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Mini-review

Oxidatively induced DNA damage: Mechanisms, repair and disease

Miral Dizdaroglu

Biochemical Science Division, National Institute of Standards and Technology, Gaithersburg, MD 20899, USA

ABSTRACT

Endogenous and exogenous sources cause oxidatively induced DNA damage in living organisms by a variety of mechanisms. The resulting DNA lesions are mutagenic and, unless repaired, lead to a variety of mutations and consequently to genetic instability, which is a hallmark of cancer. Oxidatively induced DNA damage is repaired in living cells by different pathways that involve a large number of proteins. Unrepaired and accumulated DNA lesions may lead to disease processes including carcinogenesis. Mutations also occur in DNA repair genes, destabilizing the DNA repair system. A majority of cancer cell lines have somatic mutations in their DNA repair genes. In addition, polymorphisms in these genes constitute a risk factor for cancer. In general, defects in DNA repair are associated with cancer. Numerous DNA repair enzymes exist that possess different, but sometimes overlapping substrate specificities for removal of oxidatively induced DNA lesions. In addition to the role of DNA repair in carcinogenesis, recent evidence suggests that some types of tumors possess increased DNA repair capacity that may lead to therapy resistance. DNA repair pathways are drug targets to develop DNA repair inhibitors to increase the efficacy of cancer therapy. Oxidatively induced DNA lesions and DNA repair proteins may serve as potential biomarkers for early detection, cancer risk assessment, prognosis and for monitoring therapy. Taken together, a large body of accumulated evidence suggests that oxidatively induced DNA damage and its repair are important factors in the development of human cancers. Thus this field deserves more research to contribute to the development of cancer biomarkers, DNA repair inhibitors and treatment approaches to better understand and fight cancer.

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1. Introduction

Oxygen-derived species including free radicals are formed by normal cellular metabolism in aerobic organisms and by exogenous sources such as ionizing radiations, UV radiation, redox-cycling drugs and carcinogenic compounds among others [1]. Inflammation also produces oxygen- and nitrogen-derived species and is a hallmark of cancer as a critical component of tumor progression and human pathophysiology [2,3]. The acute inflammatory response recruits activated leukocytes involving neutrophils that can extensively damage DNA bases [4]. Of particular interest among oxygen-derived species are hydroxyl radical ($^{\cdot}OH$), superoxide radical ($O_2^{\cdot-}$) and non-radical H_2O_2. However, $O_2^{\cdot-}$ and H_2O_2 possess very low chemical reactivity, and do not react with most biological molecules such as DNA, proteins and lipids. Moreover, the reaction between these two species is very slow and its rate constant is close to zero. It is only catalyzed by transition metal ions such as iron and copper ions, generating $^{\cdot}OH$ (Haber–Weiss reaction) [1]. A highly damaging agent such as ionizing radiation also produces these species plus H atom ($H^{\cdot}$), also a free radical, and hydrated electron (e_{aq}^{-}) [5]. Hydroxyl radical reacts with most

biological molecules such as DNA at or near diffusion-controlled rates, causing damage to the heterocyclic DNA bases and the sugar moiety by a variety of mechanisms. Ionizing radiation-generated $H^{\cdot}$ and e_{aq}^{-} add to double bonds of DNA bases, leading to modifications [5]. Various repair mechanisms exist in living organisms to repair DNA damage. If not repaired, oxidatively induced DNA damage may lead to mutagenesis and genetic instability, which is a hallmark of cancer [6–9]. Experimental and epidemiological evidence strongly suggests that oxidatively induced DNA damage may significantly contribute to human cancers [10]. Therefore, understanding of this type of DNA damage, its repair mechanisms and biological effects is of utmost importance.

2. Mechanisms of oxidatively induced DNA damage

Hydroxyl radical reacts with purines and pyrimidines of DNA by addition to double bonds, and by abstraction of an $H^{\cdot}$ from the methyl group of Thy and from each of the C–H bonds of 2′-deoxyribose (Fig. 1). Addition reactions occur at diffusion-controlled rates with second-order rate constants of $4–9 \times 10^9\,M^{-1}\,s^{-1}$, and preferentially at sites of DNA bases with the highest electron density, whereas the rate constant of $H^{\cdot}$ abstractions equals to approximately $2 \times 10^9\,M^{-1}\,s^{-1}$ [5]. Ionizing radiation-generated e_{aq}^{-} reacts
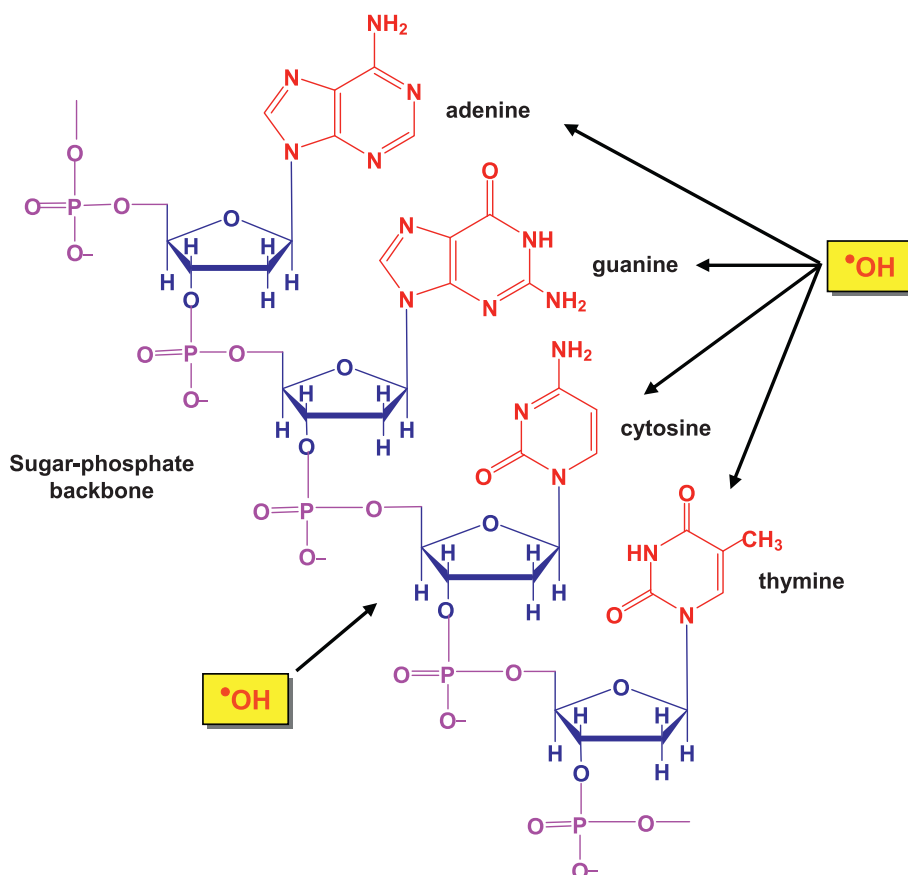
E-mail address: miral@nist.gov

Fig. 1. Attack sites of ·OH on DNA.

with DNA bases at diffusion-controlled rates with rate constants varying from 0.9×10^{10} M^{-1} s^{-1} to 1.7×10^{10} M^{-1} s^{-1}, whereas the rate constants of H· reactions amount to $1–5 \times 10^{8}$ M^{-1} s^{-1}.

2.1. Purine damage

Addition reactions of ·OH generate C4-OH-, C5-OH- and C8-OH-adduct radicals of Gua (Fig. 2), and at least C4-OH- and C8-OH-adduct radicals of Ade [11–13]. The addition of ·OH to C5 of Ade amounts to less than 5% [13]. The OH-adduct radicals of purines possess different redox properties. Thus, C5-OH- and C8-OH-adduct radicals are reducing, whereas C4-OH-adduct radicals are oxidizing. They also exist in different mesomeric forms, causing a "redox ambivalence" [11–14]. Dehydration of C4-OH- and C5-OH-adduct radicals yield neutral purine (–H)· radicals [e.g., Gua(–H)rad], which protonate to give rise to purine radical cations (e.g., Gua·$^{+}$) [12–15]. H· abstraction by ·OH from the NH$_2$ group attached to C2 (2-NH$_2$) of Gua has also been reported [16–20]. Chatgilialoglu et al. proposed that this reaction takes place to an extent of ~65% instead of addition ·OH to C4 of Gua and the thus-formed N-centered radical subsequently undergoes tautomerization to yield Gua(–H)· [18,19]. This is the same radical that results from the dehydration of the C4-OH-adduct radical as mentioned above. However, the proposed extent of the H· abstraction from 2-NH$_2$ excludes the addition of ·OH to C4 despite the well known high electron affinity in purines, making the ·OH addition an energetically favored reaction [20,21]. Phadatare et al. subsequently investigated the reactions of ·OH with Gua using quantum chemical calculations, pulse radiolysis and product analysis [20]. The results contrasted the large extent of H· abstraction by ·OH from the 2-NH$_2$ as proposed by Chatgilialoglu et al. [18,19], and

showed that the formation of C4-OH- and C8-OH-adduct radicals of Gua is the preferred reaction pathway, confirming the early work by O'Neill and Steenken et al. (see above). Furthermore, this work concluded that the H· abstraction from N9 and N1 are thermodynamically are even more favorable than that from 2-NH$_2$, also in contrast to the claim by Chatgilialoglu et al.

