Mutation Research 771 (2017) xxx–xxx

Contents lists available at ScienceDirect

Mutation Research/Reviews in Mutation Research

journal homepage: www.elsevier.com/locate/reviewsmr
Community address: www.elsevier.com/locate/mutres

Review

Repair of oxidatively induced DNA damage by DNA glycosylases: Mechanisms of action, substrate specificities and excision kinetics

Miral Dizdaroglu*, Erdem Coskun, Pawel Jaruga

Biomolecular Measurement Division, National Institute of Standards and Technology, 100 Bureau Drive, MS 8315, Gaithersburg, MD 20899, USA

ARTICLE INFO

Article history:
Received 17 November 2016
Available online 16 February 2017

Keywords:
Oxidatively induced DNA damage
DNA repair
DNA glycosylases
Substrate specificities
Excision kinetics

ABSTRACT

Endogenous and exogenous reactive species cause oxidatively induced DNA damage in living organisms by a variety of mechanisms. As a result, a plethora of mutagenic and/or cytotoxic products are formed in cellular DNA. This type of DNA damage is repaired by base excision repair, although nucleotide excision repair also plays a limited role. DNA glycosylases remove modified DNA bases from DNA by hydrolyzing the glycosidic bond leaving behind an apurinic/apyrimidinic (AP) site. Some of them also possess an accompanying AP-lyase activity that cleaves the sugar-phosphate chain of DNA. Since the first discovery of a DNA glycosylase, many studies have elucidated the mechanisms of action, substrate specificities and excision kinetics of these enzymes present in all living organisms. For this purpose, most studies used single- or double-stranded oligodeoxynucleotides with a single DNA lesion embedded at a defined position. High-molecular weight DNA with multiple base lesions has been used in other studies with the advantage of the simultaneous investigation of many DNA base lesions as substrates. Differences between the substrate specificities and excision kinetics of DNA glycosylases have been found when these two different substrates were used. Some DNA glycosylases possess varying substrate specificities for either purine-derived lesions or pyrimidine-derived lesions, whereas others exhibit cross-activity for both types of lesions. Laboratory animals with knockouts of the genes of DNA glycosylases have also been used to provide unequivocal evidence for the substrates, which had previously been found in *in vitro* studies, to be the actual substrates *in vivo* as well. On the basis of the knowledge gained from the past studies, efforts are being made to discover small molecule inhibitors of DNA glycosylases that may be used as potential drugs in cancer therapy.

Published by Elsevier B.V.

Contents

Abbreviations: $O_2^{\bullet}$, superoxide radical; $^{\bullet}OH$, hydroxyl radical; $NO^{\bullet}$, nitric oxide; e_{aq}^{-}, hydrated electron; $H^{\bullet}$, hydrogen atom; *k*, reaction rate constant; 8-OH-Gua, 8-hydroxyguanine (also called 8-oxo-Gua); Sp, spiroiminohydantoin; Gh, 5-guanidinohydantoin; cdA, 8,5′-cyclo-2′-deoxyadenosine; cdG, 8,5′-cyclo-2′-deoxyguanosine; AP site, apurinic/apyrimidinic site; BER, base excision repair; NER, nucleotide excision repair; 5-MeCyt, 5-methylcytosine; 5′-dRP residue, 2-deoxyribose phosphate residue; Pol β, DNA polymerase β; APE1, apurinic/apyrimidinic endonuclease 1; PARP1, Poly(ADP)ribose polymerase 1; UDG, *E. coli* uracil DNA glycosylase; SMUG1, single-strand selective monofunctional uracil DNA glycosylase; TDG, thymine DNA glycosylase; MBD4, methyl CpG binding domain protein 4; Fpg, formamidopyrimidine glycosylase; Nei, endonuclease VIII; H2TH, helix-two turn-helix; Nth, endonuclease III; PNKP, polynucleotide kinase phosphatase; GC–MS, gas chromatography-mass spectrometry; GC–MS/MS, gas chromatography-tandem mass spectrometry; 5-OHMeUra, 5-hydroxymethyluracil; 5-OH-Ura, 5-hydroxyuracil; FapyGua, 2,6-diamino-4-hydroxy-5-formamidopyrimidine; Me-FapyGua, 2,6-diamino-4-hydroxy-*N*7-methyl-5-formamidopyrimidine; 2-OH-Ade, 2-hydroxyadenine; FapyAde, 4,6-diamino-5-formamidopyrimidine; 5-OH-Cyt, 5-hydroxycytosine; 8-OH-Ade, 8-hydroxyadenine; *Dr*Fpg, *Deinococcus radiodurans* Fpg; 5,6-diOH-Cyt, 5,6-dihydroxycytosine; 5,6-diOH-Ura, 5,6-dihydroxyuracil; 5-OH-6-HThy, 5-hydroxy-6-hydrothymine; 5-OH-6-HUra, 5-hydroxy-6-hydrouracil; Thy glycol, thymine glycol; 5,6-diHThy, 5,6-dihydrothymine; 5,6-diHUra, 5,6-dihydrouracil; 5-OH-5-MeHyd, 5-hydroxy-5-methylhydantoin; k_{cat}/K_M, specificity constant; OGG1, 8-oxoguanine DNA glycosylase; yOGG1, *Saccharomyces cerevisiae* OGG1; hOGG1, human OGG1; dOGG1, *Drosophila melanogaster* OGG1; dS3 protein, *Drosophila* ribosomal protein S3; *At*OGG1, *Arabidopsis thaliana* OGG1; hNTH1, human NTH1; hNEIL1, human NEIL1; mNEIL1, mouse NEIL1; MmuNeil3, mouse Neil3; *Cal*Fpg, *Candida albicans* Fpg; *Ath*Fpg, *Arabidopsis thaliana* Fpg T4-pdg T4-pyrimidine dimer glycosylase; cv-pdg, Chlorella virus pyrimidine dimer glycosylase; *Mv*Nei, *Acanthamoeba polyphaga mimivirus* (Mimivirus) Nei; *Mtu*Fpg, *Mycobacterium tuberculosis* Fpg; *Mtu*Nth, *Mycobacterium tuberculosis* Mth; *Mtu*Nei, *Mycobacterium tuberculosis* Nei.

* Corresponding author.
E-mail address: miral@nist.gov (M. Dizdaroglu).

http://dx.doi.org/10.1016/j.mrrev.2017.02.001
1383-5742/Published by Elsevier B.V.

1. Introduction . . . 2
2. Oxidatively induced DNA damage . . . 2
3. Repair of oxidatively induced DNA damage . . . 3
4. Base excision repair . . . 4
5. DNA glycosylases . . . 6
5.1. Determination of the substrate specificities of DNA glycosylases . . . 8
5.2. Monofunctional DNA glycosylases . . . 8
5.3. Prokaryotic bifunctional DNA glycosylases . . . 9
5.3.1. E. coli Fpg protein . . . 9
5.3.2. E. coli Nth protein . . . 9
5.3.3. E. coli Nei protein . . . 10
5.3.4. Mycobacterial DNA glycosylases . . . 10
5.4. Eukaryotic bifunctional DNA glycosylases . . . 11
5.4.1. Saccharomyces cerevisiae OGG1 protein . . . 11
5.4.2. Human OGG1 proteins . . . 11
5.4.3. Drosophila melanogaster OGG1 and S3 proteins . . . 12
5.4.4. Arabidopsis thaliana OGG1 protein . . . 12
5.4.5. Schizosaccharomyces pombe Nth protein . . . 12
5.4.6. Human NTH1 protein . . . 13
5.4.7. Saccharomyces cerevisiae Ntg1 and Ntg2 proteins . . . 13
5.4.8. NEIL1 protein . . . 13
5.4.9. NEIL2 protein . . . 15
5.4.10. NEIL3 protein . . . 15
5.5. Fungal and plant DNA glycosylases . . . 16
5.6. Viral DNA glycosylases . . . 16
6. Comments on excision kinetics and substrate differences . . . 17
7. DNA glycosylases as biomarkers and therapy targets . . . 17
8. Conclusions . . . 19
Conflict of interest . . . 19
Acknowledgements . . . 19
References . . . 19

1. Introduction

Oxygen metabolism and exogenous sources such as ionizing radiations, UV radiation, redox cycling drugs, carcinogenic compounds, and environmental toxins generate reactive species including free radicals in aerobic organisms [1]. Reactions of such species cause damage to biological molecules including DNA, proteins and lipids, and thus can lead to increased genetic instability, inflammation, proliferation, reduction of antioxidants, cell death, apoptosis and angiogenesis [1–3]. Many of these effects are hallmarks of cancer and predispose individuals to different types of this disease [2–6]. Reactive species can derive from oxygen as well as from nitrogen as free radicals or non-radicals. Four-electron reduction of the oxygen molecule done in stages generates superoxide radical ($O_2^{\bullet -}$), non-radical H_2O_2, hydroxyl radical ($^\bullet$OH) and water in the electron-transport chain [1]. Superoxide radical and H_2O_2 possess very low or intermediate reactivity unless they are converted into $^\bullet$OH by reactions with transition metal ions. Other free radicals such as hydroperoxyl radical ($HO_2^\bullet$) (protonated $O_2^\bullet$), peroxyl radical ($RO_2^\bullet$) and alkoxyl radical ($RO^\bullet$) possess low reactivity. Under physiological conditions, traces of $HO_2^\bullet$ exist in equilibrium with $O_2^\bullet$, which exhibits essentially no reactivity toward DNA components [1]. The singlet oxygens ($^1\Delta gO_2$ and $^1\Sigma g^+O_2$), which are formed from oxygen by an input of energy, are not free radicals, but possess reactivity toward biological molecules. However, $^1\Sigma g^+O_2$ rapidly decays to $^1\Delta gO_2$ and, thus, the latter mainly plays a role in biological systems [1]. Nitric oxide ($NO^\bullet$) is also a free radical with low reactivity. Nevertheless, its reaction with $O_2^\bullet$ is diffusion-controlled [7], yielding fairly unreactive non-radical peroxynitrite (ONOO) whose protonated form peroxynitrous acid (ONOOH) can undergo homolytic fission to yield $^\bullet$OH and $NO_2^\bullet$, which are generated close to each other and can recombine to yield NO_3 and H^+; therefore, the contribution of $^\bullet$OH to the biological damage done by ONOOH (if any) may be small [1]. In reactions with cellular water, ionizing radiations also generate $^\bullet$OH and, in addition, H atom ($H^\bullet$) (also a free radical), hydrated electron (e_{aq}^-), H_2O_2 and H_2 [1,8]. Hydroxyl radical is the most reactive free radical and readily reacts with most biological molecules such as DNA and proteins in living cells [1,8]. In these reactions, a plethora of products from DNA are formed that lead to various biological consequences. These lesions are repaired in living organisms by numerous mechanisms. This article reviews mechanisms of action, substrate specificities and excision kinetics of DNA glycosylases, which are responsible for removal of DNA base lesions in the first step of the base excision repair (BER) mechanism.

