuo	Human urine	LC-MS/MS	Broedbaek et al. (2013)
	1.65		Human urine	ELISA	Dong et al. (2008)
	2.45		Human urine	CE-AD	Xu et al. (2004)
	2.19		Human urine	HPLC-ECD	Hinokio et al. (1999)
Hypertension	1.74		Human urine	HPLC-ECD	Espinosa et al. (2007)
Cardiac infarct	2.45		Human serum	ELISA	Suzuki et al. (2011)
	1.76		Human urine	ELISA	Nagayoshi et al. (2005)
Inflammation	1.79	6 % DSS**	Rat colonic mucosa	HPLC-ECD	Tardieu et al. (2000)
Inflammatory bowel disease	↗		Human blood	HPLC-ECD	D'Odorico et al. (2001)
Chronic hepatitis C	8		Human liver	HPLC-ECD	Kato et al. (2001)
Periodontitis	2		Human saliva	ELISA	Sezer et al. (2012)
Opisthorchis viverrini	↗		Hamster liver	Immunostaining	Pinlaor et al. (2004)
Cystic fibrosis	↗		Human urine	SPE-HPLC-ECD	Brown et al. (1995)
Alzheimer	5.15		Human cerebrospinal fluid	HPLC-ECD	Abe et al. (2002)
	1.76		Human lymphocyte	HPLC-ECD	Mecocci et al. (2002)
Parkinson	2.97		Human cerebrospinal fluid	HPLC-ECD	Abe et al. (2003)

Genetic diseases***	↗		Human leukocyte human urine	HPLC-ECD, ELISA	Lloret et al. (2008)
Mental					
Schizophrenia	1.21		Human urine	LC-MS/MS	Jorgensen et al. (2013)
	1.22	8-OHGuo	Human urine	LC-MS/MS	Jorgensen et al. (2013)
Bipolar disorder	1.4		Human urine		Munkholm et al. (2015)
	1.43	8-OHGuo	Human urine		Munkholm et al. (2015)
Autism	↗ $p < 0.01$		Human cerebellum	LC-MS	Rose et al. (2012)
Depression	1.13		Human serum	ELISA	Forlenza and Miller (2006)
Cortisol	$r^2 = 0.15$, $p < 0.001$	8-OHdG, 8-OHGuo	Human urine	LC-MS/MS	Joergensen et al. (2011)

*IRR: Incidence Rate Ratio
**DSS: dextran sodium sulfate
***Bloom syndrome, Fanconi anemia, Werner syndrome, Xeroderma pigmentosum

Table 6 Lifestyle and 8-OHdG

Habit	Ratio to control	Species	Sample	Method	Reference
Fruit and vegetable intake	Lower 8-OHdG (P for trend, 0.05)	Human	Urine	ELISA	Cocate et al. (2014)
Light-colored vegetable, soybean product, rice, BMI	↘	Human	Urine	HPLC-ECD	Irie et al. (2005)
Working hours, cigarette smoke	↗	Human	Urine	HPLC-ECD	Irie et al. (2005)
Fruit, daily physical activity, healthy meal	↘	Human	Urine	HPLC-ECD	Tamae et al. (2009)
Cigarette, alcohol	↗	Human	Urine	HPLC-ECD	Tamae et al. (2009)
Fish intake	↘	Human	Urine	ELISA	Muzembo et al. (2012)
Job stress	↗	Human	Urine	ELISA	Inoue et al. (2009)
Age	↗	Human	Urine	ELISA	Sakano et al. (2009)
BMI	↗ 2.7 % / unit BMI ↘	Human	Urine	HPLC-ECD	Mizoue et al. (2007)
Smoking	1.6	Human	Leukocyte DNA	HPLC-ECD	Asami et al. (1996)
	1.43	Human	Lung	HPLC-ECD	Asami et al. (1997)
	3.34	Human	Leukocyte DNA	HPLC-ECD	Lodovici et al. (2005)
Environmental smoke	1.55	Human	Leukocyte DNA	HPLC-ECD	Lodovici et al. (2005)
Physical activity (subject $n = 6{,}422$)	↘	Human	Urine	HPLC-ECD	Hara et al. (in press)
2 weeks, moderate intensity exercise after primary therapy	0.67	Human (colorectal cancer)	Urine	LC-MS	Allgayer et al. (2008)
Race (African American/ caucasian)	1.3	Human	Urine	ELISA	Huang et al. (2000)
Regular exercise	1.16	Human	Urine	ELISA	Huang et al. (2000)
Wrestling exercise	↘	Human	Serum	ELISA	Hamurcu et al. (2010)
Exercise	0.53	Human	Leukocyte DNA	HPLC-ECD	Asami et al. (1998a)
Forced exercise	1.9–2.4	Rat	Heart, lung, liver	HPLC-ECD	Asami et al. (1998b)

