

Food Factors and Oxidative DNA Damage / DNA Repair Systems

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1. Introduction

8-Oxoguanine (7, 8-dihydro-8-oxoguanine, abbreviated as 8-oxo-Gua), a form of oxidized guanine, is a mutagenic lesion formed spontaneously in the genomic DNA of aerobic organisms (Fig. 1) and by the actions of exogenous factors, such as ionizing radiation, chemical pollutants, heavy metals, food factors, and bacteria. 8-Oxo-Gua induces GC-to-TA transversion type point mutations [1]. Point mutations generated via oxidative DNA damage are involved in cancer development, because mutations are a common feature of human cancers. Therefore, 8-oxo-Gua is considered to be involved in carcinogenesis. In this context, studies of 8-oxo-Gua have significant implications for understanding the underlying mechanisms of mutation-associated diseases, including cancer [2]. Although 8-oxo-Gua is not necessarily the most abundant form of oxidative DNA damage, it has been the most extensively studied, because it is quite easily measured by a method utilizing HPLC coupled with electrochemical detection in laboratories [3, 4]. The presence of 8-oxo-Gua and 8-oxoadenine (8-oxo-Ade) in mutagenic oxidized DNA products has been extensively studied, and their frequencies of generation in mammalian DNA and degrees of mutagenicity are similar [5-8]. The relative focus-forming activity, which indicates the mutation inducibility, of 8-oxo-Gua and 8-oxo-Ade were reportedly ~1% [7, 8].



Fig. 1. Structure of 7, 8-dihydro-8-oxoguanine or 8-hydroxyguanine (8-OH-Gua). 8-Oxo-Gua is formed by hydroxylation of guanine at the C-8 position.

Extensive efforts have been made to clone the repair enzymes for 8-oxo-Gua. The first information was obtained from the studies of an enzyme, formamidopyrimidine DNA glycosylase (Fpg or MutM), which excises 8-oxo-Gua, 2, 6-diamino-4-hydroxy-5-formamidopyrimidine (FapyGua), and 4, 6-diamino-5-formamidopyrimidine (FapyAde)

from the DNA of *Escherichia coli* [9]. This enzyme has an activity to process the resulting abasic (AP) site, by cleaving both the 3'- and 5'-phosphodiester bonds by successive β - and δ -eliminations [10-12]. In 1996, an Fpg homologue was identified in *Saccharomyces cerevisiae* [13, 14]. This was the first report of an 8-oxoguanine DNA glycosylase 1 (OGG1). In the following year, mammalian (human and other mammals) homologues of OGG1 were identified and cloned [15-21]. 8-Oxo-Gua is efficiently removed from DNA via the short-patch base excision repair (BER) pathway initiated by OGG1.

Among the environmental factors that are related to human diseases, food factors have a large influence on human health. To understand the mechanisms of food-related carcinogenesis, the roles of 8-oxo-Gua have been investigated in relationship with food factors. In this review article, we will focus on and describe the relationship between food factors and 8-oxo-Gua / 8-oxo-Gua repair systems.

2. Aminoazo dyes and 8-oxo-Gua / OGG1

Food factors have been extensively investigated in association with oxidative DNA damage and its repair systems. Some food factors, such as aminoazo dyes, are known inhibitors of OGG1 expression. Aminoazo dyes were previously used as artificial color additives to food. Some of them, such as *N*-methyl-4-aminoazobenzene, *N*, *N*-dimethyl-4-aminoazobenzene, and 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB), are hepato-carcinogenic. We previously analyzed the effects of 3'-MeDAB on 8-oxo-Gua repair systems in rodent livers, and reported that 3'-MeDAB increased 8-oxo-Gua generation and decreased OGG1 expression, possibly by cleaving the protein [22]. These results suggested that the liver carcinogenicity of 3'-MeDAB was due to an increase in 8-oxo-Gua generation via 3'-MeDAB-induced downregulation of OGG1 expression.

The use of 3'-MeDAB as a food additive is now prohibited. However, other types of azo dyes are still being used. Therefore, more research is needed to define the effects of azo dyes on human health.