Oxygen reacts with purine OH-adduct radicals at varying rates. The reaction with the C4-OH-adduct radical of Gua is slow; however, C8-OH-adduct radicals and Gua(–H)· react with oxygen at diffusion-controlled rates [12–14]. Cadet et al. suggested that the reaction of Gua(–H)· generate imidazolone and oxazolone derivatives [22–25]. However, this mechanism has not been confirmed and a kinetically more favored alternative mechanism has been proposed [14]. Purine C8-OH-adduct radicals can be oxidized or reduced. In competition, they undergo a unimolecular opening of the imidazole ring by scission of the C8–N7 bond [12–14]. One-electron oxidation of purine C8-OH-adduct radicals gives rise to 8-hydroxyadenine (8-OH-Ade) and 8-hydroxyguanine (8-OH-Gua). On the other hand, 4,6-diamino-5-formamidopyrimidine (FapyAde) and 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyGua) are formed by opening of the imidazole ring and one-electron reduction as shown in Fig. 3 in the case of the C8-OH-adduct radical of Gua [7,12]. The reduction may also occur prior to ring opening giving rise to hemiorthoamides that are readily converted into formamidopyrimidines. Oxidizing agents increase the formation of 8-hydroxypurines, whereas formamidopyrimidines are preferentially formed under reducing conditions [7,12]. Both types of products are formed in the absence and presence of oxygen, albeit with different yields. Formamidopyrimidines differ from other pyrimidines such as Cyt and Thy in that they are attached to the sugar moiety of DNA through the amino group at
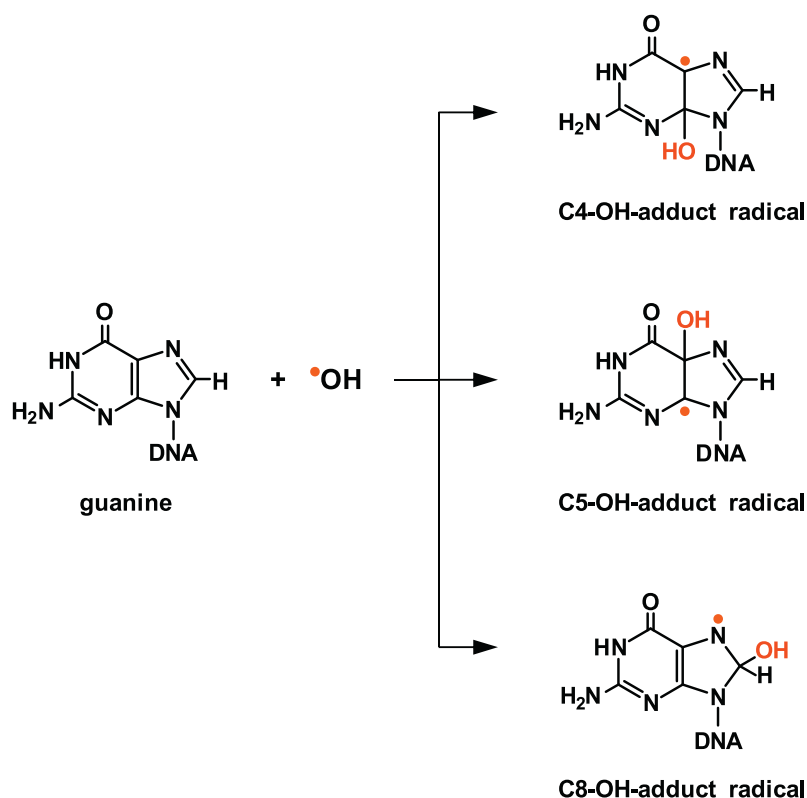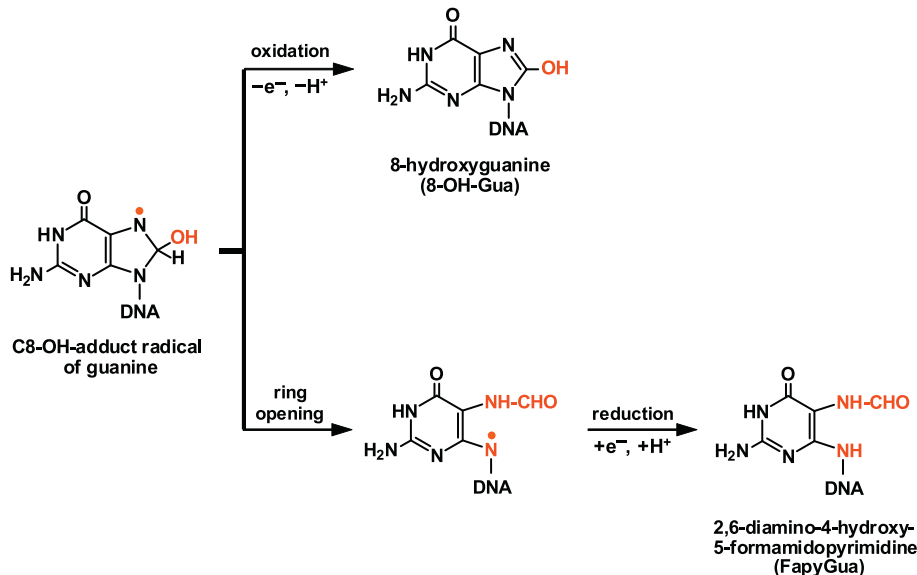
Fig. 2. Reactions of ·OH with Gua.

Fig. 3. Reactions of the C8-OH-adduct radical of Gua, resulting in formation of 8-OH-Gua and FapyGua.

the C6-position of the pyrimidine ring. It should be pointed out that FapyAde and FapyGua are chemically and mechanistically distinct from the methylation products of adenine and guanine, i.e., 4,6-diamino-5N-methylformamidopyrimidine (Me-FapyAde) and 2,6-diamino-4-hydroxy-5N-methylformamidopyrimidine (Me-FapyGua), respectively, which are formed under harsh experimental conditions by treatment with compounds such as dimethylsulfate and methylmethane sulfonate followed by alkali treatment [26–28]. Moreover, biological effects of Me-FapyAde and Me-FapyGua are substantially different from those of FapyAde

and FapyGua [29]. Direct effect of ionizing radiation causes ionization of purines forming a radical cation, which has been suggested to form the C8-OH-adduct radical upon hydration (addition of OH^-) (Fig. 4) [30–33]. As discussed above, the latter is also formed by addition of ·OH to the C8 of Gua. This means that the direct effect and indirect effect of ionizing radiation may produce identical products. It should be emphasized that, of numerous products of DNA bases, 8-OH-Gua has received much attention for the past two decades or so, and has extensively been investigated because of its relative ease of measurement and strong mutagenicity.
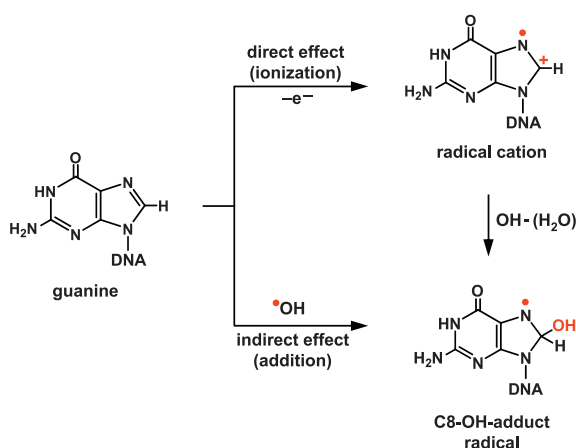
Fig. 4. Direct and indirect effects of ionizing radiation on Gua.

Unfortunately, this led to the paucity of investigation of other equally important DNA lesions in terms of mechanistic aspects and biological effects.

Oxidation of Gua as well as 8-OH-Gua by a number of oxidizing agents such as ionizing radiation, singlet oxygen, metal ions and peroxynitrate leads to a hydantoin product, spiroiminodihydantoin (Sp) [34–36]. Further oxidation of 8-OH-Gua also causes the formation of 5-guanidinohydantoin (Gh), depending on reaction conditions [35,37]. Originally, Cadet et al. misassigned the product of guanine formed by singlet oxygen to 4-OH–8-OH-Gua [38–42]. Later, the correct product has been found to be Sp [43,44]. Reactions of radical cations of guanine (Gua$^{.+}$) and 8-OH-Gua (8-OH-Gua$^{.+}$) have been proposed to lead to Sp and Gh, and to other products. Sp has also been identified in *Escherichia coli* treated with potassium dichromate [45]. This field has extensively been reviewed elsewhere [35].

2.2. Pyrimidine damage

Hydroxyl radical adds to the C5–C6-double bonds Cyt and Thy, yielding C5-OH- and C6-OH-adduct radicals. Abstraction of an H$^{.}$ from the methyl group of Thy also occurs, leading to an allyl radical
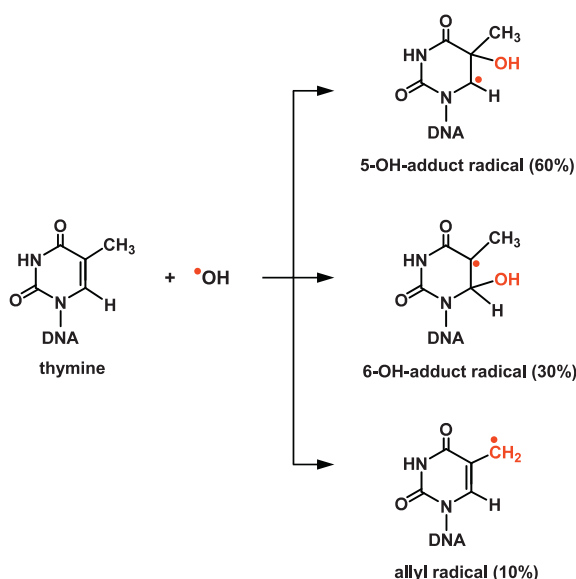

Fig. 5. Reactions of $^{.}$OH with Thy.

(Fig. 5). The distribution of the attack on Thy amounts to 60% at the C5 with the highest electron density, 30% at the C6 and 10% at the methyl group. In the case of Cyt, $^{.}$OH adds to the C5 and the C6 to an extent of 87% and 10%, respectively, because of the higher electron density at the former position. C5-OH- and C6-OH-adduct radicals of pyrimidines possess reducing and oxidizing properties, respectively [46–48]. Oxidation of C5-OH- and C6-OH-adduct radicals followed by addition of water and subsequent deprotonation produces Thy glycol (Thy gly) and Cyt glycol (Cyt gly) [7]. The allyl radical of Thy yields 5-(hydroxymethyl)uracil and 5-formyluracil upon oxidation. The types and yields of products significantly vary depending on the absence or presence of oxygen that reacts with intermediate radicals to give peroxyl radicals, which are unstable and decompose to give further products. 5,6-Dihydroxycytosine, dialuric acid, alloxan and ring reduction products 5-hydroxy-5-methylhydantoin (5-OH-5-MeHyd) and 5-hydroxyhydantoin are formed from decomposition of pyrimidine hydroxyhydroperoxides [7,49–53]. In the absence of oxygen, the reduction of C5-OH-adduct and C6-OH-adduct radicals followed by protonation yields 5-hydroxy-6-hydropyrimidines and 6-hydroxy-5-hydropyrimidines, respectively. Cyt gly and other Cyt products readily dehydrate and deaminate, giving rise to products such as 5-hydroxycytosine (5-OH-Cyt), Ura glycol (Ura gly), 5-hydroxyuracil (5-OH-Ura) and 5-hydroxy-6-hydrouracil and 5,6-dihydroxyuracil (isodialuric acid) [7,54]. Fig. 6 illustrates the structures of some major products of the DNA bases that have been identified in DNA *in vitro* and *in vivo* [7].

2.3. Sugar moiety damage

Hydroxyl radical abstracts an H$^{.}$ from each of the five C-atoms of the sugar moiety of DNA, generating a plethora of products. Mechanisms of DNA sugar damage and strand breaks by $^{.}$OH have been elucidated [55–58]. Sugar products are either released from DNA as free sugar lesions or remain within DNA or constitute end-groups of broken DNA strands. The well-understood reactions of the C4′-radical generate 2-deoxypentose-4-ulose within DNA, and strand breaks with 2,3-dideoxypentose-4-ulose and 2,3-dideoxypentose-4-ulose as 3′- and 5′-end groups, respectively. Oxidation of the C1′-radical followed by reaction with water (addition of OH^{-}) and by the release of an unaltered base generates 2-deoxyribonic acid lactone within DNA.

The formation of 2,3-dideoxypentos-4-ulose and 2,5-dideoxypentos-4-ulose are inhibited by oxygen, whereas 2-deoxypentose-4-ulose and 2-deoxyribonic acid lactone are formed under both the absence and presence of oxygen. Fragmented sugar ring products such as erythrose and 2-deoxytetradialdose are also formed. Fragmentation of the C4′-peroxyl radical yields a glycolic acid residue as a 3′-end group [59]. Moreover, the C5′-peroxyl radical when formed by neocarzinostatin gives rise to a 5′-aldehyde nucleoside as a 5′-end group of a broken DNA strand without base release [60–62]. Fig. 7 illustrates the major products of the sugar moiety of DNA.