(continued)

Table 6 (continued)

Habit	Ratio to control	Species	Sample	Method	Reference
Ultramarathon	↗ mid race ↘post race	Human	Urine	HPLC-ECD	Miyata et al. (2008)
Sunlight	OR: 4.35	Human	Urine	ELISA	Kato et al. (2011)
UVB, 280–350 nm	1.73	Rabbit	Eye	HPLC-ECD	Lodovici et al. (2009)
UVA1, 364 nm Ar laser	2.56	Mouse	Skin	HPLC-ECD	Ikehata et al. (2008)
UVA, 364 nm	2.7	Drosophila		HPLC-ECD	Negishi et al. (2007)

9 Formation of 8-OHGuo in RNA

In the previously mentioned in vitro experiments, the formation of 8-OHGuo in RNA was higher than that in DNA (Kasai and Nishimura 1984c). One reason for this may be the more open structure of single-stranded RNA than double-stranded DNA. In fact, Fiala et al. reported that the hepatocarcinogen 2-nitropropane induces 8-hydroxyguanosine (8-OHGuo) in rat liver RNA much more efficiently (11-fold as compared to control) than 8-OHdG in DNA (3.6-fold as compared to control) (Fiala et al. 1989). This may also be due to the rapid removal of 8-OHGua from DNA by repair enzymes, or to the higher reactivity of ROS, produced by the metabolism of 2-nitropropane, with cytoplasmic single-stranded RNA. When doxorubicin (adriamycin) was administered to rats, a significant increase of 8-OHGuo in the liver RNA, but not 8-OHdG in the DNA, was observed (Hofer et al. 2006). Malayappan et al. observed increased levels of 8-OHGuo and 8-OHdG in smoker's urine, as compared to control nonsmokers (Malayappan et al. 2007). As other examples, analyses of ribonucleoside 8-OHGuo levels in tissue RNA or biological fluids were reported in relation to aging, calorie restriction, exercise (rat liver RNA) (Seo et al. 2006), cisplatin treatment in cancer patients (urine) (Andreoli et al. 2012), Alzheimer's disease (cerebrospinal fluid) (Isobe et al. 2009), hereditary hemochromatosis (urine) (Broedbaek et al. 2009), exposure to benzene (human urine) (Manini et al. 2010), and the effect of antioxidants in cherry juice (human urine) (Traustadottir et al. 2009). In those studies, higher formation of 8-OHGuo than 8-OHdG was observed, which is compatible with the general tendency that the ultimate reactive forms of carcinogens, such as aflatoxin B1 (Garner and Wright 1975) or N-nitrosopyrrolidine (Wang and Hecht 1997), induced more modifications in RNA than in DNA. Therefore, the ribonucleoside 8-OHGuo is also a promising biomarker for oxidative stress (Poulsen et al. 2012).