3. Alcohol and 8-oxo-Gua / OGG1

Alcohol consumption has been associated with a variety of human cancers for several centuries. Recent studies revealed that alcohol consumption is associated with an increase in breast cancer incidence in women [23, 24], esophageal cancer [25], and colorectal cancer [26, 27]. On the other hand, the cancer-preventive effects of alcohol drinking have also been reported. It is well known that moderate consumption of wine may prevent some types of cancers [28-30]. These studies concerning wine consumption suggested that anti-oxidant agents, such as polyphenols, including catekin, quercetin and resveratrol, contributed to the cancer-preventive effect of wine [31]. Thus, anti-oxidant agents seem to play a key role in the beneficial effects of wine. It was also suggested that resveratrol could reduce the localized estrogen production that plays a crucial role in the development of breast cancer [32]. On the other hand, for alcoholic beverages other than wine, a cohort study suggested that alcohol (spirits and beer) consumption was associated with a decrease in the risk of renal cell carcinoma in male smokers [33]. A matched case-control study reported a similar result, in which regular, moderate alcohol (beer, wine, and spirits) consumption was associated with a decreased probability of leukoplakia occurrence, with respect to occasional or no alcohol consumption [34]. These results are not conclusive, but suggest that other

components of alcoholic beverages (including wine) besides polyphenols may be responsible for the beneficial effects on human health.

The evidence that not only wine but also spirits and beer have cancer-preventive effects prompted us to investigate the molecular mechanisms of these effects of alcohol consumption due to factors other than polyphenols. In fact, recent evidences have suggested that the protective effects of red wine on cancer or cardiovascular diseases were not a consequence of the anti-oxidant capacity of alcohol [35, 36]. Arendt et al. reported the reduction of DNA damage as another mechanism of the cancer-preventive function of wine [35].

In this context, we analyzed the 8-oxo-Gua accumulation level in DNA and its repair ability (8-oxo-Gua nicking activity and mouse OGG1 (mOGG1) expression) in the livers of mice treated with 3'-MeDAB, a well known hepato-carcinogen as described above, and / or ethanol, to examine the effects of alcohol consumption on carcinogenesis (Fig. 2A) [37]. The method used to determine the 8-oxo-Gua nicking activity was described elsewhere [38]. In the study, we found that 12% ethanol reduced the 3'-MeDAB-induced 8-oxo-Gua accumulation (Fig. 2B). Moreover, the 8-oxo-Gua repair activity showed a decreasing tendency in 3'-MeDAB-treated mouse livers with 12% ethanol administration, without any significant differences (Fig. 2C). The decrease in the 8-oxo-Gua repair activity seems to be a reasonable consequence of the lower 8-oxo-Gua levels. Since we speculated that OGG1 fragmentation was a key event for 3'-MeDAB-induced 8-oxo-Gua accumulation [22], we predicted that OGG1 fragmentation might be inhibited by ethanol intake, as in the inhibition of the increase in 8-oxo-Gua levels. However, 12% ethanol intake failed to inhibit the 3'-MeDAB-induced fragmentation of OGG1 (groups D, E, and F in Fig. 2D). The observations indicated that ethanol intake reduced 8-oxo-Gua accumulation, without affecting the function of OGG1. However, since other enzymes besides OGG1 can reportedly repair 8-oxo-Gua [39], we speculate that ethanol consumption might induce these 8-oxo-Gua repair systems to reduce the 8-oxo-Gua level.

4. Coffee and 8-oxo-Gua / OGG1

Coffee has been a quite popular beverage in many parts of the world for a long time. However, its effects on human health are not well understood. Some studies suggested that coffee consumption had preventive properties for metabolic diseases, such as type 2 diabetes [40, 41], or cancers, such as hepatocellular carcinoma [42, 43] and colorectal cancer [44, 45], through its content of potentially antimutagenic substances [46]. These findings led to the hypothesis that coffee consumption lowers the risk of some types of cancers.

On the other hand, some studies provided negative conclusions for the effects of coffee consumption on human health. A large cohort study in Sweden and Japan indicated that coffee consumption was not associated with the risk of colorectal cancer [47, 48]. Furthermore, another cohort study indicated that coffee consumption increased the risk of certain cancers, such as gastric cancer [49]. These carcinogenic actions of coffee were supported by evidence that coffee contained numerous substances, such as glyoxal, methylglyoxal, ethylglyoxal, propylglyoxal, diacetyl, and acetol, with potentially genotoxic and mutagenic properties [46, 49-51]. Although the polyphenols in beverages, such as green tea, black tea, and coffee, are antioxidant substances, a recent study indicated the production of hydrogen peroxide, a harmful molecule for living organisms, by polyphenol-rich beverages [52]. Therefore, although numerous studies have been performed, the effects of coffee consumption on human health have remained undefined.