2.4. 8,5′-Cyclopurine-2′-deoxynucleosides

More than four decades ago, Keck reported an $^{.}$OH-induced C5′–C8-intramolecular cyclization within adenosine-5′-monophosphate (AMP) in the absence of oxygen, giving rise to 8,5′-cyclo-AMP [63]. This highly stereospecific reaction occurs by the attack of the C5′-centered sugar radical at the C8 of the purine ring. The rate constants for the cyclization amount to $1.6 \times 10^5 \text{ s}^{-1}$ for dA and $\sim 1 \times 10^6 \text{ s}^{-1}$ for dG [64,65]. The N-centered radical is subsequently oxidized, yielding tandem lesions 8,5′-cyclopurine-2′-deoxyadenosine (cdA) from dA and 8,5′-cyclopurine-2′-deoxyguanosine (cdG) from dG. Both *R*- and
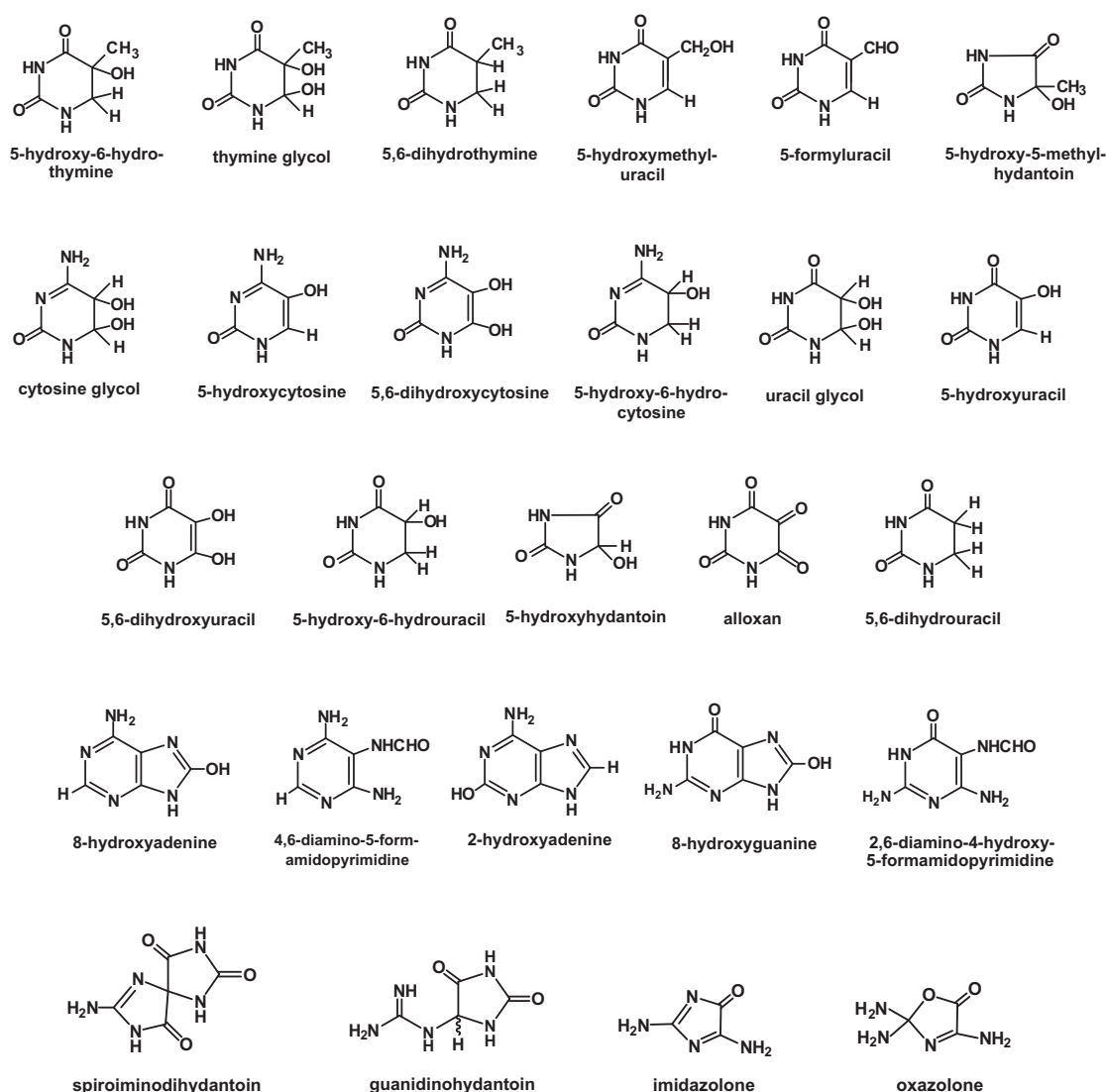
Fig. 6. Structures of the major oxidatively induced products of DNA bases.

S-diastereomers of each compound are formed. 8,5′-Cyclopurine-2′-deoxynucleosides represent a concomitant damage to both the base and sugar moieties of the same nucleoside, and thus, are regarded as tandem lesions. Fig. 8 illustrates the mechanism of formation of these compounds in the case of *R*-cdA and *S*-cdA. Oxygen inhibits the C5′–C8-intramolecular cyclization because of its reaction with the C5′-centered radical at a near diffusion-controlled reaction [64,66]. At low oxygen concentrations, however, a competition may occur between the C5′–C8-intramolecular cyclization and the reaction of oxygen with the C5′-centered radical [67]. This competition may also occur *in vivo* because of low oxygen concentration in the cell nucleus [68]. Identification of 8,5′-cyclopurine-2′-deoxynucleosides in DNA *in vivo* and in human urine attests to this fact (see, e.g., [69–81]. The C5′–C8-intramolecular cyclization causes unusual puckering of the sugar moiety [82–84]. As a consequence, the length of C–C-bonds and bond angles significantly change compared to normal nucleosides, weakening hydrogen bonds and causing substantial perturbations of the DNA double helix. Fig. 9 illustrates the structural model of cdA from two perspectives and its comparison with that of dA, clearly demonstrating the distortion caused by the C5′–C8-cyclization. An extensive review of reaction mechanisms, formation

and biological effects of 8,5′-cyclopurine-2′-deoxynucleosides can be found elsewhere [85].

2.5. Tandem lesions

Tandem lesions have been identified in oligodeoxynucleotides and DNA exposed to ionizing radiation or other ·OH-generating systems. These lesions consist of either two adjacent damaged bases on the same strand, or an intrastrand cross-link between two adjacent DNA bases on the same strand, or an interstrand cross-link between two DNA bases on opposite strands. A tandem lesion consisting of an 8-OH-Gua and an adjacent formamido residue has been identified first in Gua-Thy or Gua-Cyt dideoxynucleotides, and then in DNA [86–97]. The origin of the formamido residue has been shown to be either Thy or Cyt. These tandem lesions have been suggested to be formed from a single radical event. Intrastrand cross-links between Gua and Thy, Gua and Cyt, and Ade and Thy have been detected in oligodeoxynucleotides and DNA [91,92,98–109]. Exposure living cells to γ-irradiation caused the formation of Gua-Thy and Gua-Cyt cross-links [110,111]. An interstrand cross-link has been identified in DNA between Thy on one strand and Ade on the opposing strand [112–115]. The formation
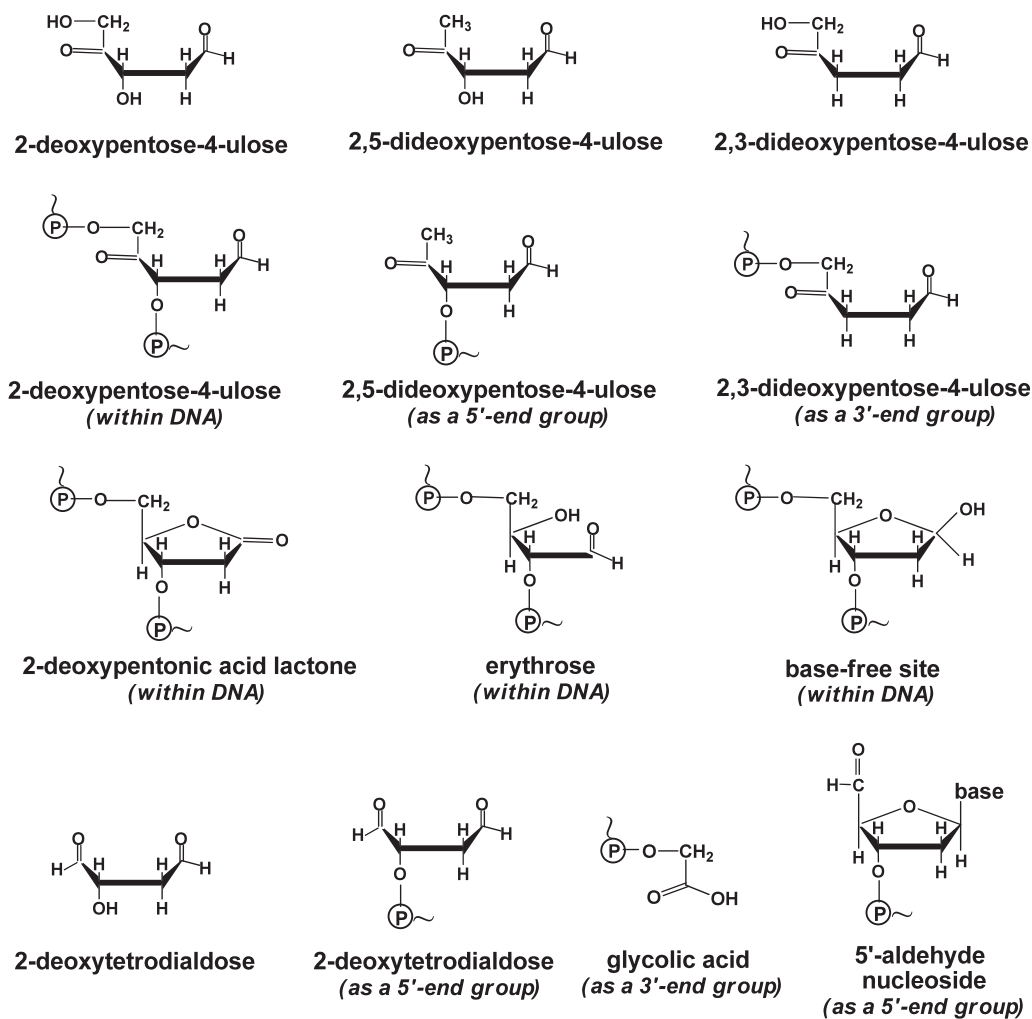
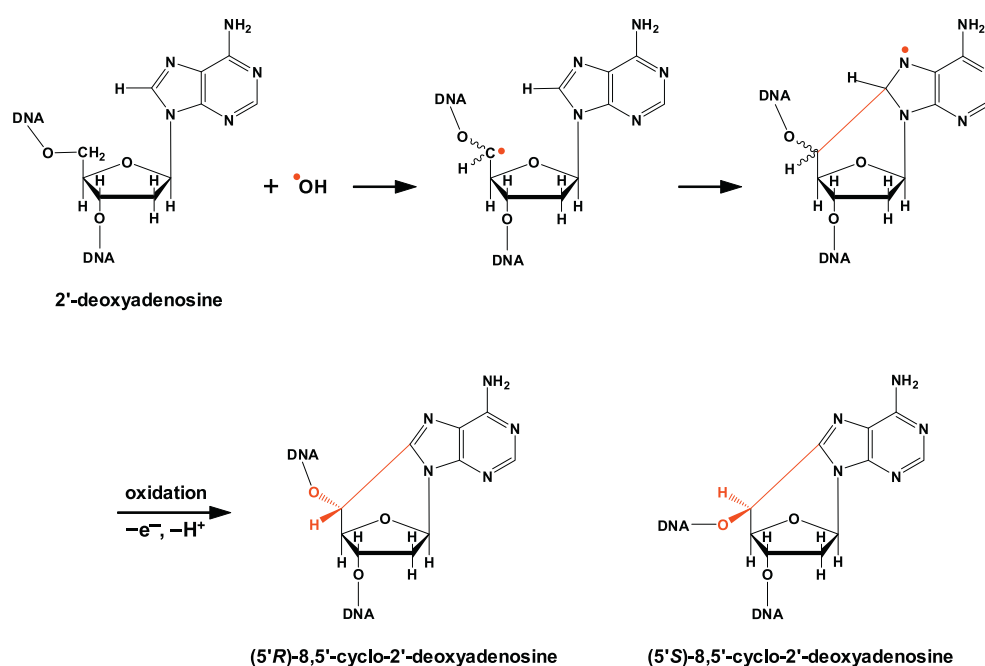**Fig. 7.** Structures of the major oxidatively induced products of the 2′-deoxyribose moiety of DNA.