2. Oxidatively induced DNA damage

Hydroxyl radical reacts with DNA constituents at or near diffusion-controlled reaction rates [1,8–10]. The second-order rate constants (k) of its reactions with DNA bases amount to 4×10^9 $dm^3\,mol^{-1}\,s^{-1}$ to 9×10^9 $dm^3\,mol^{-1}\,s^{-1}$. However, the sugar moiety of DNA (2-deoxyribose) and the methyl group of thymine react with $^\bullet$OH by H atom ($H^\bullet$)-abstraction at slower rates of $\approx 2 \times 10^9$ $dm^3\,mol^{-1}\,s^{-1}$. Addition of $^\bullet$OH to purines generates C4-OH–, C5-OH– and C8-OH–adduct radicals, although the C5-OH–adduct radical of adenine is formed to a lesser extent along with the C2-OH–adduct radical [8,10–14]. Oxidation or reduction reactions of these intermediate adduct radicals in the absence of oxygen generates final products of purines. Oxygen reacts with the OH–adduct radicals of purines at different rates from $k \leq 10^6\,dm^3\,mol^{-1}\,s^{-1}$ to $k = 4 \times 10^9\,dm^3\,mol^{-1}\,s^{-1}$ [14,15]. Subsequent reactions of thus-formed peroxyl radicals lead to final products. The yields of the products substantially depend on the presence or absence of oxygen (reviewed in [10]). Among the purine-derived products, 8-hydroxyguanine (8-OH-Gua) (also called 8-oxo-Gua) is readily oxidized by various oxidizing agents due to its low

reduction potential (0.74 V) compared to that of guanine (1.29 V) [16], giving rise to the formation of spiroiminohydantoin (Sp) and 5-guanidinohydantoin (Gh) [17–23]. Furthermore, 8-OH-Gua reacts with singlet oxygen, generating oxaluric acid and parabanic acid among other products [24,25]. These findings unequivocally show facile decomposition of 8-OH-Gua, strongly affecting its measured level in DNA (for an extensive discussion of this subject see the reviews [10,23]). Similar to purines, addition of $^{\bullet}OH$ to the C5–C6 double bonds of thymine and cytosine produces C5-OH– and C6-OH–adduct radicals; the abstraction of $H^{\bullet}$ from the methyl group of thymine gives rise to an allyl radical (reviewed in [8,10]). These intermediate radicals undergo oxidation or reduction reactions to yield a variety of products in the absence or presence of oxygen. The types and yields of the products depend on the presence or absence of oxygen, and other reaction conditions. Ionizing radiation-generated e_{aq}^- and $H^{\bullet}$ also add to the double bonds of DNA bases at diffusion-controlled rates [8,10,13,26–28]. However, no products of the e_{aq}^-– or $H^{\bullet}$–adduct radicals of adenine and guanine have been identified in DNA, likely due to electron transfer to other DNA bases prior to formation of final products [27]. Electron transfer to O_2 may also take place in the presence of O_2, yielding $O_2^{\bullet-}$, which is essentially not reactive toward DNA components [1]. One-electron reduction of e_{aq}^-– and $H^{\bullet}$–adduct radicals of thymine and cytosine result in the formation of 5,6-dihydrothymine (5,6-diHThy) and 5,6-dihydrouracil (5,6-diHUra) (following the deamination of 5,6-dihydrocytosine), respectively. These products are not formed in the presence of O_2 because of its diffusion-controlled reaction with e_{aq}^- and $H^{\bullet}$ (for reviews see [8,10]). Fig. 1 illustrates the major purine- and pyrimidine-derived products formed in DNA.

Direct effect of ionizing radiation (via ionization) generates purine radical cations such as $Gua^{\bullet+}$, which hydrates to form C8-OH–adduct radicals, as in the case of $^{\bullet}OH$ addition to C8 of the purine ring. The C8-OH–adduct radical of guanine gives rise to the formation of 8-OH-Gua and 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyGua) by one-electron oxidation and one-electron reduction, respectively [10]. The hydration of $Gua^{\bullet+}$ has been proposed first by Symons in 1987 [29]. Subsequent studies confirmed the occurrence of this reaction in DNA [10,30–35]. Moreover, the direct effect of ionizing radiation has been shown to lead to the same products of DNA bases as the indirect effect of ionizing radiation, with the major formation of guanine-derived products 8-OH-Gua and FapyGua via hydration of $Gua^{\bullet+}$ [32,33].

Abstraction of $H^{\bullet}$ by $^{\bullet}OH$ from all five carbons of 2-deoxyribose in DNA takes place in the order of H5′ > H4′ > H3′ ≈ H2′ ≈ H1′, leading to C-centered radicals [8,26,36–38]. When compared to DNA bases, these reactions may amount up to 50% depending on the cellular environment [8]. Hydrated electron and $H^{\bullet}$ do not react with 2-deoxyribose at appreciable reaction rates. The C-centered radicals of 2-deoxyribose undergo oxidation and reduction reactions in the presence or absence of O_2, leading to DNA strand breaks and products of 2-deoxyribose that are either freed from DNA or remained within DNA or are bound to DNA as end groups of broken DNA strands (for extensive reviews of this field see [8,10,39]). In addition to these reactions, the C5′-centered radical of 2′-deoxyribose adds to the C8–N7 double bond of the purine of the same nucleoside in the absence or low levels of O_2, leading to C5′–C8-intramolecular cyclization and an N7-centered purine radical. This reaction has been first discovered by Keck to take place in adenosine 5′-monophosphate, yielding 8,5′-cyclo-adenosine 5′-monophosphate upon oxidation of the N7-centered adenine radical [40]. Subsequently, the C5′–C8-intramolecular cyclization has been shown to also occur in DNA, causing the formation of (5′*R*)- and (5′*S*)-8,5′-cyclo-2′-deoxyadenosines (*R*-cdA and *S*-cdA), and (5′*R*)- and (5′*S*)-8,5′-cyclo-2′-deoxyguanosines (*R*-cdG and *S*-cdG) *in vitro* and *in vivo* (reviewed in [41–43]). These unique tandem lesions represent a concomitant damage to both the sugar and purine moieties of the same nucleoside. Although the C5′–C8-intramolecular cyclization is inhibited *in vitro* by increasing concentrations of O_2 [44], the formation of *R*-cdA, *S*-cdA, *R*-cdG and *S*-cdG takes place *in vivo*. Because of hypoxic conditions of the cell nucleus and possible steric hindrances, a competition may occur between the C5′–C8-cyclization and the reaction of O_2 with the C5′-centered radical of 2′-deoxyribose in favor of the former. In addition to the products described above, intrastrand and interstrand base–base tandem lesions, DNA-protein cross-links and clustered lesions have been shown to be formed in DNA *in vitro* and *in vivo* (for a detailed discussion of this subject see [10,42,45–49]). Extensive reviews of the mechanistic aspects of oxidatively induced DNA damage can be found elsewhere [8,10].

Finally, it should be pointed out that the type of DNA damage discussed above is collectively called “oxidatively induced DNA damage” in the literature. However, the major products 4,6-diamino-5-formamidopyrimidine (FapyAde), FapyGua, 5-hydroxy-6-hydrothymine (5-OH-6-HThy) and 5-hydroxy-6-hydrouracil (5-OH-6-HUra) are formed by one-electron reduction of the OH–adduct radicals of adenine, guanine, thymine and cytosine, respectively. Similarly, one-electron reduction of e_{aq}^-– and $H^{\bullet}$–adduct radicals of thymine and cytosine leads to the formation of 5,6-dihydrothymine (5,6-diHThy) and 5,6-dihydrouracil (5,6-diHUra), respectively (see above). This is in contrast to the one-electron oxidation of OH-adduct radicals that results in the formation of the other major products.

3. Repair of oxidatively induced DNA damage

One of the biological responses to DNA damage is DNA repair that protects genome stability, thus increasing survival and preventing mutagenesis (reviewed in [50–52]). The genomic instability caused by DNA damage is a hallmark of cancer [2,3,53–55]. If not repaired, DNA damage may cause detrimental biological effects in living organisms, leading to mutations, disease and death. DNA repair consists of various mechanisms, including BER, nucleotide excision repair (NER), mismatch repair (MMR), direct repair and repair of single- and double-strand breaks (reviewed in [52]). Almost all DNA repair processes involve enzymatic opening of the double helix and unpairing DNA bases. Dephosphorylation of modified 2′-deoxynucleoside triphosphates in the nucleotide pool also occurs preventing their incorporation by DNA polymerases into DNA, which may lead to genomic instability (reviewed in [56]). Oxidatively modified DNA bases are generally repaired by BER, although the repair of these lesions by NER also occurs to a lesser extent [57–60]. BER cannot be involved in the repair of 8,5′-cyclopurine-2′-deoxynucleosides because of the 8,5′-covalent bond between the base and sugar moieties. Thus, three decades ago, these lesions have been suggested to be the substrates of NER instead [61,62]. Indeed, subsequent studies showed that 8,5′-cyclopurine-2′-deoxynucleosides are repaired by NER [63–66]. The repair of the *R*-diastereomers was found to be more efficient than that of the *S*-diastereomers. This is on a par with the fact that the *R*-diastereomers cause greater distortion of the DNA backbone than the *S*-diastereomers. The lack of activity of BER on 8,5′-cyclopurine-2′-deoxynucleosides has been confirmed when DNA glycosylases did not act on oligodeoxynucleotides containing these lesions [65]. In agreement with this finding, these enzymes even at high concentrations failed to form DNA-protein complexes with oligodeoxynucleotides containing *S*-cdA or *S*-cdG. Other bulky lesions such as base–base tandem lesions are also substrates of NER [67–69].

Sugar lesions are formed within DNA or bound to DNA as end groups; however, some of them are released from DNA [8,10,39].