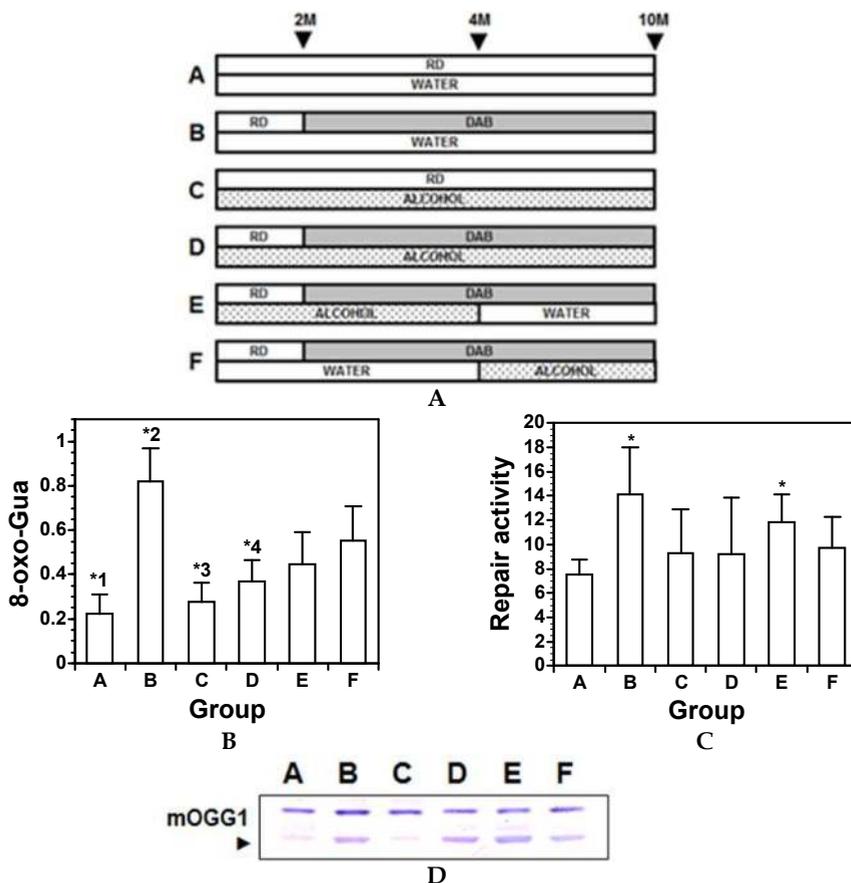


Fig. 2. (A) The experimental protocol. A: control [ND / water] for 10 months; B: [ND / water] for the first 2 months and [0.06% 3'-MeDAB / water] for the last 8 months; C: [ND / alcohol] for 10 months; D: [ND / alcohol] for the first 2 months and [0.06% 3'-MeDAB / alcohol] for the last 8 months; E: [ND / alcohol] for the first 2 months, [0.06% 3'-MeDAB / alcohol] for the next 4 months, and [0.06% 3'-MeDAB / water] for the last 4 months; F: [ND / water] for the first 2 months, [3'-MeDAB / water] for the next 4 months, and [3'-MeDAB / alcohol] for the last 4 months. ND: normal diet, DAB: 3'-MeDAB. (B) The levels of 8-oxo-Gua in the DNA of mouse livers. The 8-oxo-Gua value is expressed as the number of 8-oxo-dG per 10⁵ deoxyguanosine. *1: $P < 0.0005$ vs. group B, $P < 0.05$ vs. group E, $P < 0.01$ vs. group F; *2: $P < 0.0001$ vs. group C, $P < 0.005$ vs. group D, $P < 0.01$ vs. group E, $P < 0.05$ vs. group F; *3: $P < 0.05$ vs. group E, $P < 0.005$ vs. group F; *4: $P < 0.05$ vs. group F. (C) 8-Oxo-Gua nicking activity in the mouse livers. The activity was calculated as the ratio of the excised fragment intensity to the total substrate (unexcised substrate intensity plus excised fragment intensity). *: $P < 0.005$ vs. group A. (D) Western blotting of mOGG1 protein in the mouse livers. Mouse livers were removed and homogenized to produce crude extracts. The extracts were electrophoresed and blotted onto a PVDF membrane. A western blot analysis was performed using an anti-mouse OGG1 antibody. The arrowhead indicates fragmented mOGG1. mOGG1: mouse OGG1. This figure was published in reference [37], Copyright Elsevier (license#: 2633951132321).