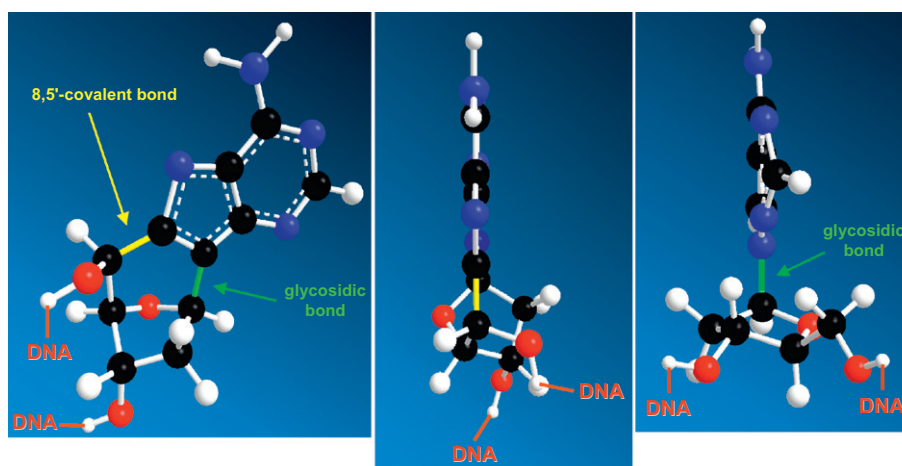**Fig. 8.** Formation mechanism of 8,5′-cyclopurine-2′-deoxynucleosides.

Fig. 9. Comparison of the structural models of 8,5′-cyclopurine-2′-deoxyadenosine (left and middle) and 2′-deoxyadenosine (right).

mechanism of this cross-link has been elucidated using isotopic labeling [115].

2.6. Clustered DNA damage

Ionizing radiation produces clustered damage (also known as locally multiply damaged sites) in DNA other than double-strand breaks (DSBs) [116–127]. Clustered sites contain two or more lesions within one or two helical turns of DNA and can be either on opposing strands or tandem on the same strand. Ionizing radiation is the almost exclusive source of these lesions, since endogenously induced damage is unlikely to produce them [128,129]. The formation of a clustered lesion by bleomycin has also been reported [130]. There is a large diversity of clustered DNA damages, which are differently processed by the cell depending on the type of lesions, distance between lesions, presence of strand breaks, etc. Bistranded or tandem clusters may be resistant to DNA repair by DNA glycosylases or endonucleases, and thus persist in cells for a significant time period [124]. Bistranded clusters may give rise to double-strand breaks, if two lesions are removed prior to excision of one lesion only. The biological consequences of clustered lesions include point mutations and lethality. This field of research has extensively been reviewed in the papers cited above, and will not be discussed here any further.

2.7. DNA–protein cross-links

DNA–protein cross-links are formed in mammalian cells by ·OH reactions with DNA bases and proteins [131–136]. A Thy-Tyr cross-link has been found *in vivo* and *in vitro* by exposure of isolated chromatin, cultured mammalian cells and animals to ionizing radiation, H_2O_2, metal ions and carcinogenic compounds [137–141]. The covalent cross-linking has been shown to take place between the allyl radical of Thy and the C3 of the Tyr ring [142–145]. Thy-Lys and Cyt-Tyr cross-links have also been identified in mammalian chromatin *in vitro* [146–149]. Mechanisms proposed for the formation of these cross-links were twofold as shown in Fig. 10A–D: 1. Addition of a DNA base radical such as the allyl radical of Thy to the aromatic ring of an amino acid such as Tyr, leading to Thy-Tyr cross-linking (Fig. 10A); 2. Combination of a DNA base radical with an amino acid radical (Fig. 10B–D). It should be noted that the phenoxyl radical of Tyr results from addition of ·OH to the C3 of the aromatic ring followed by H_2O elimination [150].

3. Maintenance of genetic stability

Oxidatively induced DNA damage can lead to genetic instability, which is a hallmark of cancer [9,151–153]. Genetic instability may affect the proteins involved in DNA replication, DNA repair, apoptosis, cell cycle regulation and chromosomal stability, and ultimately lead to cancer [152]. Furthermore, resistance to cancer therapy may also occur by genetic instability. To maintain genetic stability for survival, living organisms evolved to possess cellular mechanisms to repair DNA damage [8,154]. Failure to repair DNA lesions may lead to mutagenesis, cytotoxicity, cell death and consequently to disease processes such as carcinogenesis. Fig. 11 illustrates possible pathways resulting from damage to a DNA base in terms of a Gua lesion as an example. The DNA lesion can be removed and the DNA structure can be restored to its original state by various repair mechanisms. However, if the lesion is not repaired before replication, it can interact with replication either by blocking the DNA synthesis or by being tolerated and bypassed by DNA polymerases, which can insert a non-cognate intact base (e.g., Ade) opposite the lesion (e.g., a Gua lesion). A lesion that blocks replication would be a lethal lesion, leading to cell death, whereas a bypassed lesion mispaired with an intact base would cause mutations. The future of a cell containing a DNA lesion may be determined by the interplay between these three pathways. A DNA lesion may also pair with a cognate DNA base. Consequently, it will be neither lethal nor mutagenic. Lesions that are replication blocks can also be mutagenic when bypassed by polymerases [6].

Two major mechanisms exist to repair oxidatively induced DNA lesions. These are base-excision repair (BER) and nucleotide-excision repair (NER) [8]. It is beyond the purpose of this article to extensively review DNA repair mechanisms. However, some aspects of DNA repair concerning oxidatively induced DNA lesions will be discussed. Multiple steps and enzymes are involved in both BER and NER. A mismatch repair (MMR) mechanism also exists for repair of DNA lesions mispaired with a DNA base. In addition, repair in the nucleotide pool occurs to prevent the incorporation of modified 2′-deoxynucleotides into DNA by DNA polymerases.

3.1. Base excision repair

In BER, a DNA glycosylase removes a DNA lesion by hydrolyzing the *N*-glycosidic bond and generating an abasic site (AP-site). Some DNA glycosylases also possess an associated AP-lyase activity that
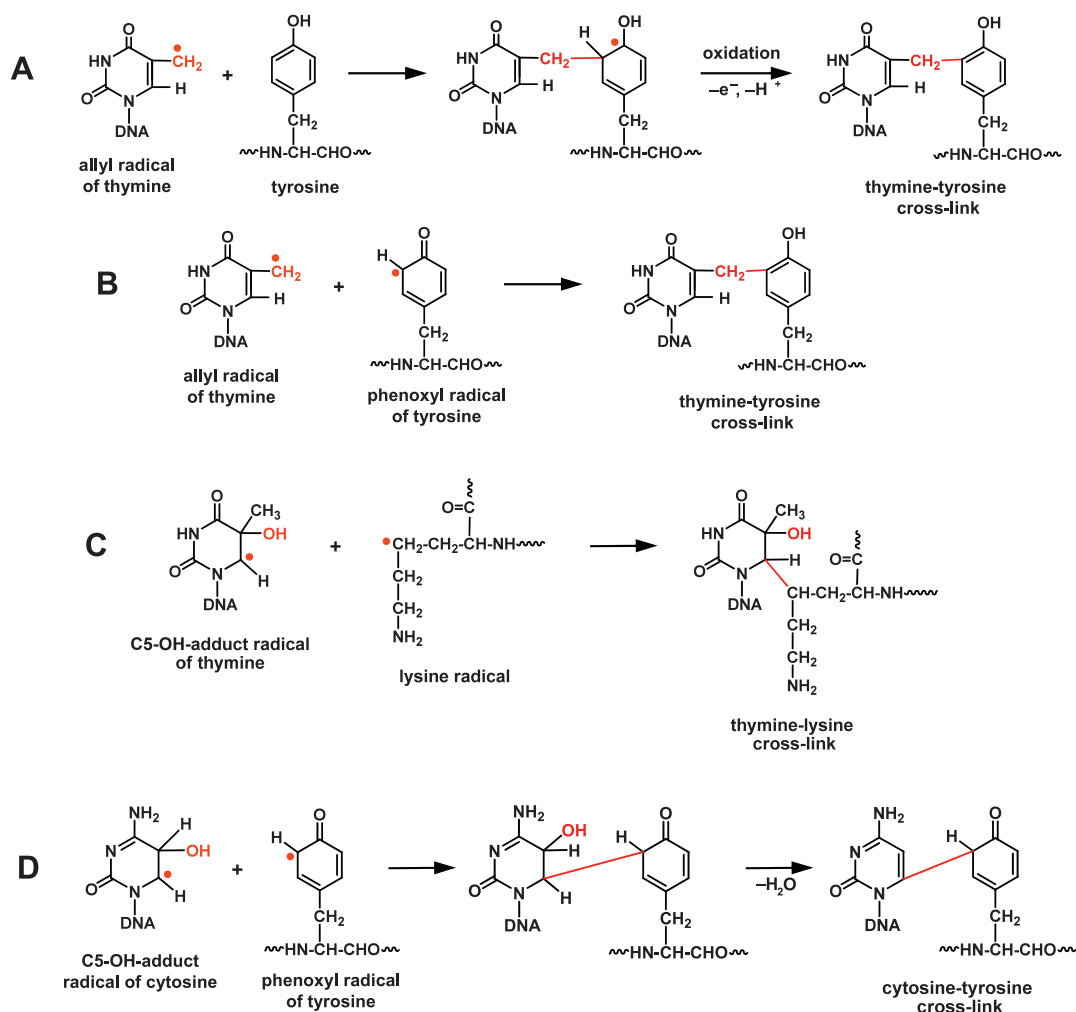
Fig. 10. Formation mechanisms of some DNA–protein cross-links detected in mammalian chromatin *in vitro* and *in vivo*.
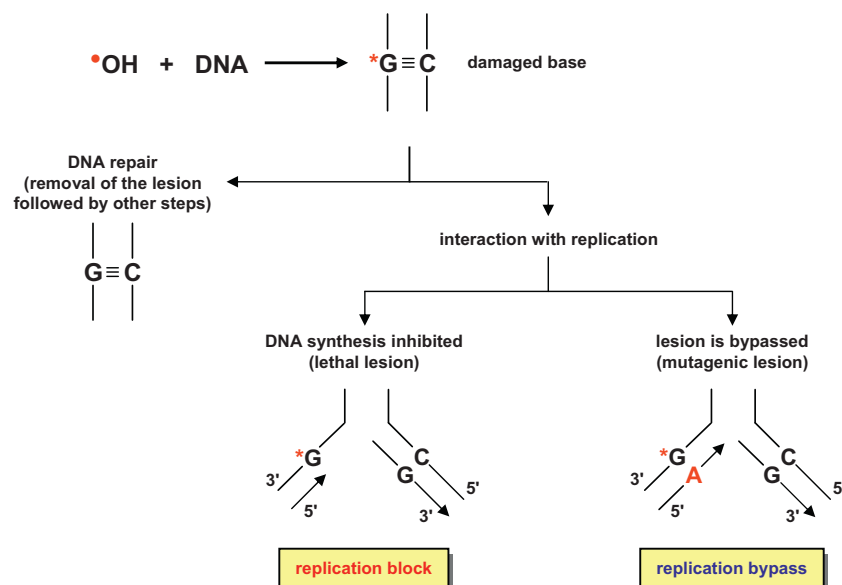
Fig. 11. Interplay between the repair and the interaction with replication of a Gua lesion.