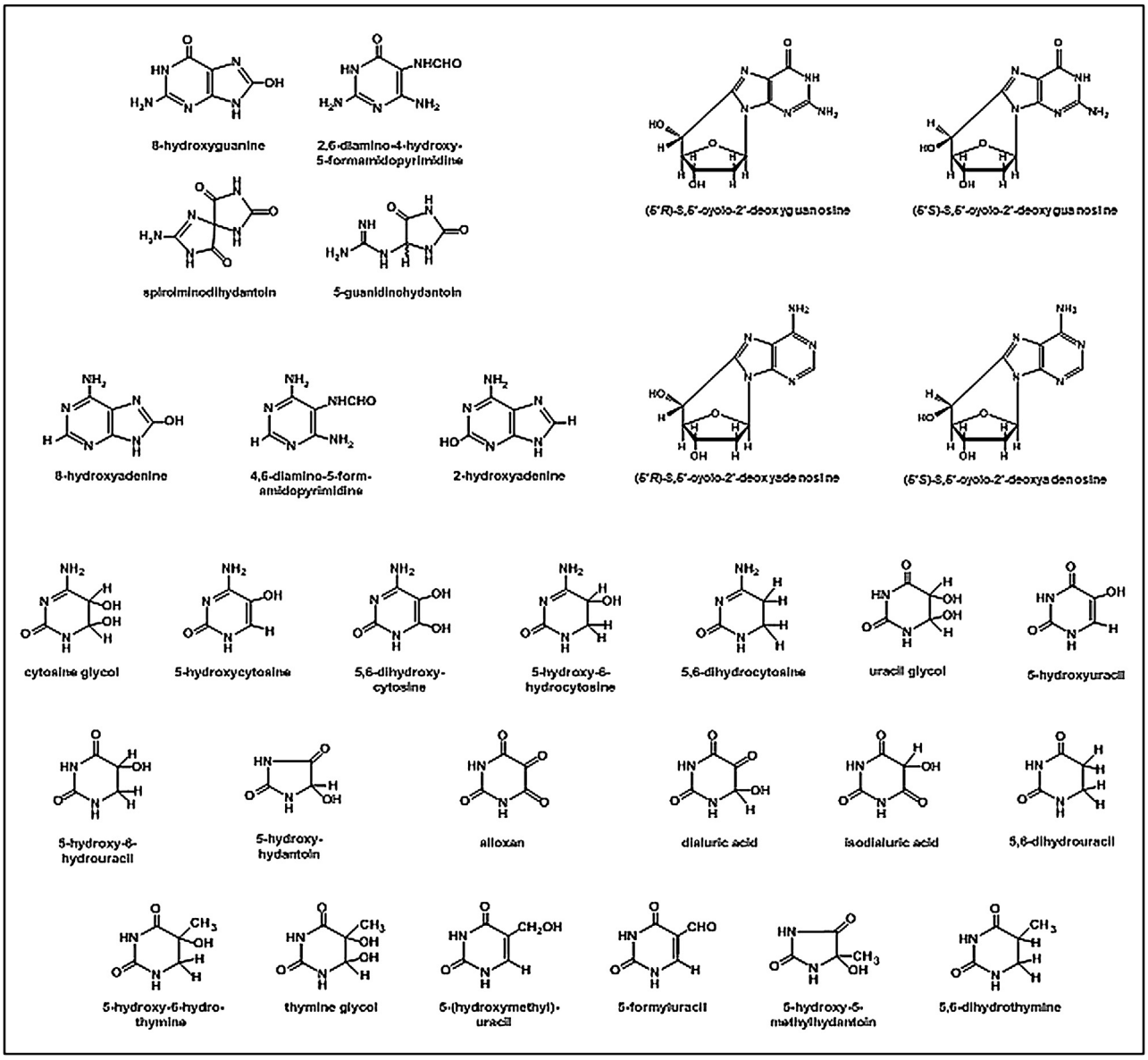

Fig. 1. Structures of oxidatively induced DNA base lesions in DNA.

The former two types of sugar lesions constitute apurinic/apyrimidinic (AP) sites with a modified 2-deoxyribose in addition to AP sites with an intact 2-deoxyribose moiety. BER is the primary pathway that repairs AP sites in mammalian cells. Sugar lesions such as 2-deoxypentose-4-ulose, erythrose and 2-deoxyribonic acid (or its lactone form 2-deoxyribonolactone) within DNA, and 2-deoxytetradialdose as an end group are the substrates of apurinic/apyrimidinic endonuclease 1 (APE1) of BER that hydrolyzes the phosphate bond 5′ to the AP site creating a single strand break with a 3′-OH group and a 5′ terminal 2-deoxyribose phosphate residue (5′-dRP residue) [70–74]. This is followed by the repair of the remaining nick by DNA polymerases β and λ. However, the repair of sugar lesions may not be as efficient as that of AP sites with the intact 2-deoxyribose moiety (for recent reviews see [75,76]). Double-strand breaks in DNA are repaired by homologous recombination or non-homologous end-joining mechanisms, whereas mechanisms similar to those in BER are involved in the repair of single-strand breaks (reviewed in [52,77,78]).

4. Base excision repair

BER is highly conserved during evolution from bacteria to humans, and repairs multiple endogenously and exogenously induced DNA lesions including oxidatively induced DNA base lesions, and also plays a role in erasing epigenetic marks from DNA [79–90]. In fact, all mammalian DNA glycosylases have functional bacterial homologs and can also function in bacteria. BER consists of short patch and long patch pathways with several sub-mechanisms that involve multiple enzymes [80], and also exists in mitochondria (for a review see [91]). In the first step, a DNA glycosylase removes a modified base from DNA by hydrolyzing the *N*-glycosidic bond between the sugar moiety and the modified base, leaving behind an AP site. Pre-catalytic steps involve non-specific DNA binding that leads to the location of damage by scanning or diffusion. This is followed by “nucleotide flipping” to extrude modified nucleotides from the double helix into the active site of the enzyme, facilitating the formation of a stable enzyme-DNA complex prior to catalysis [85,86,92–100]. Recently, however, a DNA glycosylase mechanism has been reported that functions

without the nucleotide flipping for either binding or catalysis, and leaves the double helix intact during damage recognition and removal [101]. Numerous studies elucidated mechanisms by which DNA glycosylases precisely locate and excise damaged DNA bases from DNA without initiating any repair process at intact DNA bases [85,92,94–97,99,100,102–106]. Direct visualization of the movement of DNA glycosylases along undamaged long parts of DNA has been achieved using single molecule total internal reflection fluorescence microscopy imaging [97,100,103,104]. These studies showed that DNA glycosylases scan and search DNA in bidirectional and random fashion, and insert a wedge amino acid residue into DNA that senses damaged DNA bases before turning them inside out to fit into the active site of the enzyme.

In addition, DNA-mediated charge transport chemistry has been proposed to play a role in damage recognition of DNA repair proteins [107–109]. These proteins may search damaged sites in DNA either from a distance or locally by way of redox processes. Significant differences in reduction potentials exist between intact DNA bases and modified DNA bases. An example of this fact is that 8-OH-Gua has a significantly lower reduction potential (0.74 V) than that of guanine (1.29 V) [16]. The differences between reduction potentials may play a role in damage recognition by enhancing differences between a damaged base and an intact base [107–109].

DNA glycosylases are either monofunctional removing the modified base only, or bifunctional with an associated AP-lyase activity. Short-patch BER is predominantly initiated by a bifunctional DNA glycosylase, whereas a monofunctional DNA glycosylase functions in either pathway [110]. Fig. 2 illustrates a schematic presentation of short-patch BER. Reactions showing the excision of a base lesion, and β- and δ-eliminations are illustrated in Fig. 3. Following the action of a monofunctional DNA glycosylase, APE1 hydrolyzes the phosphate bond 5′ to the AP site and generates a single strand break with a 3′-OH end group on one strand and an end 5′-dRP residue on the other strand [70,71]. The AP-lyase activity of a bifunctional DNA glycosylase hydrolyzes the 3′-phosphodiester bond of the AP site by a β- or β,δ-elimination mechanism that generates a strand break with an α,β-unsaturated aldehyde (β-elimination) or a phosphate group (β,δ-elimination) attached to the 3′-end of the broken strand, releasing the unsaturated aldehyde 4-hydroxypent-2,4-dienal [52] (Fig. 3). Following the β-elimination, APE1 removes the

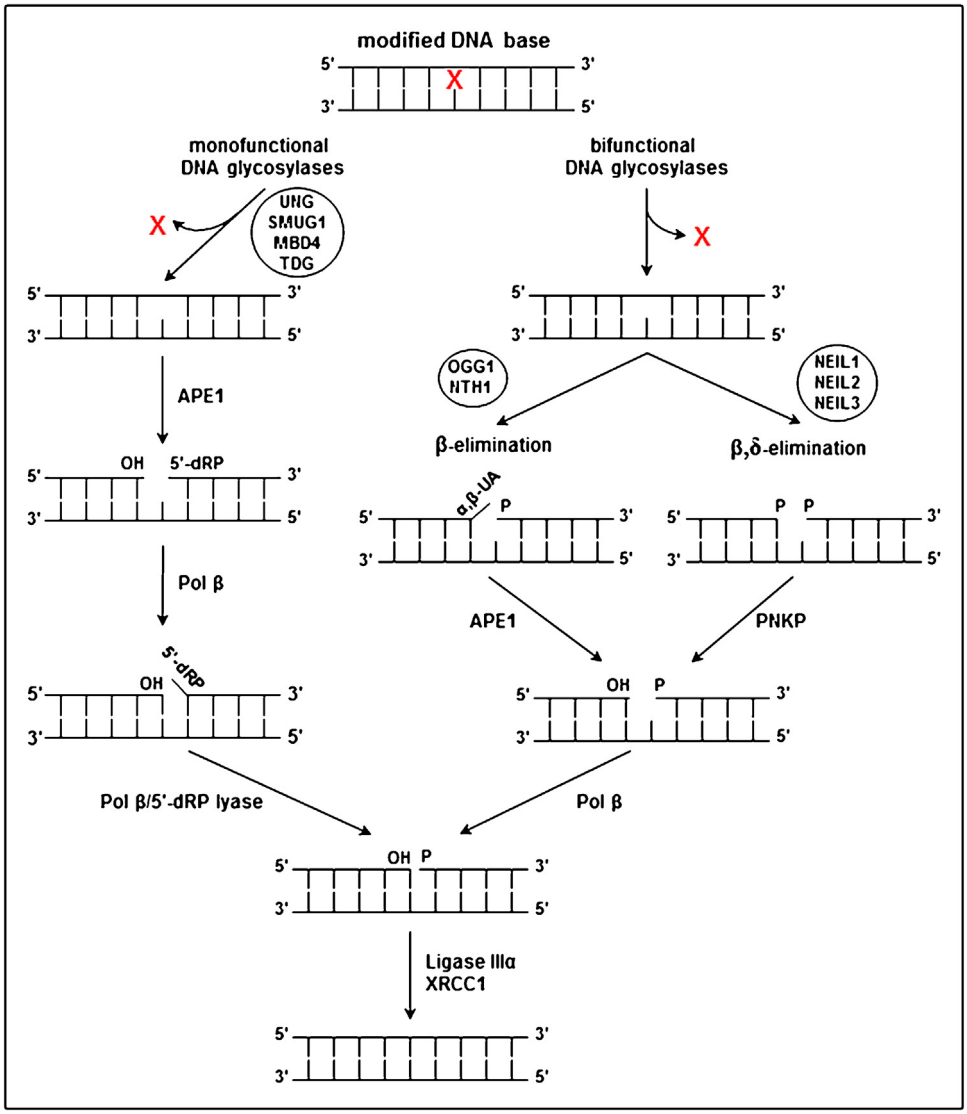

Fig. 2. Schematic presentation of short-patch base excision repair X, modified DNA base; α,β-UA, 3′-phospho-α,β-unsaturated aldehyde; P, phosphate. Other abbreviations can be found in the list of abbreviations. It should be noted that NEIL3 is listed with β,δ-elimination activity, although its δ-elimination activity is significantly weaker than its β-elimination activity [261]. (Adapted from [87]).