To address this issue, we focused on the effects of instant coffee consumption on the generation of 8-oxo-Gua. In our previous work, we analyzed the 8-oxo-Gua level and the 8-oxo-Gua repair system in the livers of mice fed with / without a 0.1% instant coffee solution. In addition, we employed an autoclaved diet (low vitamin diet; LV diet) to maintain half of the mice under low vitamin conditions. We found that instant coffee consumption does not alter the 8-oxo-Gua generation level and *OGG1* mRNA expression, although it prevents low-vitamin diet-induced 8-oxo-Gua production [53] (Fig. 3). Our study suggested that daily instant coffee consumption may provide more beneficial effects than detrimental effects. However, we have not examined other types of DNA damage. To clarify the role of coffee consumption on human health, further studies should be performed.

5. Urinary 8-oxo-Gua level and food consumption

Urinary 8-oxo-Gua levels are often analyzed, especially as a marker of oxidation [54, 55]. Among the urinary biomarkers of oxidative stresses, 8-oxo-Gua is possibly the most studied. We previously investigated the effects of age, smoking, dietary factors, and other life style factors on urinary 8-oxodeoxyguanosine (8-oxo-dG) levels [56]. Urine samples were collected from healthy employees in a steel-manufacturing company, after obtaining informed consent. The mean level of urinary 8-oxo-dG ($\mu\text{g} / \text{g}$ creatinine) in the 361 male subjects was 4.20 ± 1.47 (Table 1). The relationships between 16 categorical lifestyle factors and urinary 8-oxo-dG levels were analyzed by ANOVA. The results revealed that the urinary 8-oxo-dG level was significantly negatively related to fruit consumption ($P = 0.03$) and physical activity ($P = 0.03$). It is noteworthy that, in terms of fruit consumption, the urinary 8-oxo-dG levels of the “rarely” and “two or three times per week” groups were significantly higher than those of the “everyday” group ($P = 0.03$). The results of the Scheffe’s test also indicated that fruit consumption significantly reduced the urinary 8-oxo-dG level. Besides urinary analyses, a diet rich in fruit and vegetables was also reportedly effective in the reduction of oxidative stresses [57]. These data indicated that fruit consumption and physical activity reduce oxidative stress generation.

variables	category	n	%	urinary 8-oxo-dG	<i>P</i>
sleep	deficient	10	2.8	4.37 ± 0.25	0.53
	slightly deficient	181	50.1	4.19 ± 0.12	
	sufficient	170	47.1	4.20 ± 0.11	
holiday	little or none	2	0.6	5.41 ± 1.20	1.00
	once a week	51	14.1	3.96 ± 0.21	
	twice a week	308	85.3	4.23 ± 0.08	
fatigue	always	18	5.0	3.66 ± 0.32	0.86
	sometimes	256	70.9	4.17 ± 0.09	
	rarely	87	24.1	4.39 ± 0.17	
rhythm	irregular	66	18.3	4.05 ± 0.19	0.25
	mostly regular	215	59.6	4.20 ± 0.10	
	regular	80	22.2	4.30 ± 0.16	
refreshing	difficult	13	3.6	4.40 ± 0.38	0.48
	moderate	255	70.6	4.13 ± 0.09	
	easy	93	25.8	4.33 ± 0.17	
size of a meal	full stomach every time	24	6.6	3.87 ± 0.27	0.85
	no pattern	198	54.8	4.29 ± 0.11	
	moderation every time	139	38.5	4.12 ± 0.11	