hydrolyzes the 3′-phosphodiester bond of the AP site by a β- or β-δ-elimination mechanism generating a 3′ α,β-unsaturated aldehyde and 5′-phosphate products, and thus strand breaks [8]. AP-sites

are processed by AP-endonucleases, DNA polymerases and DNA ligases to fully restore the DNA structure. There are two families of DNA glycosylases, the Fpg/Nei family and the Nth superfamily

[155,156]. Substrate specificities and excision kinetics of these enzymes have been determined using DNA substrates containing multiple lesions as shown in Fig. 6 (reviewed in [157]). In *E. coli*, three major DNA glycosylases exist to remove oxidatively induced DNA base lesions. Formamidopyrimidine DNA glycosylase (Fpg, also called MutM) belong to the Fpg/Nei family and specifically excises FapyAde, FapyGua and 8-OH-Gua with similar excision kinetics from DNA containing multiple lesions [31,157,158]. Endonuclease VIII (Nei), also a member of the same family, predominantly acts on pyrimidine lesions and FapyAde [159]. Endonuclease III (Nth) belongs to the Nth superfamily, possesses an overlapping substrate specificity with Nei and removes pyrimidine lesions and FapyAde [51,160]. In eukaryotes, a functional homolog of Fpg, i.e., 8-hydroxyguanine-DNA glycosylase (OGG1), exists in the Nth superfamily. This enzyme, which is present in various organisms, exhibits a strong specificity for excision of FapyGua and 8-OH-Gua, but not FapyAde, unlike Fpg [161–166]. OGG1 exhibits no specificity for Gh or Sp [167]. Human NTH1, which is also an AP lyase, is specific for pyrimidine lesions; however, it possesses a narrower substrate specificity than *E. coli* Nth [168].

E. coli Nei-like DNA glycosylases have also been discovered in eukaryotes and named NEIL1, NEIL2 and NEIL3 [169–175]. NEIL1 is located to both the nucleus and mitochondrion [176], suggesting a role for this protein in the protection of genetic stability. FapyAde and FapyGua have been found to be the major substrates of both NEIL1 and NEIL3 [169,176–181]. Moreover, NEIL1 acts on pyrimidine lesions Thy gly and 5-OH-5-MeHyd, albeit to a lesser extent. NEIL3 excises 5-OH-Ura and 5-OH-Cyt from DNA in addition to Thy glycol and 5-OH-5-MeHyd more efficiently than NEIL1. In contrast to Fpg and OGG1, NEIL1 and NEIL3 exhibit no detectable activity for 8-OH-Gua. However, mouse NEIL1 and NEIL3 efficiently remove the oxidation products of 8-OH-Gua, Sp and Gh from synthetic oligodeoxynucleotides [181,182]. Recent data suggested that NEIL1 may also play a role in NER besides being a DNA glycosylase in BER [183]. NEIL2 exhibits a unique preference for excision from DNA bubbles, and preferentially excises 5-OH-Ura, and also 5-OH-Cyt and 5,6-dihydrouracil to a lesser extent, when oligodeoxynucleotides containing a single lesion are used as substrates [171,184]. Excision of DNA base lesions by NEIL2 from DNA containing multiple lesions has not yet been reported.

3.2. Nucleotide excision repair

NER is responsible for removal of bulky DNA-distorting lesions from DNA [185–187]. Two distinct mechanisms of NER exists, global genome repair and transcription-coupled repair, which are responsible for the repair of the entire genome and preferential repair of transcribing DNA strands, respectively [188–190]. An excinuclease, which is a multisubunit enzyme system, makes dual incisions in the DNA strand to remove an oligodeoxynucleotide containing the lesion. The remaining gap is then filled and ligated by polymerases to complete the repair. The length of the removed oligodeoxynucleotide differs between prokaryotes and eukaryotes [185,191]. Oxidatively induced lesions Thy gly and 8-OH-Gua are reportedly repaired by NER as well [192,193]. BER cannot repair 8,5′-cyclopurine-2′-deoxynucleosides because of the 8,5′-covalent bond. NER is the major mechanism for cellular repair of these lesions [69,194–196].

3.3. Mismatch repair

Mismatch repair (MMR) is involved in the repair of mismatches such as 8-OH-Gua·Ade mismatch [8]. In *E. coli*, a DNA glycosylase, MutY removes Ade from this mismatch and thus facilitates the pairing of 8-OH-Gua with the cognate base Cyt, which is then repaired by BER [197]. The human homolog MUTYH, which belongs

to the Nth superfamily, is targeted to both the nucleus and the mitochondrion [197–202]. MUTYH also removes 2-OH-Ade from opposite all four intact DNA bases [202]. There is evidence that inherited mutations in *mutyh* predispose individuals to colorectal cancer and somatic G → T mutations, indicating the important role of MUTYH in cancer prevention [36,197,203–211]. No other oxidatively induced DNA base lesions in mismatches have been found to be substrates of MUTYH. FapyGua, which also mispairs with Ade and gives rise to G → T mutations [212,213], is a potential candidate to be a substrate of MUTYH and thus to play a role in colorectal cancer as well as 8-OH-Gua.

3.4. Repair in the nucleotide pool

A unique repair mechanism exists in the cellular nucleotide pool to repair modified 2′-deoxynucleoside triphosphates, before they can be incorporated into DNA by DNA polymerases and potentially cause mutations [214–216]. In *E. coli*, MutT hydrolyzes 8-OH-dGTP to 8-OH-dGMP, preventing its incorporation into DNA [214]. Mammalian and human homologs of MutT have been discovered [215,217,218]. Human MTH1 also hydrolyzes 8-OH-dATP and 2-OH-dATP [219]. Deletion of *mth1* in mice led to spontaneous carcinogenesis with tumors found in lungs, livers and stomachs, pointing to the importance of this gene in cancer prevention [218,220].

3.5. Repair of DNA strand breaks

Oxidatively induced damage also causes single- and double-strand breaks in DNA, which lead to genetic instability and detrimental biological consequences [5,8]. Single-strand breaks are repaired by similar mechanisms discussed in the case of BER. Repair of DSBs generally occurs by either homologous recombination (HR) or non-homologous end-joining (NHEJ) mechanisms. When NHEJ is deficient, HR proteins such as BRCA1 are induced and DSBs are processed by HR, pointing to an interplay between BER and HR/NHEJ pathways [221]. Deficiency in BRCA1 or in repair of DSBs adversely affect processing of oxidatively induced DNA lesions [75,222,223]. Repair of DNA strand breaks has extensively been reviewed in the past [8,224,225], and will not be discussed here any further.

4. Biological consequences of oxidatively induced DNA lesions

4.1. Purine-derived lesions

DNA base lesions may be lethal or mutagenic or both depending on the action of DNA polymerases [6]. 8-OH-Gua is the most extensively studied DNA base lesion among those discussed above. It mispairs with Ade leading to G → T transversion mutations; however, it also pairs with cognate Cyt [226–229]. G → T mutations constitute the second most common somatic mutations found in human cancers, with 14.6% of all mutations in the tumor suppressor gene *TP53* following C → T transition mutations (44.2%) [230] (also see http://www-p53.iarc.fr/). However, these mutations may result not only from 8-OH-Gua, but also from other DNA base lesions. Thus, FapyGua being the other equally important Gua lesion also mispairs with Ade, resulting in G → T mutations [212]. This lesion has been found to be even more mutagenic than 8-OH-Gua in simian kidney cells [213]. Fig. 12 illustrates the pathways leading to G → T mutations by 8-OH-Gua and FapyGua. FapyAde mispairs with Ade and leads to A → T transversions [213,231]. 8-OH-Ade induces A → G transitions and A → C transversions in mammalian cells [232–234]. Sp and Gh predominantly mispair with Ade and Gua, leading to G → T and G → C mutations,
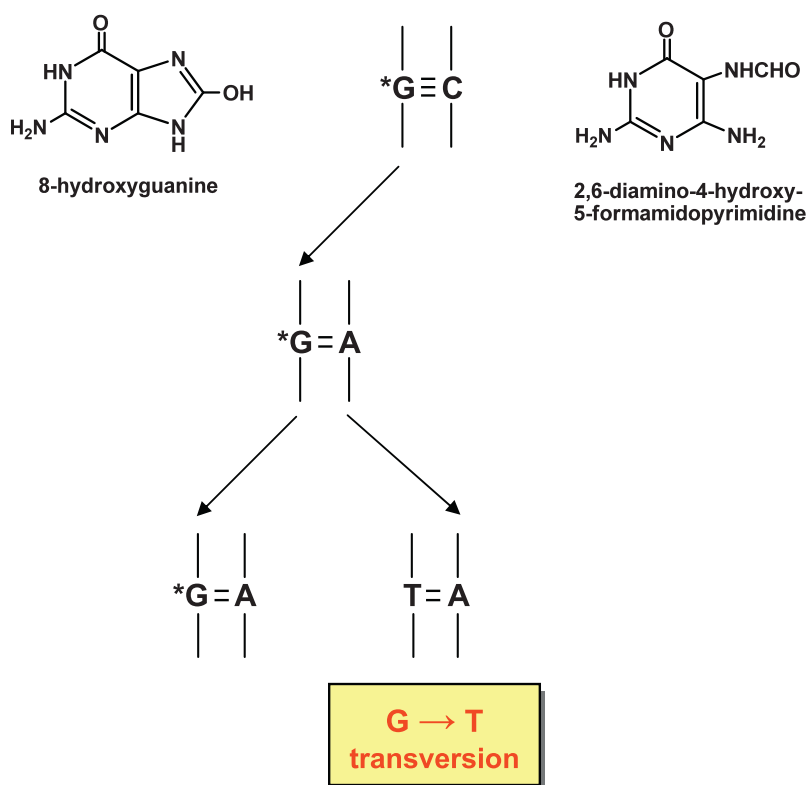
Fig. 12. Formation of G → T transversion mutations resulting from the mispairing of 8-OH-Gua or FapyGua with Ade.

respectively [35,235–238]. In a different sequence context, however, these products almost entirely mispair with Ade and cause G → T mutations [239].

4.2. Pyrimidine-derived lesions

Cyt-derived products Ura glycol and 5-OH-Ura induce C → T transition mutations by mispairing with Ade [6,240–242]. 5-OH-Cyt also leads to C → T mutations as well as C → G transversion mutations [240,241,243,244]. C → T transitions are the most frequently observed mutations that are generated by oxidatively induced DNA damage [243,245–247]. These mutations are also the most frequent mutations found in human tumors and in TP53 [230,248]. Thy gly correctly pairs with Ade and is poorly mutagenic [6,249,250]. In several sequences contexts, it is bypassed by DNA polymerases and mispairs with Gua, leading to T → C transitions [251–253]. Thy gly is a strong block to most DNA polymerases and is a lethal lesion in vivo [6,249–251,254–257]. 5-Hydroxy-6-hydrothymine strongly blocks E. coli DNA polymerase I Klenow fragment (exo-) [258]. Ionizing radiation-induced Thy-derived product, 5,6-dihydrothymine is neither lethal nor mutagenic, because it is not a block to DNA polymerases and correctly pairs with Ade [259,260].