High levels of the ribonucleoside triphosphate 8-OHGTP may also be produced in cells, in addition to 8-OHdGTP (see next paragraph). The MTH1 protein, a

Table 7 Antioxidants and 8-OHdG

Antioxidant	Ratio to control	oxidative stress	Sample	Method	Reference
Ascorbic acid	0.62	Atherosclerosis	Rat serum	ELISA	Ekuni et al. (2009)
	↘	Periodontitis	Rat gingival	ELISA	Tomofuji et al. (2009)
	↘	Ischemia	Human serum	ELISA	Cangemi et al. (2007)
	0.82	Hemodialysis	Human lymphocyte	HPLC-ECD	Tarng et al. (2004)
Alpha-tocopherol	↘	Down syndrome	Human urine	ELISA	Nachvak et al. (2014)
	0.48	Training	Human urine	ELISA	Tsakiris et al. (2006)
	↘		Human urine	ELISA	Lee and Wan (2000)
Alpha-tocopherol + ascorbic acid	0.75	Exercise	Human blood	ELISA	Bloomer et al. (2006)
	↘		Human urine	ELISA	Hong et al. (2013)
	↘		Human serum	ELISA	Goldfarb et al. (2007)
Alpha-tocopherol + ascorbic acid + beta-carotene	0.95	Nontreat	Rat liver	HPLC-ECD	Wawrzyniak et al. (2013)
Ascorbic acid + acetylsalicylic acid	↘	Neuroinflammation	Rat	ELISA	Kara et al. (2014)
alpha-tocopherol + sesamin	↘	Aging	Rat urine	ELISA	Noguchi et al. (2001)
Carotenoid	↘		Human urine	ELISA	Cocate et al. (2015)
Astaxanthin	↘	Exercise	Mouse heart	HPLC-ECD	Aoi et al. (2003)
Lycopene	↘		Human urine	ELISA	Devaraj et al. (2008)
Lycopene + beta-carotene	0.3	Iron	Rat prostate	HPLC-ECD	Matos et al. (2006)
Lycopene + genistein	0.55	DMBA	Rat serum	ELISA	Sahin et al. (2011)
Resveratrol	0.59	UV B	Mouse skin	LC-MS/MS	Sirerol et al. (2015)
	0.58	Exercise	Rat serum	ELISA	Xiao (2015)
	0.71	Periodontitis	Mouse urine	ELISA	Tamaki et al. (2014)
	0.62	Sodium fluoride	Rat plasma	ELISA	Atmaca et al. (2014)

Green tea	0.7		Rat urine	HPLC-ECD	Shen et al. (2008)
Green tea polyphenols	↘ Dose dependent		Human urine	HPLC-ECD	Luo et al. (2006)
Coffee	↘ Trend $p = 0.046$		Human urine	HPLC-ECD	Hori et al. (2014)
Polyphenol (vegetables, red wine)	↘		Human urine	ELISA	Pedret et al. (2012)
CoQ10	0.88	Placebo	Human urine	HPLC-ECD	Ito et al. (2015)
Pterostilbene	0.69	UV B	Mouse skin	LC-MS/MS	Sirerol et al. (2015)
Quercetin	↘	Ionizing radiation	Rat tissue	ELISA	Ozyurt et al. (2014)
Ursolic acid	0.64	Carbon tetrachloride	Mouse kidney	HPLC-ECD	Ma et al. (2014)
Vitex honey	0.8	Paracetamol	Mouse serum		Wang et al. (2015)
Curcumin	↘	Formaldehyde	Rat brain, urine		Ciftci et al. (2015)
	↘	Fe-NTA	Mouse kidney	ELISA	Okada et al. (2001)
Fermented papaya	0.6	Alzheimer	Human urine	ELISA	Barbagallo et al. (2015)
	↘	Hepatitis C virus	Human leukocyte	HPLC-ECD	Marotta et al (2007)
Almond	0.72	Smoker	Human urine	HPLC-ECD	Li et al. (2007)
Tomato sauce	0.79	Prostate cancer	Human leukocyte	HPLC-ECD	Chen et al. (2001)
Pigmented potato	↘		Human plasma	ELISA	Kaspar et al. (2011)

(continued)

Table 7 (continued)