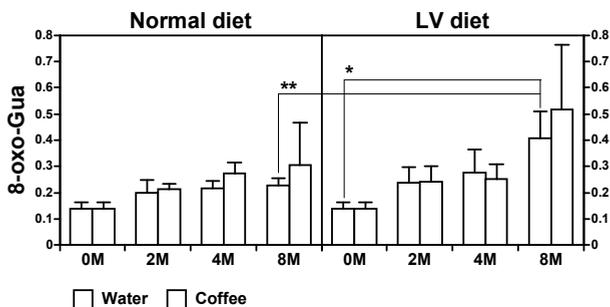
variables	category	n	%	urinary 8-oxo-dG	P
healthy meal combination	rarely	46	12.7	4.25 ± 0.20	0.11
	consider sometimes	187	51.8	4.33 ± 0.12	
skipping meals	consider every time	128	35.5	3.99 ± 0.11	0.62
	one meal every day	63	17.5	4.37 ± 0.20	
	2 or 3 meals a week	103	28.5	4.09 ± 0.15	
light-colored vegetable	rarely	195	54.0	4.20 ± 0.10	0.78
	once a day	268	74.2	4.22 ± 0.09	
	each meal	76	21.1	4.09 ± 0.14	
green- and yellow-colored vegetables	rarely	26	7.2	4.10 ± 0.32	0.75
	2 or 3 times a week	244	67.6	4.21 ± 0.10	
	everyday	91	25.2	4.18 ± 0.12	
fruit	rarely	140	38.8	4.24 ± 0.12	0.03
	2 or 3 times a week	187	51.8	4.28 ± 0.11	
	everyday	34	9.4	3.57 ± 0.19	
meat, fish, egg, etc.	rarely	11	3.0	4.72 ± 0.49	0.16
	twice a day	194	53.7	4.25 ± 0.11	
	each meal	156	43.2	4.09 ± 0.11	
milk	rarely	118	32.7	4.32 ± 0.16	0.23
	2 or 3 times a week	171	47.4	4.10 ± 0.10	
	everyday	72	19.9	4.23 ± 0.15	
oil	rarely	9	2.5	4.41 ± 0.58	0.55
	2 or 3 times a week	192	53.2	4.15 ± 0.12	
	everyday	160	44.3	4.24 ± 0.10	
seaweed	rarely	58	16.1	3.99 ± 0.18	0.75
	2 or 3 times a week	266	73.7	4.26 ± 0.09	
	everyday	37	10.2	4.04 ± 0.21	
physical activity	light	192	53.2	4.39 ± 0.11	0.03
	moderate	119	33.0	4.09 ± 0.12	
	moderately heavy	12	3.3	3.85 ± 0.48	
	heavy	38	10.5	3.68 ± 0.19	

P: One-way analysis of variance

Urinary 8-oxo-dG data are expressed as µg / g creatinine ± SE

These data are derived from a report by Tamae et al. [56] with permission from Wiley-Blackwell.

Table 1. The characteristics of categorical lifestyle factors and urinary 8-oxo-dG levels in 361 male subjects