4.3. 8,5′-Cyclopurine-2′-deoxynucleosides

S-cdA strongly blocks transcription and DNA polymerases including DNA polymerase δ and the bypass polymerase η, and reduces transcription and causes transcriptional mutagenesis [195,196,261–263]. RNA polymerase II bypasses S-cdA and incorporates adenosine opposite to the next 5′- to S-cdA, leading to multiple nucleotide deletions [263]. S-cdG is a strong block to replication and a highly mutagenic lesion leading to G → A transitions with G → T transversions to a lesser extent [264]. By inference,

S-cdA may also be a strongly mutagenic lesion. Elevated levels of 8,5′-cyclopurine-2′-deoxynucleosides in genomic DNA in vivo in cancer and other diseases point to a possible role of these lesions in carcinogenesis and other disease processes [70,72–77,85].

5. Oxidatively induced DNA damage and disease

Unrepaired DNA lesions can accumulate in the genome and progressively lead to mutations, and consequently to disease including cancer. Elevated levels of oxidatively induced DNA base lesions have been observed in precancerous and cancerous tissues [71,72,85,265–274], in agreement with the fact that persistent oxidative stress exists in cancer [275,276]. This strongly implicates this type of DNA damage in the etiology of cancer, but does not necessarily mean that such DNA damage would be responsible for carcinogenic events. However, most of oxidatively induced DNA base lesions are mutagenic and may thus be major contributors to carcinogenesis. Mutations can also occur in DNA repair genes, destabilizing DNA repair machinery. In this respect, 60% of cancer cell lines have somatic mutations in DNA repair genes (http://www.sanger.ac.uk.genetics/CGP). Defects in DNA repair are associated with carcinogenesis [9,152,277–285]. Defective DNA repair in tumors may cause therapy resistance, adversely affecting the outcome of cancer and survival of patients [283,285–289]. Recent evidence suggests that some type of malignant tumors may possess increased DNA repair capacity. Resistance to chemotherapy has been found in non-small-cell lung cancer, and this has been associated with elevated NER in cancerous tissues [286–288,290]. In some cancer lung cell lines, an increased expression of ogg1 has been observed when compared to control lung cell lines [291]. Levels of ethano-DNA adducts in cancerous colon tissues were lower than in surrounding non-cancerous tissues of colorectal cancer patients, pointing to an increase in DNA repair in cancerous tissues [292,293]. Recent evidence

suggested that repair of oxidatively induced DNA damage may be upregulated in human colorectal cancer [294]. Increased rate of mutations leading to an increase in genetic instability may cause cell death late in tumor evolution. However, tumors that over-express DNA repair genes may be favored by natural selection to become capable of surviving and thus develop greater DNA repair capacity than non-cancerous tissues. Increased DNA repair in tumors may cause resistance to DNA damage-based therapeutic agents and adversely affect the outcome of therapy. It appears that DNA repair capacity in cancerous tumors compared to non-cancerous tissues would be a determining factor for patient survival. In this context, DNA repair proteins are increasingly regarded as important predictive, early detection, prognostic and therapeutic factors in cancer [283,285,295]. DNA repair pathways are potential drug targets for treatment. DNA repair inhibitors are being developed and tested in clinical trials to increase the efficacy of therapy [283,285,295]. Development of DNA repair inhibitors for combination therapy or as single agents for monotherapy that target BER, NER and MMR pathways will contribute to selective killing of tumors and thus to future advances in cancer therapy. To this end, further understanding of DNA repair pathways will be of fundamental importance.

Polymorphisms in DNA repair genes are also a risk factor for cancer [154,281,283,285,296]. Polymorphic variants of DNA repair enzymes such as NEIL1 and OGG1 involved in BER have been discovered in humans. Defects in repair by these and other DNA repair enzymes have been shown to lead to detrimental biological consequences. It is beyond the scope of this article to review the role of all DNA repair enzymes in disease processes. Only the consequences of defects in DNA repair by DNA glycosylases such as NEIL1, NTH1, NEIL3 and OGG1 will be presented. The consequences of defects in MUTYH and MTH1 involved in MMR and nucleotide pool repair, respectively, have briefly been discussed above.

5.1. NEIL1

Since its discovery, numerous studies demonstrated a critical role for NEIL1 in maintaining the genetic stability and in disease prevention. Inactivating mutations in *neil1* correlated with human gastric cancer [297]. Embryonic stem cells were sensitized to killing effects of ionizing radiation by downregulation of NEIL1 expression [174]. Significantly decreased levels of NEIL1 led to increase in spontaneous mutations in human and Chinese hamster cell lines, and the mutation frequency was further enhanced by oxidative stress [298]. NEIL1 expression was increased in human carcinoma cells by oxidative stress [299]. In this respect, four polymorphic variants of human NEIL1, i.e., NEIL1-Cys[82], NEIL1-Asp[83], NEIL1-Asn[252] and NEIL1-Arg[136] have been isolated and characterized [178]. An AP site-containing 33-mer oligodeoxynucleotide, a Thy glycol-containing 30-mer oligodeoxynucleotide and DNA substrates with multiple lesions have been used to evaluate the effect of mutations on the AP-lyase and glycosylase activities of NEIL1. As Fig. 13A illustrates, NEIL1-Cys[82] (Ser82Cys) and NEIL1-Asn[252] (Asp252Asn) exhibited a β,δ-elimination activity on the AP-site as wild type NEIL1. In contrast, NEIL1-Asp[83] (Gly83Asp) had a β-elimination activity only and NEIL1-Arg[136] (Cys136Arg) was not active at all. In agreement with these data, an efficient excision of Thy glycol from the 30-mer oligodeoxynucleotide (Fig. 13B), and that of FapyAde and FapyGua from DNA (Fig. 13C,13D) by wild type NEIL1, NEIL1-Cys[82] and NEIL1-Asn[252] was observed, whereas NEIL1-Asp[83] and NEIL1-Arg[136] were completely devoid of DNA glycosylase activity. NEIL1-Cys[82] appeared to have a lower activity on FapyGua than on FapyAde (Fig. 13C,13D). In all three cases, the specificity constant (k_{cat}/K_M) for excision of FapyAde was significantly greater than that for excision of FapyGua, suggesting a preference of these enzymes for FapyAde over FapyGua. The reason

may be that FapyGua is also a substrate of OGG1, which does not act on FapyAde. In the case of DNA substrates, NEIL1-Arg[136] could not be used, because it precipitated under the experimental conditions used. Taken together, these data suggested that individuals carrying *neil1* mutations may be at risk for disease development.

Recently, a NEIL knockout (*neil1*$^{-/-}$) mouse model has been used to investigate the consequences of NEIL1 deficiency *in vivo* [300]. Without exogenous oxidative stress, *neil1*$^{-/-}$ and heterozygotic (*neil1*$^{+/-}$) animals developed the typical symptoms of human metabolic syndrome such as severe obesity, dyslipidemia, fatty liver disease and hyperinsulinemia. Mitochondrial (mt) DNA damage and deletions also increased, pointing to a deficiency of mtDNA repair and/or increased levels of oxidatively induced damage in mtDNA. Male animals were most severely affected. These results strongly pointed to an important role of NEIL1 in prevention of disease processes. In the same context, there is evidence that metabolic syndrome may be associated with certain types of cancer [301–304]. Another study has recently been conducted using *neil1*$^{-/-}$, *nth1*$^{-/-}$ and *neil1*$^{-/-}$/*nth1*$^{-/-}$ mice [179]. In the second year of life, these animals developed pulmonary adenomas and adenocarcinomas, and hepatocellular carcinomas, nodular hyperplasia and severe hepatocellular displasia. A much greater tumor incidence was observed in *neil1*$^{-/-}$/*nth1*$^{-/-}$ mice than in either of the single knockouts. Table 1 shows the number of male and female animals used in this study, and the resulting numbers and percentages of tumor incidence. Moreover, activating GGT → GAT transitions were observed in single and double knockouts in codon 12 of *K-ras* of pulmonary tumors. This is in contrast to the GGT → GTT transversions of codon 12 in *K-ras* in the lung tumors of mice lacking both *ogg1* and *mutyh* [305].

Oxidatively induced DNA lesions have also been measured in several organs of *neil1*$^{-/-}$, *neil1*$^{-/-}$/*nth1*$^{-/-}$ and *nth1*$^{-/-}$ mice. Fig. 14 illustrates the levels of FapyAde, FapyGua and 8-OH-Gua in livers, kidneys and brains of these mice. When compared to wild type animals, significantly increased levels of FapyAde were observed in all three organs of *neil1*$^{-/-}$ and *neil1*$^{-/-}$/*nth1*$^{-/-}$ mice. The kidneys of *nth1*$^{-/-}$ mice also contained slightly but significantly elevated level of this lesion. FapyGua also accumulated in livers and kidneys of *neil1*$^{-/-}$ and *neil1*$^{-/-}$/*nth1*$^{-/-}$ mice. However, no significant increase in the level of this lesion was observed in the brains of knockout mice. In contrast, 8-OH-Gua did not accumulate in any organ of knockout animals. These findings are in complete agreement with the substrate specificity of NEIL1 observed *in vitro* using DNA containing multiple lesions (see above), and provide the evidence that FapyAde and FapyGua, but not 8-OH-Gua, are also the major *in vivo* substrates of NEIL1. Increased levels of FapyAde in kidneys of *nth1*$^{-/-}$ mice can be explained by the fact that this lesion is also an *in vivo* substrate of mouse NTH1 [176]. The levels of OGG1 was normal in all knockout mice. This is likely to be the reason for the observed differences in the accumulation levels of FapyAde and FapyGua, because FapyGua is a major substrate of OGG1, but not FapyAde. Besides the lack of NEIL1 activity on 8-OH-Gua, normal levels of OGG1 apparently prevented accumulation of 8-OH-Gua in knockout mice. In contrast, accumulation of 8-OH-Gua has been reported in lacking both MUTY and OGG1 [306] or OGG1 only [176,183]. Significantly greater levels of FapyAde and FapyGua in cancer-prone *neil1*$^{-/-}$ and *nth1*$^{-/-}$ mice than in wild type mice strongly suggest a role for these compounds in carcinogenesis, and for the involvement of NEIL1 and NTH1 in cancer prevention. The absence of 8-OH-Gua accumulation and GGT → GTT transversions of codon 12 in *K-ras*, which is typical of tumors in *ogg1*$^{-/-}$ and *muty*$^{-/-}$ mice, unequivocally excludes the involvement of 8-OH-Gua in the tumor incidences observed in *neil1*$^{-/-}$ and *nth1*$^{-/-}$ animals.