Antioxidant	Ratio to control	oxidative stress	Sample	Method	Reference
Ginseng	0.68	Gentamicin	Rat urine	ELISA	Shin et al. (2014)
	↘		Human urine	HPLC-ECD	Lee et al. (1998)
Vegetable	p for trend < 0.001		Human urine	ELISA	Cocate et al. (2014)
Fruit and vegetable	p for trend $= 0.028$		Human urine	ELISA	Cocate et al. (2014)
	0.68		Human lymphocyte	HPLC-ECD	Thompson et al. (1999)
Ursolic acid, luteolin	↘		Caco-2 cell	comet assay	Ramos et al. (2010)
Olive oil	0.87		Human urine	LC-MS/MS	Machowetz et al. (2007)

mutT-related protein that catalyzes the hydrolysis of 8-OHdGTP to 8-OHdGMP, also hydrolyzed the ribonucleotide 8-OHGTP (Fujikawa et al. 2001). In oxidative stress-related diseases induced by aging, 8-OHGuo formation in RNA, by either the incorporation of 8-OHGTP or the direct oxidation of RNA, caused a reduction in translation or an increase in mistranslation, which induced the accumulation of nonfunctional proteins (Poulsen et al. 2012). For example, in Alzheimer's disease patients, increased 8-OHGuo in RNA- and reduced MTH1 activity were observed in their hippocampi (Song et al. 2011). These results suggested that increased oxidative stress and MTH1 deficiency during aging might be causative factors for this disease.

10 The Nucleotide Pool Is a Significant Target

In the initial in vitro study, the formation of 8-OHdG in the monomer nucleoside (dG) was 15 times higher than that in the DNA (Kasai and Nishimura 1984c). This suggests that the modification of dGTP to 8-OHdGTP in the nucleotide pool is more important than the formation of 8-OHdG in the DNA. In vivo, an *E. coli mutT*-deletion mutant, which lacks the 8-OHdGTP sanitization system, showed a 100–10,000 times higher spontaneous mutation rate than the wild type (Maki and Sekiguchi 1992), while the rate in a *mutM*-deletion mutant, which lacks the system to remove 8-OHGua from DNA, was only 6–14 times higher than that of the wild type (Cabrera et al. 1988; Michaels et al. 1992). In fact, Russo et al. reported that 8-OHdGTP is a significant contributor to genetic instability in mismatch repair-deficient cells (Russo et al. 2004). Harms-Ringdahl and his collaborators detected considerable amounts of 8-OHdG in the nucleotide pool fraction, which were much higher (35-fold) than those in the DNA fraction, and concluded that the nucleotide pool is a significant oxidative modification target (Haghdoost et al. 2006). They also reported that the reduction of 8-OHdGTP in the nucleotide pool by hMTH1 leads to fewer mutations in the human lymphoblastoid cell line TK6, exposed to UVA (Fotouhi et al. 2011). Kaczmarek et al. described the efficient formation of 8-OHdGTP from the Ni(II)-dGTP or Ni(II)-dGTP-His complex in the presence of H_2O_2, which may be an underlying mechanism of the potent carcinogenic effects of nickel compounds (Kaczmarek et al. 2005). Together, these results suggest that 8-OHdG formation in the nucleotide pool is more important than that in the DNA, in relation to mutagenesis and carcinogenesis (Fig. 3). It is worth mentioning that the nucleotide pool is also a significant target of alkylation in N-methyl-N-nitrosourea-induced mutagenesis and carcinogenesis (Topal and Baker 1982).

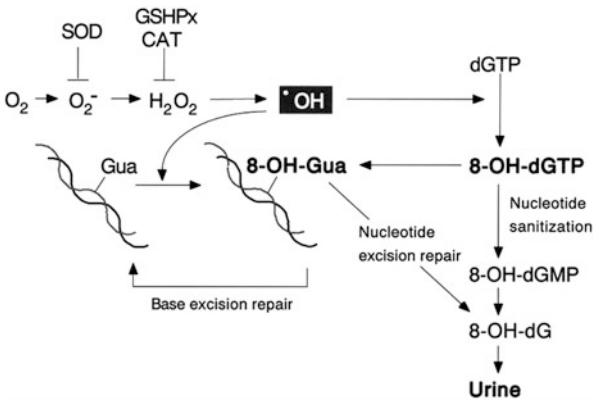

Fig. 3 8-OHdG formation and repair in vivo

11 Accurate Measurement of 8-OHdG as a Reliable Marker

The need to accurately measure 8-OHdG has long been discussed (Kasai 1997). In the case of 8-OHdG measurements in cellular DNA, special precautions must be taken to prevent sample auto-oxidation. An antioxidant (NaI) and a metal chelator (Desferal, EDTA) must be used during DNA isolation, especially in the lysis step. When a DNA digest was stored at 10 °C, the 8-OHdG levels significantly increased in a few hours. In contrast, when stored at −80 °C, no increase was observed (Kawai et al. 2007).