A

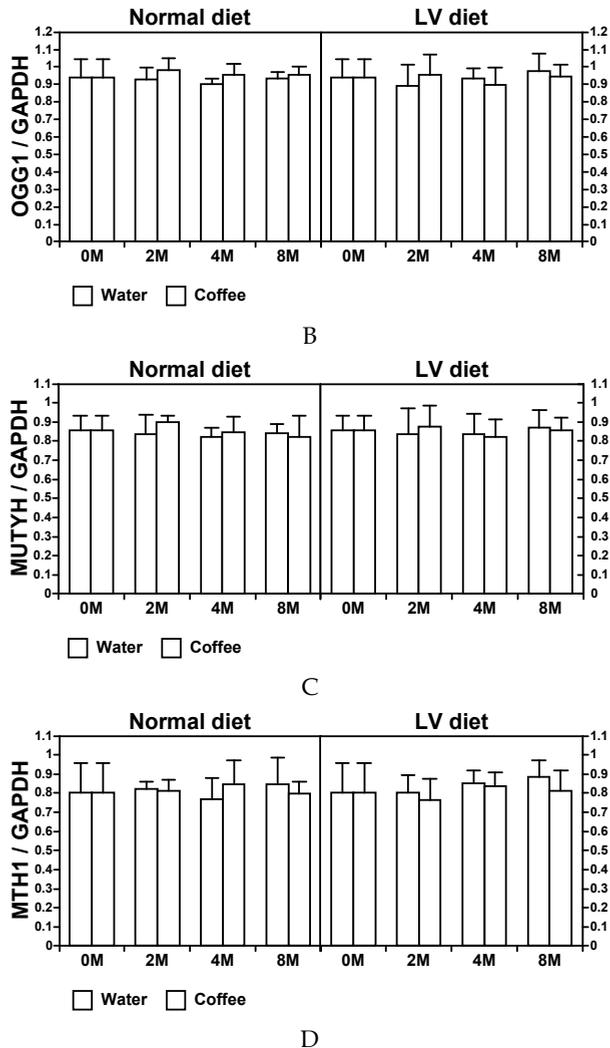


Fig. 3. (A) The 8-oxo-dG level in mouse liver DNA. The 8-oxo-dG value is expressed as the number per 10^5 deoxyguanosine. $n=3$ for data of 4 and 8 months, $n=4$ for data of 2 months. (B) *Ogg1* gene expression level. $n=4$ for LV diet + water for 8 months, $n=5$ for others. (C) *Mutyh* gene expression level. $n=4$ for LV diet + water for 8 months, $n=5$ for others. (D) *Mth1* gene expression level. $n=4$ for LV diet + water for 8 months, $n=5$ for others. The *GAPDH* gene was used as an internal standard. The total value of the gene expression level was calculated by the ratio of the expression of each gene to *GAPDH* expression. The values are mean + SD. * $P < 0.005$, ** $P < 0.05$. LV diet: low vitamin diet. *Mutyh*: eukaryotic homologue of MutY (mismatched adenine DNA glycosylase), *Mth1*: eukaryotic homologue of MutT (8-oxo-dGTPase). This figure was published in reference [53], Copyright Blackwell Publishing (license#: 2634430504476).

6. Dietary factors and OGG1 polymorphism

Interestingly, Sørensen et al. reported that the effect of vegetable consumption was associated with the *OGG1* Ser326Cys polymorphism [58]. A non-synonymous (associated with an amino acid change) genetic polymorphism at codon 326, Ser326Cys, in the *OGG1* gene is a strong candidate as a genetic factor for cancer risk [59, 60]. In fact, the *OGG1* Ser326Cys enzyme exhibited functional defects [61]. *OGG1* Ser326Cys excised 8-oxo-Gua from duplex DNA and cleaved abasic sites at rates 2- to 6-fold lower than those of the wild-type enzyme. Yamane et al. reported that 8-oxo-Gua-induced mutations were more efficiently suppressed in *OGG1*-Ser326 transduced cells than *OGG1*-Cys326 transduced cells, suggesting that *OGG1*-Cys326 has reduced ability to prevent mutagenesis by 8-oxo-Gua than *OGG1*-Ser326 *in vivo* in human cells [62]. Sørensen et al. observed a 54% decrease in lung cancer risk per 50% increase in vegetable intake among homozygous Cys326Cys carriers, and no decrease in risk among carriers of Ser326Ser or Ser326Cys. Therefore, to evaluate the effect of food factors on carcinogenesis, the *OGG1* polymorphism should be considered.

7. Conclusions

As described above, dietary factors influence 8-oxo-Gua generation and its repair systems in a variety of manners. They may contribute to human diseases, including cancer, by causing DNA damage and affecting DNA repair systems. The effects of food factors on the generation of 8-oxo-Gua and the expression of *OGG1* must be further clarified, to reduce the risk of food factor-related diseases, such as cancer or diabetes.

In addition, DNA double-strand break (DSB) is also a well-known DNA damage. Datta *et al.* reported that 8-oxo-formation was associated with ¹²⁵I-induced double-strand break (DSB) formation. Therefore, analyses of food factors and DSB formation should be interested as a further study [63].

8. Acknowledgements

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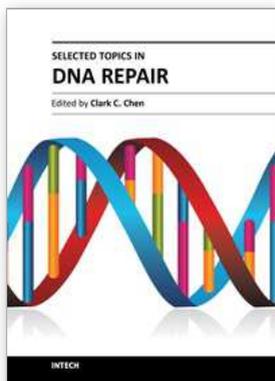
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This book is intended for students and scientists working in the field of DNA repair, focusing on a number of topics ranging from DNA damaging agents and mechanistic insights to methods in DNA repair and insights into therapeutic strategies. These topics demonstrate how scientific ideas are developed, tested, dialogued, and matured as it is meant to discuss key concepts in DNA repair. The book should serve as a supplementary text in courses and seminars as well as a general reference for biologists with an interest in DNA repair.

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