Recent findings suggested an additional function for NEIL1. Greater levels of *R*-cdA and *S*-cdA have been observed in livers of
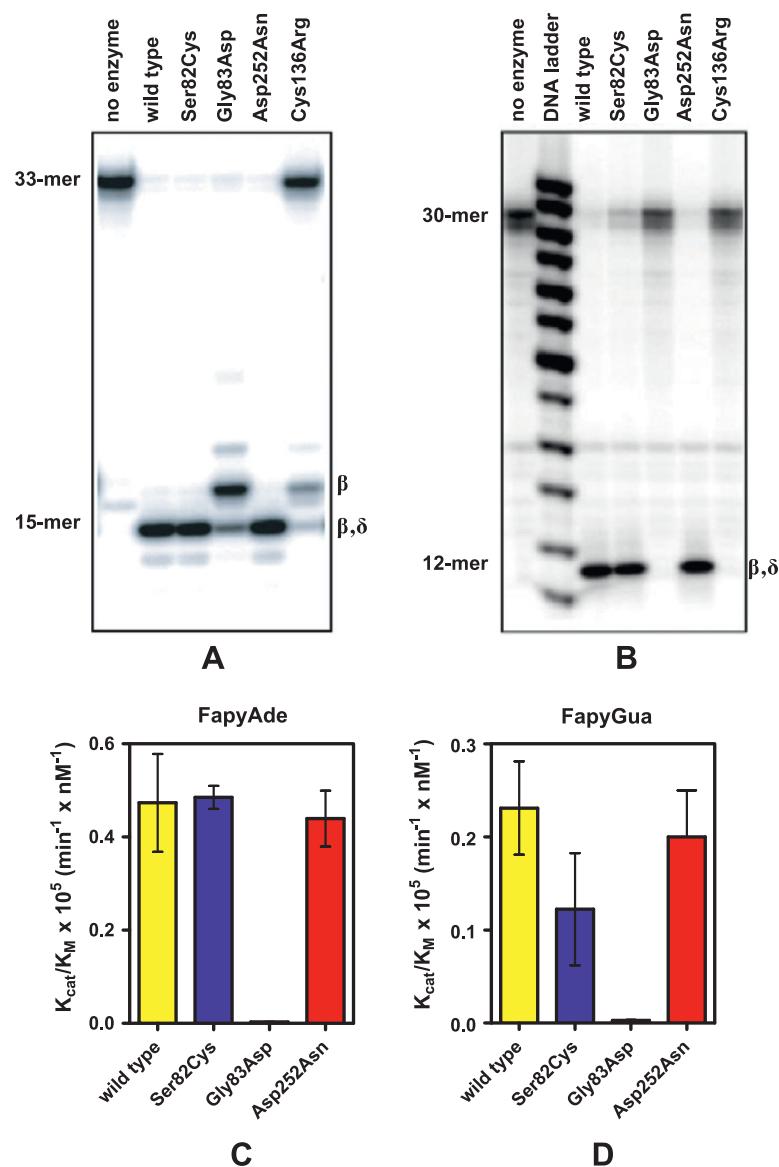
Fig. 13. (A) Lyase activities of wild type NEIL1 and its polymorphic variants on an abasic site-containing oligodeoxynucleotide, (B) lyase activities of wild type NEIL1 and its polymorphic variants on a Thy gly-containing oligodeoxynucleotide, (C and D) the k_{cat}/K_M values for excision of FapyAde and FapyGua from DNA by wild type NEIL1 and its polymorphic variants. Uncertainties are standard deviations (data from [178]).

Table 1
Numbers and percentages of tumor incidence in lungs and livers of $neil1^{-/-}$, $nth1^{-/-}$, and $neil1^{-/-}/nth1^{-/-}$ mice (data from [179]).

Genotype	Males			Females		
	Total number	Lung[a] number (%)	Liver[b] number (%)	Total number	Lung[a] number (%)	Liver[b] number (%)
$neil1^{-/-}$	25	3 (12%)	4 (16%)	18	0 (0%)	2 (11.1%)
$nth1^{-/-}$	52	1 (1.9%)	8 (15.4%)	54	2 (3.7%)	7 (13%)
$neil1^{-/-}/nth1^{-/-}$	43	32 (74.4%)	20 (46.5%)	29	12 (41.4%)	5 (17%)

[a] Adenoma, adenocarcinoma.
[b] Hepatocellular carcinoma, nodular hyperplasia, severe dysplasia.

$neil1^{-/-}$ mice than in those of wild type and $ogg1^{-/-}$ mice (Fig. 15) [183]. As was discussed above, R-cdA and S-cdA can only be repaired by NER; therefore, this finding points to a role of NEIL1 in NER as well, in addition to being a DNA glycosylase in BER. It may well be that NEIL1 interacts with proteins of the NER complex. To this end, there is evidence that excision of FapyAde and FapyGua by NEIL1 is stimulated by Cockayne syndrome B protein (CSB) [180]. Furthermore, accumulation of S-cdA has been observed in liver, kidney and brain of $csb^{-/-}$ mice, providing evidence that CSB is involved in repair of S-cdA [78], as in repair of 8-OH-Gua, 8-OH-Ade, FapyAde and FapyGua [180,307–309]. These facts strongly suggest an interaction between NEIL1 and CSB in repairing DNA lesions. Future studies may elucidate the mechanism of action of NEIL1 in NER. In contrast, no direct functional stimulation of hOGG1 by CSB occurs, although a defective csb decreases the efficiency of 8-OH-Gua removal by BER and expression
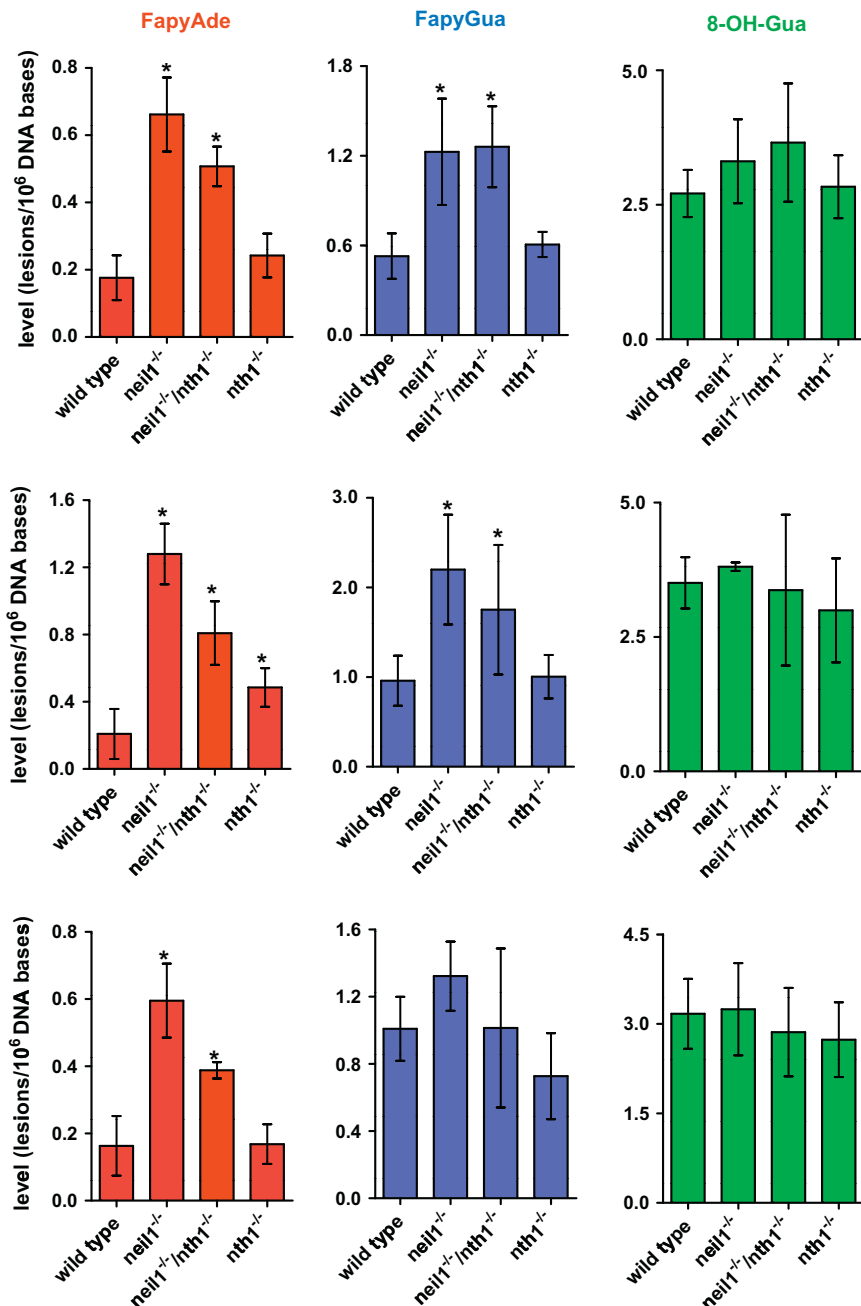
Fig. 14. Levels of FapyAde, FapyGua and 8-OH-Gua in livers, kidneys and brains (from the top) of wild type, *neil1*$^{-/-}$, *neil1*$^{-/-}$/*nth1*$^{-/-}$ and *nth1*$^{-/-}$ mice. The uncertainties are standard deviations. Stars denote statistical significance ($p < 0.05$) (data from [179]).

of hOGG1 [310]. Other NER proteins, Cockayne syndrome A (CSA) and xeroderma pigmentosum C (XPC) also play a role in removal of the aforementioned DNA lesions [73,76]. It may well be that CSA and XPC interact with NEIL1 as well as CSB in repair of oxidatively induced DNA lesions.

Accumulated data as discussed above suggest an important role for NEIL1 in the prevention of cancer and metabolic syndrome-associated diseases. Thus far, it is not clear as to how a deficiency in a DNA glycosylase such as NEIL1 *in vivo* may lead to carcinogenesis and other disease processes. NEIL1 possesses a substrate specificity, which is distinct from that of most other known DNA glycosylases. Moreover, its possible role in NER in addition to being a DNA glycosylase in BER makes it a unique DNA repair enzyme.

NEIL1 may also have a primary role in transcription- and replication-coupled repair [169,184]. On the basis of all these compelling facts, one may strongly argue that NEIL1 is not simply a backup DNA glycosylase for other DNA glycosylases in the BER pathway as was assumed originally, when it was first discovered. Another important question arises from the specificity of NEIL1 about the role of its substrates, FapyAde, FapyGua, *R*-cdA and *S*-cdA in disease processes observed in NEIL1 knockout animals. The lack of its activity on 8-OH-Gua *in vitro* and *in vivo*, which has almost always been presented in the literature as the major lesion that contributes to the mutagenic and carcinogenic effects of oxidatively induced DNA damage, clearly excludes this lesion from the adverse effects of NEIL1 deficiency *in vivo*. The known mutagenic and other
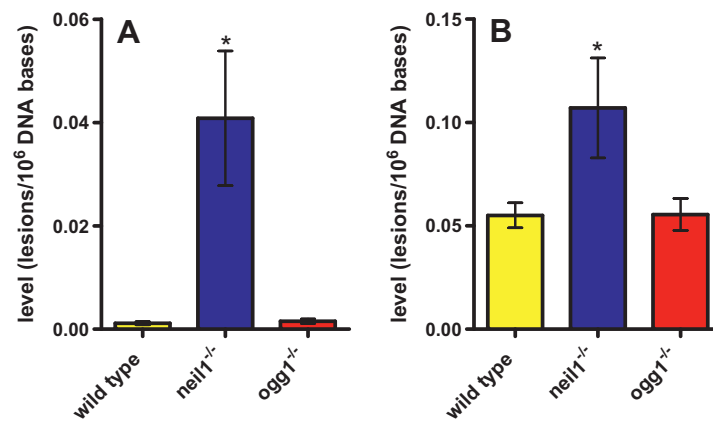
Fig. 15. Levels of *R*-cdA (A) and *S*-cdA (B) in livers of wild type, *neil1*$^{-/-}$ and *ogg1*$^{-/-}$ mice. The uncertainties are standard deviations. Stars denote statistical significance ($p < 0.05$) (data from [183]).

properties of NEIL1 substrates should add a new dimension to efforts for understanding repair and biological effects of oxidatively induced DNA damage.