For the measurement of urinary 8-OHdG, an automated HPLC-ECD system to analyze urinary 8-OHdG with higher accuracy was developed (Kasai 2003). Disparity in the results has occurred frequently, depending upon the measurement methods (Shimoi et al. 2002). There are considerable discrepancies between the results obtained by the ELISA and HPLC methods. Usually, the 8-OHdG levels are 2–3 times higher in the ELISA methods, as compared to the HPLC methods, and the data observed with ELISA are quite variable. Recently, urea was recognized as a major cause of this problem (Song et al. 2009). A high concentration of urea in the sample (urine or blood) could cross-react with the anti-8-OHdG antibody in the ELISA. Although various approaches, including the performance of the ELISA at 4 °C, a pretreatment with urease, and a pretreatment by solid-phase extraction (SPE), have been taken to resolve this issue, satisfactory results have not been achieved (Rossner et al. 2013). Regarding this situation, Watanabe et al. reported a good correlation between the ELISA and HPLC methods for the 8-OHdG values by the ELISA method, following urease treatment and ethanol precipitation. Urea is considered to be a major interfering substance in ELISA, but there are still other cross-reacting components, such as 8-OHGuo (Song et al. 2012) and creatinine (Rossner et al. 2008). Most reports of the 8-OHdG levels in serum or saliva were obtained by the direct use of ELISA for these fluids. The levels of 8-OHdG in plasma and saliva measured by LC-MS/MS were several hundred times lower than

those reported by scientists using the commercial ELISA kit (Hu et al. 2010b). Although serum and saliva are quite useful materials, pretreatments for concentration and cleanup, such as SPE treatment, are needed before ELISA and HPLC measurements because of the low concentration of 8-OHdG, and for the removal of cross-reacting materials, especially in ELISA. From an overall consideration, although ELISA measurements have revealed certain rough trends in large-scale analyses, the HPLC methods (HPLC-ECD or LC-MS/MS) are recommended for the accurate measurement of 8-OHdG. The urine analysis data obtained by our method (HPLC-ECD) are almost identical to those obtained by LC-MS/MS, as judged by ESCULA (European Standard Committee on Urinary Lesion Analysis) (Barregard et al. 2013). For urinary 8-OHGua analysis, diets containing 8-OHGua must be considered, because 90 % of the 8-OHGua administered to rats was excreted into the urine (Kawai et al. 2006). The CE-2 diet, which is generally used for animal experiments, contains a large amount of 8-OHGua. Therefore, in animal experiments, nucleic acid-free diets, such as those with egg white as the protein source, should be used. For human studies, the intake of various 8-OHGua-containing foods, especially fish products, must be minimized before urine collection.

It is also important to check the stability of 8-OHdG under various conditions, and to determine whether it is formed from dG in biological fluids, such as urine, for its general use as an oxidative stress marker. Urinary 8-OHdG is stable at −20 °C for 15 years (Loft et al. 2006) and at 25 °C for 24 h (nonsmokers) (Matsumoto et al. 2008). However, the levels of urinary 8-OHdG from smokers showed a tendency to increase over 24 h at 25 °C (Matsumoto et al.). This may occur because (1) smoker's urine contains lower levels of antioxidants than that of nonsmokers, and/or (2) smoking-related substances in urine generate ROS. Shigenaga et al. injected ^{3}H-8-OHdG into the tail veins of rats, and 24 h urine samples were analyzed by HPLC (Shigenaga et al. 1989). They found no degradation of 8-OHdG after administration and excretion. When ^{3}H-dG was stored in urine for 19 days at 4 °C, no 8-OHdG was produced, indicating that the chemical transformation of dG to 8-OHdG did not occur in rat urine (Shigenaga et al. 1989).