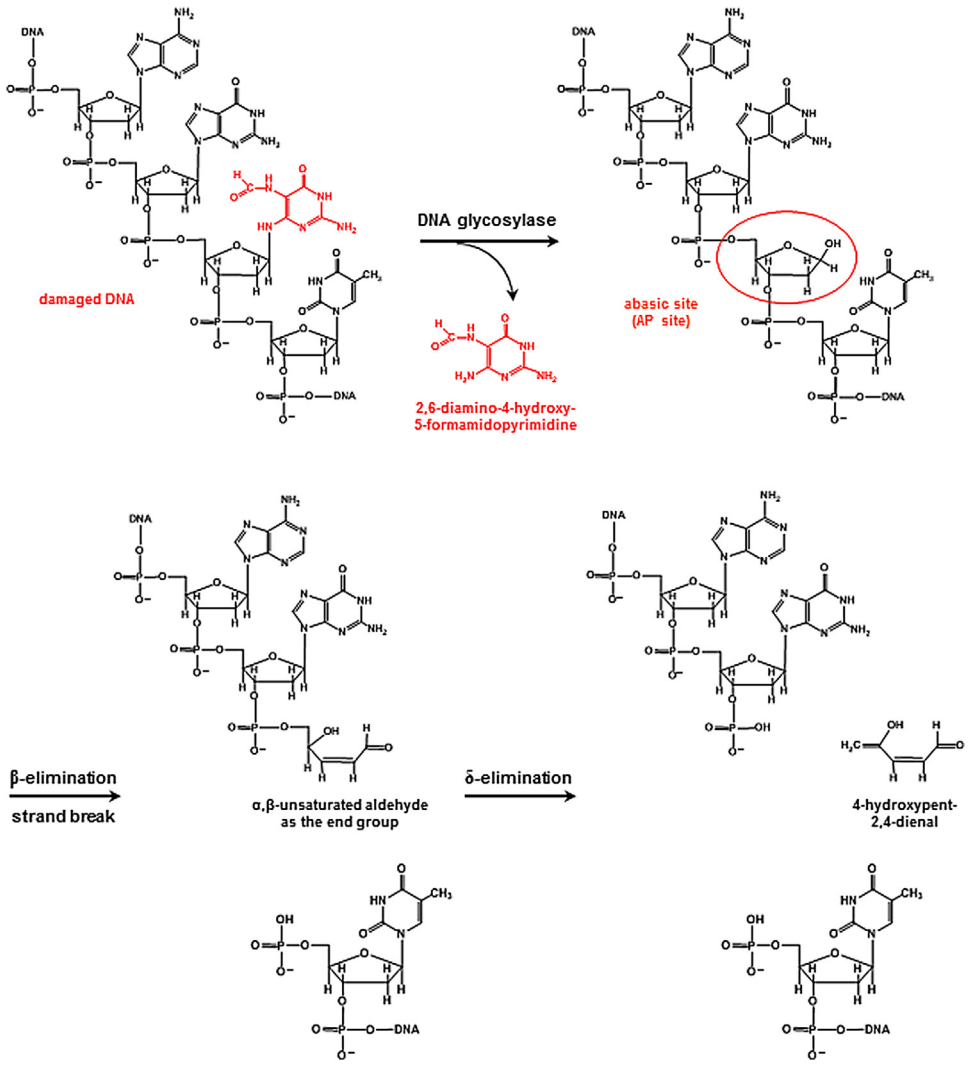

Fig. 3. Removal of a modified DNA base by a bifunctional DNA glycosylase followed by β- and δ-eliminations.

α,β-unsaturated aldehyde, leaving behind a 3′-OH group [111]. The phosphate group left on the 3′-end of the break after the β,δ-elimination is removed by polynucleotide kinase phosphatase (PNKP) [112]. The β,δ-elimination is an APE1-independent pathway. The AP-lyase activity is generally associated with DNA glycosylases that remove oxidatively induced DNA base lesions. Following the APE1 activity, DNA polymerase β (Pol β) removes the blocking 5′-dRP residue and performs DNA synthesis, inserting an intact DNA base. Subsequently, ligase 1 or a complex of X-ray repair complementing protein 1 (XRCC1) and ligase IIIα seals the resulting gap to complete the repair [88,113–116].

In long patch BER, Pol β performs gap filling followed by addition of deoxynucleotides past the AP site by DNA polymerases δ and/or ε, generating an overhang polydeoxynucleotide with a number of deoxynucleotides (5′ flap) and the 5′-dRP residue. Flap endonuclease I (FEN1) removes this 5′ flap and then DNA ligase I seals the remaining nick completing the repair [117–122]. Poly (ADP)ribose polymerase 1 (PARP1) and Pol λ also play important roles in BER [88,123–125]. PARP1 is activated by ADP ribosylation, and binds to DNA breaks and recruits other DNA repair proteins to the DNA damage site.

In addition to DNA repair, BER also plays an essential role in demethylation that converts 5-methlcytosine (5-MeCyt) and its derivatives back to Cyt in a multistep process, thus modulating the levels of cytosine methylation [90,126–133]. Cytosine is converted enzymatically to 5-MeCyt by DNA methyltransferases, generating an epigenetic signal for many cellular processes. Methylation generally occurs at CpG sites; however, there is also evidence for methylation of non-CpG sites. There is evidence for an emerging role of DNA glycosylases such as 8-oxoguanine DNA glycosylase 1 (OGG1) and thymine DNA glycosylase (TDG) in basic regulatory mechanisms such as transcription (epigenetic regulation) and signal transduction. Proposed mechanisms of excision of 5-MeCyt by monofunctional and bifunctional DNA glycosylases are similar to those of oxidatively induced DNA base lesions (see below), although such mechanisms in plants remain elusive (for an extensive review see [90]).

5. DNA glycosylases

The first discovered DNA glycosylase was the *E. coli* uracil DNA glycosylase (UDG) [79]. It is a member of the UDG superfamily, all members of which are monofunctional [134–137]. Other DNA glycosylases are divided into two families, the Fpg/Nei family and the Nth superfamily on the basis of sequence homology and structural motifs [86,87,138–141]. The members of both families are bifunctional. DNA glycosylases of the Fpg/Nei family are sparsely distributed across the phylogeny, whereas the Nth

superfamily members are widely found in bacteria, archaea and eukaryotes. The Fpg/Nei family DNA glycosylases contain a helix-two turn-helix (H2TH) motif and a zinc finger or a zincless finger motif for DNA binding, and have a common catalytic mechanism that involves a conserved *N*-terminus with a Pro or Val residue [86,140]. The Fpg/Nei family members are named after bacterial members formamidopyrimidine glycosylase (Fpg, also called MutM) and endonuclease VIII (Nei), and also include NEIL1, NEIL2 and NEIL3. The Nth superfamily is characterized by a helix-hairpin-helix (HhH) motif followed by a loop that contains mainly Gly, Pro and Val residues, and a conserved catalytic Asp residue [141–143]. Its members include *E. coli* endonuclease III (Nth), yeast Ntg1 and Ntg2, mammalian NTH1, *E. coli* MutY, eukaryotic MUTYH and OGG1, and bacterial and yeast AlkA. Substrate specificities of DNA glycosylases differ from one another, albeit overlapping substrates exist.

The hallmark reaction of bifunctional DNA glycosylases is the formation of a covalent enzyme-substrate Schiff base (imino) intermediate, whereas monofunctional DNA glycosylases directly hydrolyze the glycosidic bond using water as the active site nucleophile that prevents the lyase action [93,105,140,144–152]. The Schiff base is formed by the attack of the NH_2-group of an amino acid of the enzyme at the C1′ of 2′-deoxyribose displacing the modified base as an anion. This is followed by proton transfers between the NH_2-group of the amino acid and the modified base, and then between the O4′ of 2′-deoxyribose and the modified base opening the 2′-deoxyribose ring, leading to the protonated Schiff base. The β-elimination step causes the protonated Schiff base to give rise to the broken DNA strand with a 5′-phosphate end and the formation of an α,β-unsaturated Schiff base, which is then hydrolyzed to release the amino acid, leaving behind α,β-unsaturated aldehyde as the end group of the broken DNA strand. A subsequent δ-elimination forms the broken DNA strand with a 3′-phosphate end and releases 4-hydroxypent-2,4-dienal. Fig. 4 illustrates some steps of this mechanism, where *E. coli* Fpg is depicted as the DNA glycosylase. Also shown is the trapping of the Schiff base by reduction with $NaBH_4$, resulting in a stable covalent DNA-enzyme cross-link that can be readily detected as the proof for the formation of the Schiff base intermediate, and is amenable to further structural studies. A more detailed mechanism of the

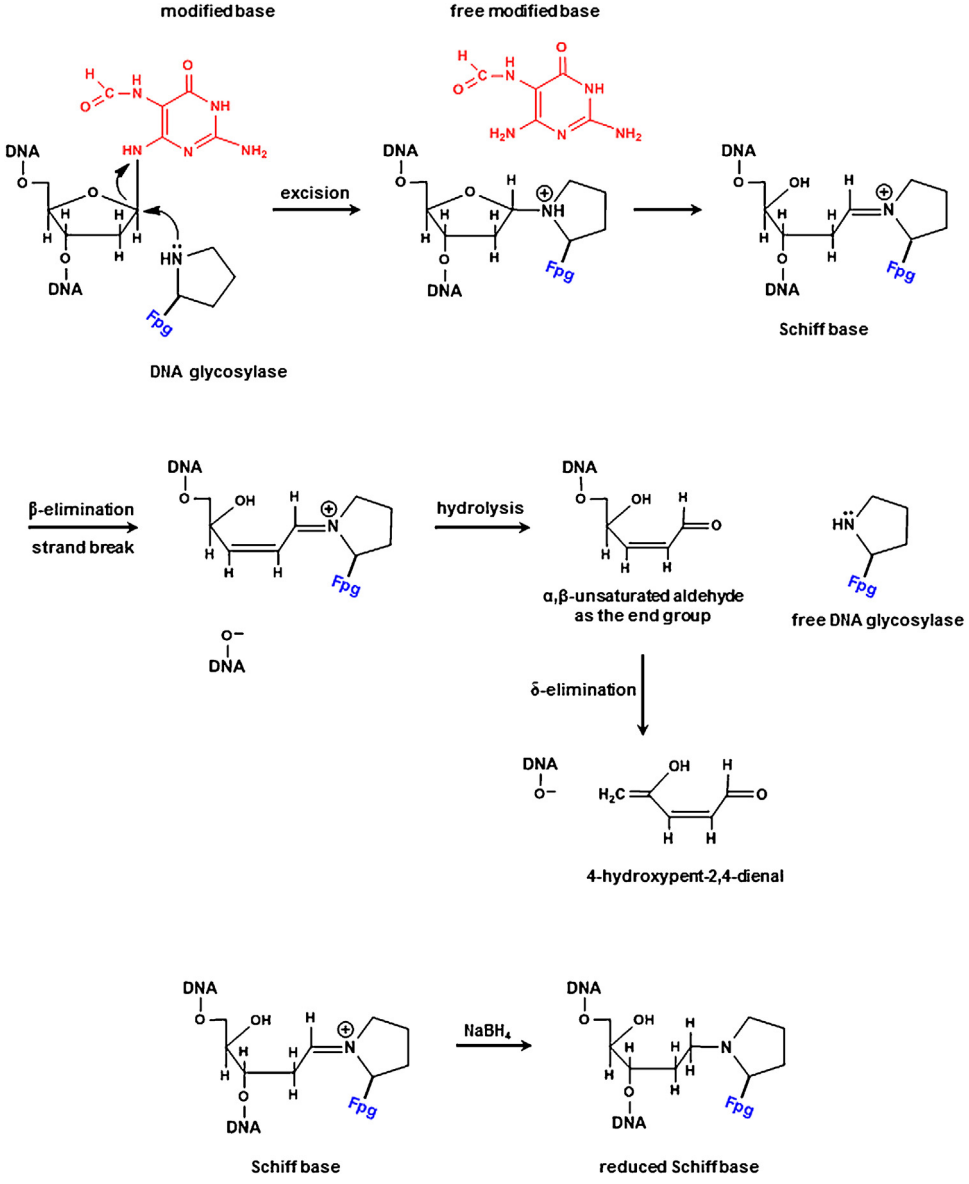

Fig. 4. Mechanism of action of a bifunctional DNA glycosylase. *E. coli* Fpg and FapyGua are depicted as the DNA glycosylase and the modified DNA base, respectively. Also shown is the trapping of the Schiff base by $NaBH_4$, leading to a covalent DNA-amino acid cross-link. (For more details of this mechanism see [140,148,150,153]).

excision of a modified base can be found elsewhere [140,148,150,153].