Moreover, a recent study demonstrated the ability of NEIL1 and NEIL3 in the prevention of mutagenesis *in vivo* [181]. An *E. coli fpg mutY nei* mutant strain, which spontaneously exhibits a high G → T transversion mutation frequency, has been used for this purpose. As Fig. 16A illustrates, the expression of NEIL1 or NEIL3 in this strain significantly reduced the mutation frequency. The expression of *E. coli* Nei also reduced the mutation frequency, albeit at a lower level. When DNA samples were extracted from these strains and analyzed for DNA lesions, a significantly greater level of FapyGua was observed in the *fpg mutY nei* mutant than in the wild type strain, most likely due to the absence of Fpg (Fig. 16B). A significant reduction in the FapyGua amount was observed by expression of NEIL1 or NEIL3. In contrast, there was no reduction of FapyGua in the triple mutant expressing Nei. This is likely due to the previously reported lack of specificity of Nei for this lesion [159]. These results confirm the specificity of NEIL1 for *in vivo* repair of FapyGua and suggest that NEIL3 also recognizes FapyGua *in vivo*. Furthermore, the reduction of both the mutation frequency and the level of FapyGua suggests that the G → T transversion

mutations observed in the triple mutant result from FapyGua at least to a great extent. This lesion is known to lead to this type of mutations [212,213].

5.2. OGG1

Many single-nucleotide polymorphisms have been found in human *ogg1*, fourteen of which change the sequence of the major protein isoform OGG1-1a (http://www.ncbi.nlm.nih.gov/sites/entrez?db=snp) [311–315]. Function, substrate specificity and kinetics of only a few proteins encoded by these genes have been reported [162,163,166,314]. The most widely encountered polymorphic form is the *ogg1* 326C allele with varying frequencies from ∼0.1 in African Americans to >0.5 in some Japanese populations (http://www.ncbi.nlm.nih.gov/sites/entrez?db=snp). Most attention has been given to the product protein OGG1-Cys^{326}, whose association has been demonstrated with the risk of esophageal, colon, orolaryngeal, lung, gastric, cervical, gallbladder, head, neck, kidney and bladder cancers [311,316–334]. However, no association has been reported between the OGG1-Cys^{326} polymorphism and the risk of squamous cell head and neck carcinoma [335]. Other mutant forms OGG1-His^{154}, OGG1-Gln^{46} and OGG1-Gln^{209}
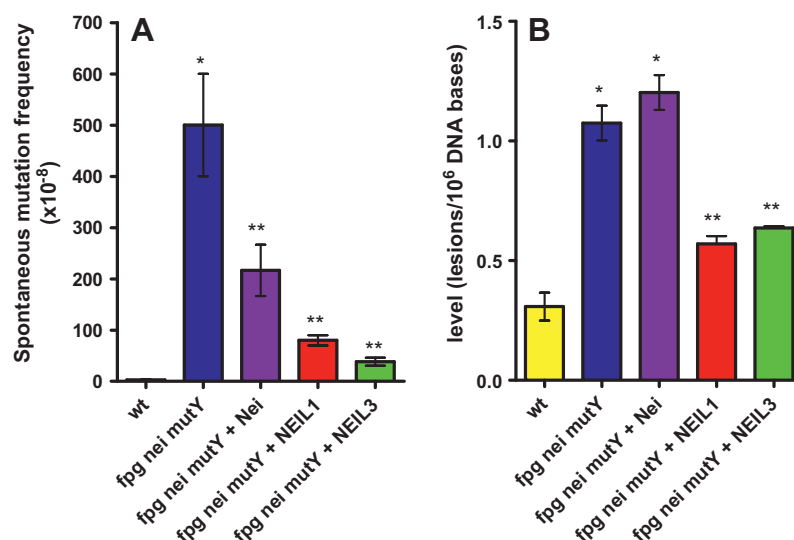
Fig. 16. Levels of spontaneous mutation frequency (A) and FapyGua (B) in wild type, *fpg nei mutY E. coli* and *fpg nei mutY E. coli* expressing Nei, NEIL1 or NEIL3. The uncertainties are standard deviations. *Denotes statistical significance ($p < 0.01$) in relation to wild type *E. coli*. **Denotes statistical significance ($p < 0.01$) in relation to *fpg nei mutY E. coli* (A), and to *fpg nei mutY E. coli* and *fpg nei mutY E. coli* expressing Nei (B) (data from [181]).

have been found in a human gastric cancer cell line, human kidney tumors and a leukemic cell line, respectively [315,317,336]. OGG1-Val[288] has been observed in Alzheimer's disease patients with its activity being lower than that of the wild type OGG1 [314]. Low OGG1 activity has been shown to constitute a risk factor in lung, head and neck cancers [337–341]. Substrate specificities and excision kinetics of a variety of polymorphic variants of OGG1 have been determined using oligodeoxynucleotides containing a single lesion or using DNA with multiple lesions. For excision of both FapyGua and 8-OH-Gua from DNA, OGG1-Val[288] exhibited excision kinetics similar to that of the wild type OGG1, whereas the activities of OGG1-Cys[326], OGG1-His[154], OGG1-Gln[46], and OGG1-Asn[322] were significantly lower than that of wild type OGG1 [162,163, 166]. However, OGG1-Val[288] was ~30% less efficient than the wild type OGG1 when an oligodeoxynucleotide containing 8-OH-Gua paired with Cyt was used as the substrate [166].

Thus far, there has been no clear connection between deficiencies in *ogg1* and human carcinogenesis. There were also conflicting reports in the literature about the disease development in *ogg1* knockout animals, although greater levels of 8-OH-Gua have been observed than in wild type animals. In certain organs of $ogg1^{-/-}$ mice, an increase in G → T transversions has been found with a simultaneous accumulation of 8-OH-Gua; however, the animals exhibited no malignancies and no pathological changes [342,343]. No tumor formation has been observed in $ogg1^{-/-}$ mice treated with $KBrO_3$, despite a much greater level of 8-OH-Gua found in these mice than in wild type mice [344]. Upon exposure of both wild type and $ogg1^{-/-}$ mice to low doses of ionizing radiation, $ogg1^{-/-}$ mice exhibited a significant increase in G → T transversions in their brains; however, no tumor development has been observed [345]. On the other hand, $ogg1^{-/-}$ mice accumulated 8-OH-Gua in their genomes and developed lung adenoma/carcinoma after about 1.5 years after birth [346]. No other DNA lesions have been measured to unequivocally conclude that this effect had been due to accumulation of 8-OH-Gua only. Exposure to chronic UVB made $ogg1^{-/-}$ mice susceptible to skin carcinogenesis upon radiation [347]. A greater level of 8-OH-Gua has been observed in these mice than in wild type ones, suggesting this type of oxidatively induced DNA damage plays a role, although levels of no other major lesions have been measured in this case, either. Only in the case of deficiencies in both *ogg1* and *mutyh*, lung and ovarian tumors, and lymphomas significantly occurred in the majority of mice, with accompanying G → T transversions in lung tumors at codon 12 of the *K-ras* oncogene [305]. Mice with missing *mutyh* alone developed no tumors similar to $ogg1^{-/-}$ mice. These findings may indicate the requirement of several DNA repair genes for prevention of mutagenesis and tumorigenesis. This notion is supported by the fact that a greater level of tumor formation occurred in $neil1^{-/-}/nth1^{-/-}$ mice than in single knockout mice [179]. Wide population studies may contribute to a better understanding of the role of defects in *ogg1* in carcinogenesis.

6. Oxidatively induced DNA lesions and DNA repair proteins as biomarkers

Accumulated evidence strongly suggests that oxidatively induced DNA lesions and DNA repair proteins may be used as potential sentinels for cancer risk assessment and therapy monitoring. For more than 20 years, a large number of studies have been conducted to measure DNA base lesions in human urine as non-invasive biomarkers for diagnosis, early detection and therapy monitoring as well as for epidemiological investigations. First studies suggested two modified 2′-deoxynucleosides, 8-hydroxy-2′-deoxyguanosine (8-OH-dG) and 2′-deoxythymidine glycol as suitable biomarkers for oxidatively induced DNA damage [348,349].

Subsequent studies mainly measured 8-OH-dG and its free base 8-OH-Gua in human urine (reviewed in [350]). 5-OH-Ura, 8-OH-Ade and FapyGua have also been identified in urine as potential biomarkers [351,352], although these lesions have not received as much attention as 8-OH-dG and 8-OH-Gua. There has been a significant controversy about the measurement techniques in different laboratories and the source of these lesions in urine. The contribution of diet and cell death has been excluded [353–356]. BER has been suggested to be a likely source for the excretion of 8-OH-Gua into urine because of its efficient removal by OGG1 [357]. In contrast, it is not clear as to how BER would be responsible for the presence of 8-OH-dG. Moreover, no oligodeoxynucleotides containing 8-OH-dG have been identified in human urine, excluding NER for excretion of this lesion into urine [354]. There is evidence that the nucleotide pool may also be a major source of 8-OH-dG in urine [358,359]. Recently, the presence of both *R*-cdA and *S*-cdA as free nucleosides has been discovered in human urine [80]. Since these lesions are repaired by NER, their excretion into urine has been proposed to result from repair by this pathway. *R*-cdA and *S*-cdA may serve as alternative well-suited disease biomarkers.

DNA repair proteins may serve as early detection, prognostic and therapeutic biomarkers in cancer [283,285]. To be used as biomarkers for cancer and other diseases, these proteins must be accurately measured in relevant tissues by proper chemical and physical techniques. Recently, methodologies using isotope-dilution tandem mass spectrometry have been developed for positive identification and accurate quantification of some DNA glycosylases [360]. For this purpose, stable isotope-labeled analogues of these proteins have been isolated, purified and characterized to be used as internal standards [361]. More efforts will be necessary to develop mass spectrometric assays for the accurate measurement of a variety of DNA repair proteins in tissues using proper stable isotope-labeled internal standards. There is no doubt that such measurements will be of fundamental importance for understanding of the role of DNA proteins in carcinogenesis, for their use as biomarkers in cancer detection, prognosis and therapy, and for development of DNA repair inhibitors to increase the efficacy of the therapy.

7. Conclusions

Normal cellular metabolism and exogenous sources generate oxygen-derived species including free radicals that can damage biological molecules such as DNA, proteins and lipids. Oxidatively induced DNA damage by these damaging agents may lead to mutagenesis and genetic instability, which is a hallmark of cancer. Accumulated evidence suggests that this type of DNA damage may significantly contribute to human cancers. Oxidatively induced damage to DNA components generates a plethora of products by a variety of mechanisms. Most of these DNA lesions are known to be strongly mutagenic leading to mutations that are commonly found in human cancers. They accumulate in cancerous tissues, possibly contributing to genetic instability and metastatic potential. To maintain genetic stability and survive, living organisms are endowed with a number of different mechanisms involving numerous proteins to repair DNA damage. Unrepaired DNA lesions may cause detrimental biological consequences. Evidence suggests that defective DNA repair, and mutations and polymorphisms in DNA repair genes significantly contribute to cancer development. Recent findings showed that some types of tumors possess increased DNA repair capacity, which may cause resistance to therapeutic agents and affect the outcome of therapy and survival. Apparently, DNA repair capacity in cancerous tissues will be an important factor to be considered for future therapeutic

approaches in cancer treatment. Moreover, DNA repair proteins are increasingly emerging as important predictive, early detection, prognostic and therapeutic factors in cancer. DNA repair inhibitors are being developed to target DNA repair pathways in order to increase the efficacy of therapy. Evidence accumulated for over two decades suggests that oxidatively induced DNA lesions and DNA repair proteins may be used as potential cancer biomarkers for risk assessment, early detection and therapy monitoring. Analytical techniques such as isotope-dilution mass spectrometry will be needed for accurate measurement of DNA lesions and repair proteins as suitable biomarkers. More research in the field of DNA damage and repair will be essential to develop cancer biomarkers, DNA repair inhibitors and treatment approaches to better understand and fight cancer.

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