8-OHGua is rather unstable, as compared to 8-OHdG (Hu et al. 2010a). Its solution (pH 7) is stable at room temperature for 6 days, at 4 °C for 45 days, and at −20 °C for 87 days. After these periods, its degradation was observed.

12 Sources of 8-OHdG, 8-OHGuo, and 8-OHGua Generation and Validity of Their Analyses

Urinary 8-OHdG is generated by either nucleotide excision repair (NER) from oxidized DNA or hydrolysis of 8-OHdGTP by the sanitization enzyme MTH1. The free 8-OHGua base is produced by base excision repair (BER) from oxidized DNA or by the oxidation of guanine (formed by the hydrolytic degradation of DNA,

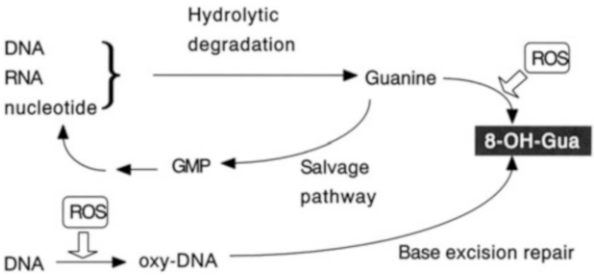

Fig. 4 8-OHGua formation and repair in vivo

RNA, and the nucleotide) before the salvage pathway (Kasai et al. 2008) (Fig. 4). 8-OHGuo may be produced by the hydrolysis of 8-OHGTP by MTH1 or by the degradation of oxidized RNA.

A human study revealed a correlation between the 8-OHdG levels in lymphocyte DNA and the urinary 8-OHdG levels (Gedik et al. 2002). A correlation between the concentrations of 8-OHdG in human urine, plasma, and saliva was also observed (Hu et al. 2010b), based on accurate LC-MS/MS measurements. In mouse experiments, correlations were observed between the urinary 8-OHdG and 8-OHGua levels, between the serum 8-OHGua and urinary 8-OHdG levels, and between the serum 8-OHGua and urinary 8-OHGua levels (Li et al. 2013a).

There are few direct studies of the relationship between 8-OHdG-related oxidative markers and cancer risks in humans, such as cohort studies, because of the length of time required to form conclusions (Loft et al. 2006). Considering the time needed to collect data for the large-scale analysis of 8-OHdG-related markers, the amounts of direct evidence for use as a predictor of cancer development are expected to increase in the future.

As described in this chapter, many chemical carcinogens, as well as UV- and ionizing radiation (UVA, gamma-ray, X-ray, etc.), induced 8-OHdG in animal experiments, while many antioxidants, which are known to suppress cancer, reduced the 8-OHdG levels, as indicated in Tables 4 and 7. In human studies, asbestos, azo-dyes, benzene, and chemicals used in the rubber industry, which were all concluded to be human carcinogens with sufficient evidence by the IARC (Lagorio et al. 1994; Tagesson et al. 1993), induced an increase in the urinary 8-OHdG level.

Furthermore, many lifestyle habits for cancer prevention, such as cessation of smoking, avoiding drinking and a high-fat diet, following the recommended levels of fish, fruit and vegetable consumption, and exercising moderately, are supported by the data showing increased or decreased 8-OHdG levels by these factors, in human studies. Urinary analyses of cancer high-risk groups (dermatomyositis, polymyositis, systemic sclerosis, cholangiocarcinogenesis) revealed higher levels of urinary 8-OHdG, as compared to those of the healthy control groups (Kasai et al. 2007; Thanan et al. 2008). In cancer- or aging-related genetic diseases, such as Fanconianemia, Bloom syndrome, and Xeroderma pigmentosum, the urinary 8-OHdG levels were also increased (Lloret et al. 2008).

Based on the direct and indirect evidence described herein, we consider 8-OHdG (or its related compounds) to be a useful marker for monitoring the oxidative stress involved in the induction of cancer and ROS-related diseases, if analyses are performed with the precautions mentioned above.

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