5.1. Determination of the substrate specificities of DNA glycosylases

Since the discovery of DNA glycosylases, the substrate specificities of these enzymes have been studied and determined using various types of methodologies and single- or double-stranded oligodeoxynucleotides with a single DNA base lesion embedded at a defined position. In general, these substrates consisted of up to approximately 20 to 40 deoxynucleotides. In such an experiment, a DNA glycosylase encounters a single DNA base lesion without a competitor lesion, having one choice only to act upon. As a result, this concept permits the study of the excision of a single DNA base lesion one at a time. In addition, the enzyme-substrate ratio may be far greater than that in a cellular environment. In 1985, a different concept has been proposed to use gas chromatography-mass spectrometry (GC–MS) and damaged high-molecular weight DNA samples containing multiple pyrimidine- and purine-derived lesions for the determination of the substrate specificities and excision kinetics of DNA glycosylases [154]. It has been shown that the GC–MS technique permits the simultaneous identification and quantification of multiple DNA base lesions in a given DNA sample. Subsequent development of stable isotope-labeled analogs of these analytes to be used as internal standards ascertained their accurate quantification (GC–MS with isotope-dilution) [155]. GC–MS enables the determination of substrate specificities of DNA glycosylases by identifying which DNA base lesions are or are not excised from DNA by a given glycosylase, and also permits the accurate measurement of excision kinetics of released base lesions. The use of high-molecular weight DNA with multiple lesions facilitates a quantitative comparison of substrate specificities and excision kinetics of DNA glycosylases for various lesions under identical experimental conditions. Under such conditions, the enzyme simultaneously encounters a number of DNA base lesions that may be competitive inhibitors for one another. These conditions may be more representative of those in a living cell than the use of oligodeoxynucleotides with a single base lesion as a substrate.

DNA substrates are generally prepared by treatment of DNA in buffered aqueous solution with H_2O_2 containing Fe(III)- or Cu(II)-ions, or with γ-rays in the presence of oxygen with air-saturation or in the absence of oxygen with N_2O-saturation. These treatments generate a multiplicity of pyrimidine- and purine-derived products from all four DNA bases. The types and yields of the products depend on experimental conditions (reviewed in [10]). DNA substrates are incubated with a DNA glycosylase, and then treated with ethanol to stop the reaction and to precipitate DNA. The pellet and the supernatant fractions are separated. The DNA pellet is analyzed with GC–MS after acidic hydrolysis, lyophilization and derivatization. The analysis of the supernatant fraction, which will contain released DNA base lesions, is performed after lyophilization and derivatization without acidic hydrolysis. Control samples are generated by incubating DNA without the enzyme or with the heat-deactivated enzyme. The removal of the substrate lesions from DNA and their appearance in the supernatant fraction unequivocally prove the specificity of a given DNA glycosylase for a removed base lesion. Fig. 5 shows the experimental scheme of this approach. The dependence of excision on time and enzyme concentration can also be performed to support the findings. The measurement of excision depending on the levels of the substrates in DNA permits the determination of the Michaelis-Menten kinetics. This concept using the GC–MS methodology has been applied to numerous bacterial, viral, yeast, plant and mammalian DNA glycosylases. This review includes the results of those studies. It should be pointed out that the use of the GC-tandem MS technique (GC–MS/MS) with isotope-dilution has recently been introduced for this purpose as well [156–158].

5.2. Monofunctional DNA glycosylases

In mammalian cells, several uracil-DNA glycosylases (UDGs) are expressed that include mitochondrial uracil *N*-glycosylase (UNG1), nuclear UNG2 and a single-strand selective monofunctional uracil DNA glycosylase (SMUG1); there are also two mismatch DNA glycosylases TDG and methyl CpG binding domain protein 4 (MBD4) [134–136,159–172]. All UDGs possess an α/β fold structured catalytic domain [173]. UNG2 and SMUG1 remove deaminated cytosine residues and uracil from DNA, which arises either by deamination of cytosine or by misincorporation of 2′-deoxyuridine triphosphate into DNA from the nucleotide pool. UNG2 has also been found to reduce DNA methylation [171]. In addition, UNG and SMUG1 have been discovered to excise isodialuric acid (5,6-dihydroxyuracil), 5-hydroxyuracil (5-OH-Ura) and alloxan from DNA containing multiple lesions [174–176]. These compounds are formed in DNA by reactions of $^{\bullet}OH$ with cytosine followed by oxidation and deamination (reviewed in [10]). 5-Hydroxymethyluracil (5-OHMeUra) and 5-formyluracil, which are the products of $^{\bullet}OH$ reactions with the methyl group of thymine, are also substrates of SMUG1 [177–179] (see Fig. 1 for the structures of these products). In addition to their activities described above, UNG1, UNG2 and SMUG1 act on 5-halogenated uracils such as 5-flurouracil [169].

TDG acts on uracil and thymine with a preference on the former, and also on 5-OHMeUra when paired with Gua in double-stranded DNA [159,161,169,170]. 5-Formylcytosine and 5-carboxylcytosine, which are formed by oxidation of 5-MeCyt, are also substrates of TDG [170,172,180]. In addition, TDG exhibits specificity for the removal of 5-halogenated pyrimidines such as 5-fluorouracil, 5-bromouracil and 5-chlorouracil, and to a lesser extent, for that of 5-iodouracil, 5-fluorocytosine and 5-bromocytosine [169,181,182].

MBD4 removes uracil and thymine paired with guanine, resulting from deamination of CpG and methylated CpG, and also 5-OHMeUra paired with Gua in CpG dinucleotides [170,183,184].

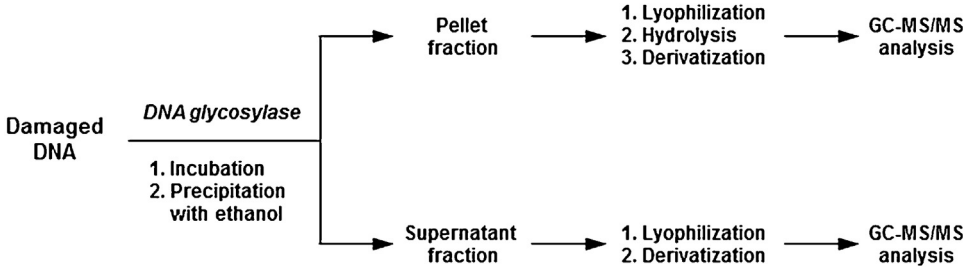

Fig. 5. Experimental scheme for the determination of substrate specificities of DNA glycosylases using the GC–MS methodology and high-molecular weight DNA with multiple lesions.

Several 5-halogenated uracils such as 5-fluorouracil, 5-chlorouracil, 5-bromouracil and 5-iodouracil are also substrates of MBD4 [169,170,185–188]. The glycosylase domain of MBD4 is homologous to the Nth superfamily of DNA glycosylases [170,183,189]; however, this enzyme does not act on analogous cytosine derivatives.

Another DNA glycosylase MUTYH, which is a member of the HhH superfamily and also contains an iron sulfur cluster, removes Ade mispaired with 8-OH-Gua [190–193]. Similarly, *E. coli* homolog MutY acts on FapyGua paired with non-cognate Ade and removes Ade [194,195]. MUTYH has been shown to cleave double-stranded oligodeoxynucleotides containing 2-hydroxyadenine (2-OH-Ade) paired with Gua or Ade, suggesting a DNA glycosylase activity for this lesion [196].

3-Methylpurine DNA glycosylase (MPG) or alkyladenine DNA glycosylase (AAG) has a broad substrate specificity and removes alkylated bases including 3-methyladenine, 3-methylguanine and 7-methylguanine as well as ethanoadenine, ethanoguanine, hypoxanthine and 8-OH-Gua [197–202]. MPG and AlkA (bacterial and yeast) have similar substrate specificities; however, they are not structurally related [203].

5.3. Prokaryotic bifunctional DNA glycosylases

5.3.1. E. coli Fpg protein

E. coli Fpg (also called *E. coli* MutM) of the Fpg/Nei family has been discovered as a DNA glycosylase that removed 2,6-diamino-4-hydroxy-*N*7-methyl-5-formamidopyrimidine (Me-FapyGua) from DNA [204,205]. The *fpg* gene has been cloned that encodes this protein with an average molecular mass of 30.2 kDa and 263 amino acids [206]. Fpg has a four cysteine-zinc finger motif for binding to DNA and for enzymatic activity with its active site located within the first 73 amino acid residues of the N-terminus [207–209]. In addition to DNA glycosylase activity, *E. coli* Fpg possesses AP-lyase activity with β,δ-elimination and an activity excising the 5′-dRP residue [210–212]. The elucidation of the crystal structure of the Fpg-DNA complex revealed its catalytic mechanism [213]. The substrate specificity of Fpg has been investigated using various methodologies and substrates. Besides Me-FapyGua, the excision of urea and FapyAde from γ-irradiated polydA has been demonstrated [214,215]. Subsequent work reported the excision of 8-OH-Gua, and pyrimidine-derived lesions 5-hydroxycytosine (5-OH-Cyt) and 5-OH-Ura from oligodeoxynucleotides containing a single lesion [216,217]. Fpg has also been reported to efficiently remove Sp from DNA, which is a further oxidation product of 8-OH-Gua, even more efficiently than 8-OH-Gua [17,218].

The GC–MS methodology was applied for the first time to the determination of the substrate specificity of *E. coli* Fpg using high-molecular weight DNA as a substrate containing multiple pyrimidine- and purine-derived lesions [30]. This work paved the way to study the substrate specificities and excision kinetics of numerous other DNA glycosylases acting simultaneously on multiple DNA base lesions (see above). 8-OH-Gua, FapyGua and FapyAde have been determined to be the major substrates of *E. coli* Fpg with no significant excision of pyrimidine-derived lesions. 8-Hydroxyadenine (8-OH-Ade) was also a substrate, albeit to a lesser extent. The low activity has been suggested to result from the absence of the C6-keto group in 8-OH-Ade [219]. No DNA glycosylase specific for 8-OH-Ade has thus far been reported, although this lesion is repaired in living cells [220–222]. Michaelis-Menten kinetics of excision of 8-OH-Gua, FapyGua and FapyAde by *E. coli* Fpg from DNA with multiple lesions have been shown to be similar [223]. A significant dependence of excision on the nature of DNA substrates has been observed. Taken together, these results provided the evidence that FapyGua and FapyAde may also be the main physiological substrates of *E. coli* Fpg. This fact is in contrast to the claim that 8-OH-Gua were the main physiological substrate of Fpg, although no data had been provided on the excision of FapyGua and FapyAde [219,224].

The effect of single point mutations in the *fpg* gene on the specificity of *E. coli* Fpg has been investigated [225]. Five mutant forms were generated targeting the highly conserved amino acids Lys-57, Lys-155 and Pro-2. These single mutations dramatically affected the specificity of *E. coli* Fpg up to a complete loss of activity. Similarly, two variants of *Bacillus stearothermophilus* Fpg containing either Phe114Ala or Met77Ala have been expressed and purified, and shown to exhibit significant loss of activity toward 8-OH-Gua in oligodeoxynucleotides [153]. The data suggested that the highly conserved residues Phe-114 and Met-77 play a role in the extrusion of 8-OH-Gua from DNA and in the hydrolysis of the *N*-glycosidic bond.

Oligodeoxynucleotides with FapyAde or FapyGua embedded at a defined position have been synthesized to enable the study of repair mechanisms and biological effects of these lesions [226–229]. Efficient excision of FapyAde and FapyGua by *E. coli* Fpg from these oligodeoxynucleotides has been shown [194,230]. This is on a par with the substrate specificity of *E. coli* Fpg determined using the GC–MS methodology and DNA with multiple lesions. The oligodeoxynucleotides containing FapyAde and FapyGua also facilitated the determination of the effect of base-pairing on the excision by *E. coli* Fpg. Thus, FapyAde opposite all four intact bases was removed indiscriminately, whereas FapyGua paired with cognate Cyt was a much better substrate than when it was paired with non-cognate Ade.

A protein homologous to *E. coli* Fpg has been isolated from the ionizing radiation-resistant bacterium *Deinococcus radiodurans* (*Dr*Fpg) [231–233]. Similar to *E. coli* Fpg, *Dr*Fpg efficiently excised 8-OH-Gua, FapyGua and FapyAde, but with significantly lower excision rates. FapyGua and FapyAde were preferred substrates over 8-OH-Gua in contrast to the similar preference of *E. coli* Fpg for all three lesions [234].

5.3.2. E. coli Nth protein

E.coli Nth (endonuclease III) of the Nth superfamily has been one of the most investigated DNA glycosylases since its discovery and isolation [235]. The *nth* gene has been cloned and sequenced [236–238]. *E. coli* Nth has 211 amino acids and an average molecular mass of 23.6 kDa, and possesses a [4Fe-4S] cluster [237,238]. Its crystal structure has been elucidated [143]. This protein is endowed with both DNA glycosylase and AP-lyase activities, and possesses a broad substrate specificity for pyrimidine-derived lesions with some substantial differences in excision kinetics [98,217,236–241]. Most of the pyrimidine-derived lesions shown in Fig. 1 have been found to be the substrates of *E.coli* Nth. The use of the GC–MS methodology demonstrated the excision of substrates from DNA with multiple lesions, and confirmed and extended the substrate specificity of *E. coli* Nth [242,243]. Thus, FapyAde has been identified as the first purine-derived substrate of *E. coli* Nth, and 5,6-dihydroxycytosine (5,6-diOH-Cyt) and its deamination product 5,6-dihydroxyuracil (5,6-diOH-Ura) as additional cytosine-derived substrates. Excision kinetics was also measured using three differently prepared DNA substrates [242,243]. A significant dependence of excision on the nature of DNA substrates has been observed as in the case of *E. coli* Fpg. In general, the excision kinetics of the substrate lesions were quite similar with the same DNA substrate. It should be noted that 5,6-diOH-Cyt is not formed significantly in the absence of oxygen (N_2O-saturation), whereas oxygen completely inhibits the formation of 5-OH-6-HThy and 5-OH-6-HUra [10]. Moreover, *E. coli* Nth efficiently excised FapyAde from synthetic FapyAde–containing oligodeoxynucleotides, whereas FapyGua was a poor substrate for

excision from FapyGua–containing oligodeoxynucleotides [244]. These findings are in excellent agreement with those results obtained using DNA with multiple lesions [243].

5.3.3. E. coli Nei protein

Another member of the Fpg/Nei family has been discovered in *E. coli* and named endonuclease VIII (*E. coli* Nei) [245]. This DNA glycosylase has been found to mainly recognize modified pyrimidines in DNA [86,217,245–249]. The *nei* gene has been cloned [247]. The encoded protein with an average molecular mass of 29.7 kDa and 263 amino acids has been shown to exhibit strong homology to *E. coli* Fpg and other bacterial Fpg proteins in N- and C-terminal sequences [247,250]. The crystal structure of *E. coli* Nei confirmed its structural similarity to Fpg [251]. This protein also possesses an AP-lyse activity with β,δ-elimination and a 5′-phosphodiesterase activity that removes the 5′-dRP residue [247]. Despite the sequence similarity, the only substrate overlap of *E. coli* Fpg and Nei is the excision of 8-OH-Gua by *E. coli* Nei from oligodeoxynucleotides that depends on the base-pairing [252,253]. On the other hand, the substrate specificity of *E. coli* Nei strongly overlaps with that of *E. coli* Nth of the Nth superfamily [86,217,240], although these proteins have no sequence homology and no similar functional motifs [246,248]. Originally, the substrates of *E. coli* Nei included thymine glycol (Thy glycol), 5,6-diHThy, β-ureidoisobutyric acid and urea [245]. Subsequently, 5-OH-Cyt, 5-OH-Ura and uracil glycol have been found to be substrates as well [239,247]. In most of these studies, oligodeoxynucleotides containing a single modified base were used as substrates. The use of DNA with multiple lesions showed that *E. coli* Nei is also specific for pyrimidine-derived 5-hydroxy-5-methylhydantoin (5-OH-5-MeHyd), 5-OH-6-HThy, 5-OH-6-HUra, 5,6-diOH-Cyt, 5,6-diOH-Ura (isodialuric acid) and 5,6-diHThy, and adenine-derived FapyAde [254] (see Fig. 1 for the structures of these compounds). Other purine-derived lesions were not excised. No significant excision of 5-OH-Cyt was observed most likely because of its complete deamination into 5-OH-Ura under the experimental conditions used. A naturally occurring mutant form of *E. coli* Nei involving Leu–90 → Ser (Nei-Leu90Ser) has been isolated and shown to efficiently excise the same substrates from DNA, albeit with somewhat different excision kinetics [254]. Similar to *E. coli* Fpg and Nth, some differences in excision kinetics of *E. coli* Nei were observed depending on the preparation of DNA substrates, i.e., γ-irradiation of aqueous solutions of DNA with N_2O- or air-saturation. When synthetic FapyAde– or FapyGua–containing oligodeoxynucleotides were used, *E. coli* Nei efficiently removed FapyAde from the FapyAde/Ade or FapyAde/Thy pairs; however, the excision from the mispair was more significant than that from the native pair [244]. *E. coli* Nei had a very low activity on FapyGua when paired with cognate Cyt or non-cognate Ade. These results are in excellent agreement with those showing that *E. coli* Nei efficiently excises FapyAde, but not FapyGua from DNA with multiple lesions [254]. A novel OGG2 activity has been discovered in *E. coli* and the enzyme has been identified as endonuclease VIII (Nei) [253]. Interestingly, Nei removed 8-OH-Gua paired with non-cognate Gua or Ade in oligodeoxynucleotides, but exhibited relatively weak activity for 8-OH-Gua paired with cognate Cyt in contrast to the preference of Fpg for the 8-OH-Gua when paired with Cyt. A homolog of Nei has also been found in *D. radiodurans* [232].

5.3.4. Mycobacterial DNA glycosylases

Four DNA glycosylases of the Fpg/Nei family and one Nth protein have been identified in *Mycobacterium tuberculosis* (*M. tuberculosis*), which causes tuberculosis and thus millions of deaths around the world [255]. These proteins named *Mtu*Fpg1, *Mtu*Fpg2, *Mtu*Nei1, *Mtu*Nei2 and *Mtu*Nth have been overexpressed, isolated and purified, and biochemically characterized [218,256–258]. *Mtu*Fpg1 acted on AP sites with β,δ-elimination, although the AP/Ade pair was less susceptible to hydrolysis [218]. When double-stranded oligodeoxynucleotides were used, 8-OH-Gua paired with cognate Cyt was efficiently excised by *Mtu*Fpg1. Under identical conditions, the k_{cat}/K_M value of excision by *Mtu*Fpg1 was even significantly greater than that by *E. coli* Fpg. Reduced excision from the 8-OH-Gua/Gua or Thy pairs was observed, and none from the 8-OH-Gua/Ade pair in contrast to *E. coli* Fpg. Gh and, to a lesser extent, Sp were also good substrates; however, the activity on 5,6-diHUra, 5-OH-Ura, 5-OH-Cyt and urea was limited. Thy glycol/Ade and 5,6-diHThy/Ade pairs were not recognized, presumably due to fact that *Mtu*Fpg1 lacks the N-terminal Pro-2, Glu-3 and Lys-53, which are essential for glycosylase activity and hydrogen bonding [218]. *Mtu*Fpg2 did not exhibit any DNA glycosylase activity, presumably due to the lack of the N-terminal Pro-2, Glu-3 and Lys-53, which are essential for the DNA glycosylase/lyase activity [213,218,251,259,260]. *Mtu*Nei1 acted on AP sites, Thy glycol, 5,6-diHUra, urea, Gh and Sp with β,δ-elimination in single- and double-stranded oligodeoxynucleotides, but exhibited low activity on 5,6-diHThy, 5-OH-Ura and 5-OH-Cyt in single-stranded oligodeoxynucleotides, and none against 8-OH-Gua [218]. *Mtu*Nei1 also exhibited uracil DNA glycosylase activity. The substrate specificity of *Mtu*Nei2 could not be satisfactorily determined. In double-stranded oligodeoxynucleotides, *Mtu*Nth recognized AP sites with β-elimination, and 5,6-diHUra and, to a lesser extent, 5-OH-Cyt and Thy glycol but not 8-OH-Gua or Sp. The kinetic parameters of *Mtu*Nth were similar to those of *E. coli* Nth. Stereospecific excision of Thy glycol diastereomers by *Mtu*Nth and *Mtu*Nei has been observed as the *S[(5S,6R), (5S,6S)]*-diastereomers were preferentially excised by *Mtu*Nth, whereas *Mtu*Nei1 preferred the *R[(5R,6S), (5R,6R)]*-diastereomers. Overall, *M. tuberculosis* enzymes exhibited lower rate constants than those of *E. coli*.

The substrate specificities of *Mtu*Fpg1, *Mtu*Nei1 and *Mtu*Nth along with their *E. coli* counterparts have been determined under identical conditions using DNA with multiple lesions [218]. FapyAde, FapyGua and 8-OH-Ade have been found as additional substrates of the *M. tuberculosis* enzymes. Both *Mtu*Fpg1 and *E. coli* Fpg efficiently excised FapyAde, FapyGua and 8-OH-Gua, with the latter enzyme showing at least 2-fold greater activity than the former. Both enzymes exhibited substantially lower activity for 8-OH-Ade and very low activity for 5-OH-5-MeHyd. There was no excision of Thy glycol, 5-OH-Cyt and 5-OH-Ura. *Mtu*Nei1 and *E. coli* Nei efficiently acted on pyrimidine-derived lesions, and on FapyAde and FapyGua. Neither 8-OH-Gua nor 8-OH-Ade was excised. In some cases, the activity of *E. coli* Nei was greater than that of *Mtu*Nei1. Both *Mtu*Nth and *E. coli* Nth efficiently excised all pyrimidine- and purine-derived lesions with the exception of 8-OH-Gua. Again, *E. coli* Nth had somewhat greater activity for almost all lesions. It should be pointed out that the results obtained with the *E. coli* enzymes in this work were in excellent agreement with those previously observed (see above).

*Mtu*Nei1 and *Mtu*Nei2 along with *E. coli* Nei were overexpressed in the *E. coli fpg mutY nei* triple mutant and the *E. coli nei nth* double mutant, which accumulate G → T transversions and C → T transitions, respectively, to determine whether these enzymes reduce the extremely high spontaneous mutation frequency observed in these mutants [252,261]. The expression of *Mtu*Nei1, *Mtu*Nei2 and *E. coli* Nei significantly reduced the mutation frequency. Since *Mtu*Nei1 and *E. coli* Nei mainly remove pyrimidine-derived lesions, and FapyAde and FapyGua, but not 8-OH-Gua, these results suggested that the mutations arise from their substrates, which are known to cause such mutations. It is known that FapyGua leads to G → T transversions [195,262,263], whereas 5-OH-Cyt and 5-OH-Ura cause C → T transitions [239,264–268]. Reduction of mutations observed with *Mtu*Nei2 as well suggests that this enzyme can

prevent G→T transversions, probably by removing Gua-derived products [218].

Taken together, these studies show that *M. tuberculosis* possesses DNA repair mechanisms that efficiently act on oxidatively induced DNA lesions. Efficient DNA repair may help *M. tuberculosis* survive DNA-damaging insults by endogenous and exogenous sources and thus contribute to its pathogenic effects. The elucidation of DNA repair mechanisms in this dangerous pathogen may help develop novel treatment strategies to fight and eradicate tuberculosis.

5.4. Eukaryotic bifunctional DNA glycosylases

5.4.1. Saccharomyces cerevisiae OGG1 protein

A functional homolog of *E. coli* Fpg with common substrates has been discovered in *Saccharomyces cerevisiae* (*S. cerevisiae*) with an average molecular mass of 42.8 kDa and 376 amino acids [269–271]. A spontaneous mutator strain of *E. coli fpg muty* has been used to clone the *ogg1* gene. The encoded protein has been named 8-oxoguanine DNA glycosylase 1 (OGG1) because of its strong activity on 8-OH-Gua embedded in double-stranded oligodeoxynucleotides when paired with Cyt or Thy. *S. cerevisiae* OGG1 (yOGG1) possesses an additional AP-lyase activity with β-elimination, when the AP-site is opposite Cyt, and also excises Me-FapyGua, albeit to a much lesser extent than 8-OH-Gua [269,271,272]. Furthermore, it exhibits significant activity for 8-OH-Ade in double-stranded oligodeoxynucleotides when paired with non-cognate Cyt only [272]. yOGG1 localizes to both the nucleus and mitochondria, indicating that it plays a role in the maintenance of overall genome integrity [273,274]. Despite the common substrates, there exists no significant homology between yOGG1 and *E. coli* Fpg [269]. yOGG1 belongs to the Nth superfamily, whereas *E. coli* Fpg is a member of the Fpg/Nei family [98]. Using DNA substrates with multiple lesions, FapyGua has been shown to be also a substrate of yOGG1 along with 8-OH-Gua, but not FapyAde in contrast to *E. coli* Fpg [275]. No other lesions were excised significantly. Four different DNA substrates were used. Excision of 8-OH-Gua and FapyGua significantly varied among the DNA substrates indicating the profound effect of the nature of DNA substrates on excision kinetics as in the case of *E. coli* DNA glycosylases (see above).

Another enzyme named OGG2 has been discovered in *S. cerevisiae* and shown to preferentially remove 8-OH-Gua from the 8-OH-Gua/Ade mispair that may arise from incorporation of 8-OH-dGTP during replication [276].

5.4.2. Human OGG1 proteins

Two human homologs of yOGG1 have been discovered and designated α-hOGG1 and β-hOGG1 with 345 and 424 amino acids, and an average molecular mass of 38.8 kDa and 47.2 kDa, respectively [277–284]. These two forms of hOGG1 result from an alternative splicing after transcription of the *ogg1* gene on chromosome 3p25 [285,286]. They have the first 316 amino acids identical; however, the carboxyl termini are different with α-hOGG1 exhibiting similarity to yOGG1. α-hOGG1 and β-hOGG1 are targeted to the nucleus and mitochondria, respectively [287–289]. However, there is evidence that α-hOGG1 also exists in mitochondria and plays a critical role in the repair of DNA damage [290–293]. OGG1 is expressed mainly in the thymus, testis, intestine, brain and B cells, with an increase in age [277,284,288,294]. In analogy to yOGG1, α-hOGG1 possesses an AP-lyase activity with β-elimination, which cleaves the AP site preferably, when it is opposite Cyt [269,272]. The proposed catalytic mechanism of hOGG1 involves a nucleophilic attack by Lys-249 on the C1′ of the sugar moiety followed by the removal of 8-OH-Gua and the formation of a transient covalent imino enzyme-DNA intermediate (α,β-unsaturated Schiff base) [85,146–148,295,296]. Subsequent reactions lead to a β-elimination of the 3′-phosphate with strand cleavage, the liberation of the enzyme and the formation of a trans-α,β-unsaturated aldehyde product as the end group of the broken DNA strand as shown in Fig. 3. Mutation of Lys-249 to the non-nucleophile Gln-249 and that of Asp-268 to Asn-268 generate variants that are void of base excision activity, but recognize 8-OH-Gua in DNA [146,147,295,297,298]. Asp-268 has been suggested to play a role in the AP-lyase activity by abstracting a proton from Lys-249 in the first step of the β-elimination reaction [147,297]. On the other hand, there is recent biochemical and structural evidence that points to a concurrent and independent monofunctional water-catalyzed hydrolysis of the glycosidic bond being the *in vivo* relevant reaction of hOGG1 [299]. This is followed by a nucleophilic attack on the resulting AP site by an opportunistically positioned Lys-249 that is not important for the glycosylase reaction. This uncoupled mechanism was revealed through the construction of a series of site-directed mutants of hOGG1 in which the two reactions could be structurally uncoupled, with mutants totally devoid of either the glycosylase activity, while maintaining AP-lyase activity, or a complete loss of AP-lyase activity and maintaining glycosylase function. In this mechanism, Asp-268 is the key catalytic residue for the base hydrolysis reaction, whereas Lys-249 appears to be indispensable for the specific recognition and alignment of the substrate lesion during hydrolysis.

α-hOGG1 has been shown to efficiently excise 8-OH-Gua and Me-FapyGua from oligodeoxynucleotides [277–279,281–283,300,301], and 8-OH-Gua and FapyGua from DNA γ-irradiated in aqueous solution saturated with N_2O or air [301]. FapyAde or 8-OH-Ade were not excised. In excellent agreement with these findings, human OGG1 efficiently excised FapyGua paired with cognate Cyt from synthetic oligodeoxnucleotides, whereas FapyAde was removed when mispaired with non-cognate Cyt only [272,302]. When double-stranded oligodeoxynucleotides containing 8-OH-Gua were used, the highest efficiency of excision was observed when this lesion was paired with Cyt [277]. Mispairing 8-OH-Gua with Thy significantly reduced the activity of α-hOGG1, whereas a very weak activity was observed for 8-OH-Gua/Gua or 8-OH-Gua/Ade pairs. 8-OH-Ade was efficiently removed from double-stranded oligodeoxynucleotides when mispaired with non-cognate Cyt only [272,301].

A polymorphic form of α-hOGG1 (hOGG1-Ser326Cys) exists in human cells, due a genetic polymorphism at codon 326 [303]. α-hOGG-Ser326Cys has frequently been found in Japanese population in both healthy individuals and in 23% to 41% of Caucasian populations [304]. This polymorphism has been associated not only with various types of cancers including lung, colorectal, bladder, ovarian, head and neck, and kidney cancers, but also with ocular and cochlear disorders as well as neurodegenerative and cardiovascular diseases, and Type II diabetes [303,305–310]. α-hOGG1-Ser326Cys has been isolated and purified, and shown to efficiently excise 8-OH-Gua and FapyGua from DNA with multiple lesions, similar to wild-type α-hOGG1 [301]. However, the measurement of excision kinetics showed that wild-type α-hOGG1 possesses an approximately 2-fold greater activity than α-hOGG1-Ser326Cys for excision of 8-OH-Gua and FapyGua. Both forms exhibited a greater preference for FapyGua than 8-OH-Gua. Two variants of α-hOGG1, α-hOGG1-Arg46Gln and α-hOGG1-Arg154His have been found in a gastric cancer cell line and human kidney tumors [311,312]. Both proteins have been purified and shown to efficiently excise 8-OH-Gua and FapyGua with similar excision kinetics from DNA with multiple lesions; however, the activity of wild-type α-hOGG1 for both substrates was approximately 2-fold greater than the mutant forms

[272,301,313]. When double-stranded oligodeoxynucleotides containing 8-OH-Gua paired with four DNA bases were used, 8-OH-Gua was removed from the mismatches less efficiently than from the 8-OH-Gua/Cyt pair. Taken together, the results showed that the mutant forms found in tumors exhibit defective catalytic capacities. Recognition variants of hOGG1 have also been reported with active site point mutations at Gly-42, His-270 and Gln-315 [296]. Moreover, OGG1 deficiency in mice (*ogg1*$^{-/-}$ mice) has been shown to increase susceptibility to obesity, metabolic dysfunction, infections and UVB-induced skin carcinogenesis, and to decrease inflammatory responses and to exhibit defects in the maintenance of telomere length [314–319]. On the other hand, 8-OH-Gua, which is one of the main substrates of OGG1, can be increased to very high levels in *ogg1*$^{-/-}$ mice upon oxidative stress without any biological consequences including carcinogenesis [320,321].

In another work, the substrate specificity and excision kinetics of two natural polymorphic variants and phosphomimetic Ser → Glu mutants of hOGG1 have been investigated using double-stranded oligodeoxynucleotides containing 8-OH-Gua/Cyt and 8-OH-Gua/Ade pairs as well as DNA with multiple lesions [322]. hOGG1-Ala288Val and hOGG1-Asp322Asn were chosen because Ala288 forms a direct contact with DNA and Asp322 plays a role in positioning His270, which binds to the 5′-phosphate of the damaged nucleotide [147]. Furthermore, hOGG1-Ala288Val has been found in the germline of Alzheimer's disease patients and exhibited lower activity than the wild-type hOGG1 [323]. hOGG1-Asp322Asn had not been investigated. The kinetic constants were determined for the cleavage of 8-OH-Gua/Cyt and 8-OH-Gua/Ade pairs by wild-type and mutant hOGG1 proteins. Except for hOGG1-Ser231Glu, all radiomimetic mutants were approximately 2-fold less active than the wild-type hOGG1 [322]. The specificity of hOGG1-Ala288Val for the opposite base was similar to that of wild-type hOGG1; however, hOGG1-Asp322Asn exhibited greater specificity for the cognate base than the wild-type hOGG1. All hOGG1 variants excised FapyGua and 8-OH-Gua from DNA with multiple lesions, with hOGG1-Ser326Cys and hOGG1-Asp322Asn being the least active for excision of 8-OH-Gua. The activity of hOGG1-Ala288Val for both FapyGua and 8-OH-Gua was similar to that of wild-type hOGG1. Phosphomimetic mutants exhibited somewhat reduced abilities for excision of FapyGua; however, they were significantly less active on 8-OH-Gua than wild-type hOGG1. Furthermore, the stimulation of hOGG1 activity by hAPE1 was also investigated, because such a stimulation had been previously observed [324–327], and because the posttranslational phosphorylation may affect protein–protein interactions [328]. All phosphomimetic mutants were significantly less stimulated by hAPE1 than wild-type hOGG1. Overall, the results indicated that phosphorylation of wild-type hOGG1 may not affect its activity.

Another enzyme named OGG2 with β-elimination activity and an average molecular mass of 36 kDa has been discovered in human cells and shown to remove 8-OH-Gua when mispaired with Ade [329]. This activity is analogous to that of *S. cerevisiae* OGG2, which is discussed above [276]. The substrate specificity of this enzyme has not been investigated using DNA with multiple lesions.

5.4.3. Drosophila melanogaster OGG1 and S3 proteins

In *Drosophila melanogaster*, a homolog of hOGG1 has been discovered, and the *ogg1* gene has been cloned [330]. The encoded protein, dOGG1 has been isolated and shown to have a 33% and 37% identity with yOGG1 and hOGG1, respectively. dOGG1 possesses additional AP-lyase/β-elimination activity and is composed of 343 amino acids with an average molecular mass of 39.4 kDa. In analogy to yOGG1 and hOGG1, dOGG1 excised 8-OH-Gua and FapyGua from DNA with multiple lesions with a preference for the former. In addition, this protein efficiently acted on double-stranded oligodeoxynucleotides containing 8-OH-Gua paired with Cyt or Thy, whereas the sites with 8-OH-Gua/Ade or 8-OH-Gua/Gua pairs were cleaved at a very slow rate. 8-OH-Ade and an AP-site opposite Cyt were also good substrates, but not when paired with other bases.

A ribosomal protein has been discovered in *Drosophila melanogaster* with 246 amino acids and an average molecular mass of 27.5 kDa, and named *Drosophila* ribosomal protein S3 (dS3 protein) [331–333]. This protein has been shown to possess AP endonuclease and β- and δ-elimination activities and to be tightly associated with the nuclear matrix, suggesting a function in DNA repair. Interestingly, it also acted on double-stranded oligodeoxynucleotides containing 8-OH-Gua, suggesting that this protein may also possess a DNA glycosylase activity. However, the actual release of 8-OH-Gua has not been definitely shown. The use of DNA substrates with multiple lesions unequivocally demonstrated that dS3 protein indeed possesses a DNA glycosylase activity and efficiently releases 8-OH-Gua and also FapyGua from DNA [334]. Both lesions were removed with similar excision kinetics, suggesting that FapyGua is also an important physiological substrate of this protein. In addition, dS3 protein efficiently acted on the 8-OH-Gua/Cyt pair in double-stranded oligodeoxynucleotides as in the case of DNA substrates, but failed to cleave the substrates with mismatched pairs of 8-OH-Gua with Ade, Gua or Thy. In analogy to other DNA glycosylases [144], S3 protein has been found to form a Schiff base intermediate that can be trapped by $NaBH_4$, as shown in Fig. 4. All these findings strongly suggested that dS3 protein possesses all the properties to play an important role in DNA repair. Human S3 protein also exists with 80% identity to its *Drosophila* homolog; however, it lacks δ-elimination and DNA glycosylase activities, and does not act on 8-OH-Gua [335–338]. Its substrate specificity has not been determined using DNA with multiple lesions.

5.4.4. Arabidopsis thaliana OGG1 protein

A functional homolog of OGG1 proteins in *Arabidopsis thaliana* (*At*OGG1) has been discovered, cloned and isolated [339]. *At*OGG1 has 365 amino acids with an average molecular mass of 40.3 kDa and exhibits a high degree of homology with other OGG1 proteins in several highly conserved regions [146,147,330,339–342]. In agreement with the results of previous studies in yeast, *Drosophila* and human OGG1 proteins, *At*OGG1 efficiently removed 8-OH-Gua and FapyGua with similar excision kinetics from DNA containing multiple lesions [76]. A significant dependence of excision on the nature of DNA substrates has also been observed. In the case of double-stranded oligodeoxynucleotides with 8-OH-Gua paired with each of the DNA bases, excision from the 8-OH-Gua/Cyt pair was most effective, albeit some activity on 8-OH-Gua paired with Thy or Ade was also observed in agreement with activities of other eukaryotic OGG1 proteins.

5.4.5. Schizosaccharomyces pombe Nth protein

A gene has been identified in *Schizosaccharomyces pombe* that encodes a protein with a strong sequence similarity to *E. coli* Nth [343]. This gene has been cloned and the protein has been isolated and purified. The functional analysis showed that this protein is a functional homolog of *E. coli* Nth. *S. pombe* Nth possesses 355 amino acids with an average molecular mass of 40.2 kDa, and exhibits both DNA glycosylase and AP-lyase activities. Efficient excision of urea and Thy glycol has been demonstrated using OsO_4– or $KMnO_4$–treated double-stranded oligodeoxynucleotides, respectively. No activity was detected on single-stranded oligodeoxynucleotides. Subsequently, the substrate specificity of *S. pombe* Nth has been determined using DNA with multiple lesions [344]. Pyrimidine-derived lesions 5-OH-Cyt, 5-OH-Ura, 5,6-diOH-Cyt, Thy glycol and 5-OH-6-HThy were efficiently excised by *S. pombe* Nth, exhibiting a narrower substrate specificity than *E. coli* Nth that

acts on additional pyrimidine-derived lesions, and purine-derived FapyAde [242,243]. The excision of Thy glycol agreed with previous results on Thy glycol-containing oligodeoxynucleotides [343]. Excision kinetics was also measured using four differently damaged DNA samples as substrates, and differed slightly among the lesions. However, a profound effect of the type of DNA substrate on excision kinetics has been observed as in the case of other DNA glycosylases (see above).

5.4.6. Human NTH1 protein

A human gene has been discovered that encodes a protein (hNTH1) with extensive sequence similarity with *E. coli* Nth and *S. pombe* Nth, including the HhH motif and the four highly conserved Cys residues involved in binding the [4Fe–4S] cluster [345]. hNTH1 has been overexpressed and purified, and shown to possess both DNA glycosylase and AP-lyase activities. It consists of 312 amino acids with an average molecular mass of 34.4 kDa. Similar to *S. pombe* Nth, hNTH1 efficiently excised urea, N-substituted urea lesions and Thy glycol from OsO_4– or $KMnO_4$–treated double-stranded oligodeoxynucleotides. hNTH1 also exhibited some incision activity on UV- or γ-irradiated plasmid DNA. Using DNA with multiple lesions, hNTH1 has been shown to remove the same substrates 5-OH-Cyt, 5-OH-Ura, 5,6-diOH-Cyt, Thy glycol and 5-OH-6-HThy from differently damaged DNA substrates as *S. pombe* Nth, albeit with significant differences in excision kinetics [346]. Again, excision kinetics of the lesions varied among DNA substrates. Subsequent work found FapyAde to be also a major substrate of hNTH1 [347]. Moreover, FapyAde accumulated in *nth1*$^{-/-}$ mice, providing the evidence that FapyAde is the physiological substrate of mammalian NTH1 [347,348]. FapyAde–containing oligodeoxynucleotides, and liver mitochondrial and nuclear extracts of wild-type mice and *nth1*$^{-/-}$, *ogg1*$^{-/-}$ and *ogg1*$^{-/-}$/*nth1*$^{-/-}$ mice have been used to confirm that FapyAde is a substrate of mammalian NTH1, but not that of OGG1 [347], as previously shown in *in vitro* experiments [301]. NTH1 is expressed in most tissues, although some tissues such heart and brain tissues exhibit higher expression levels [85,294,349,350]. A variant of hNTH1, i.e., hNTH1-Asp239Tyr occurs in approximately 6.2% of the global population (www.ncbi.nlm.nih.cov/SNP). This variant has been overexpressed and purified, and found to be an inactive DNA glycosylase, which was unable to excise modified DNA bases such as Thy glycol and 5,6-diHUra from oligodeoxynucleotides, and exhibited little AP-lyase activity [351]. Expression of hNTH1-Asp239Tyr in human cells also expressing wild-type hNTH1 resulted in genomic instability, cellular transformation and chromosomal aberrations, and sensitivity to ionizing radiation and H_2O_2–treatment resulting in accumulation of DNA double strand breaks. These results suggested that the individuals carrying the germline hNTH1-Asp239Tyr variant might be at risk for genomic instability and carcinogenesis. Other studies also provided evidence that hNTH1 function is essential for the maintenance of genomic integrity. Thus, cytoplasmic overexpression of hNTH1 has been detected in almost half of the cases of colorectal cancer, which correlated with disease-free survival [352]. Cytoplasmic localization of hNTH1 with its associated low expression in the nucleus in cancers may cause accumulation of the mutagenic/cytotoxic substrates of NTH1 in the nucleus. Altered expression and abnormal localization of hNTH1 have been reported to be involved in the pathogenesis of gastric cancer [353]. Mutations have been identified in the *nth1* gene, predisposing individuals to colorectal cancer and other types of cancer [354–356]. Another study reported the accumulation of FapyAde in kidneys and livers of *nth1*$^{-/-}$ mice when compared to wild-type mice, and the development of pulmonary and hepatocellular tumors in *nth1*$^{-/-}$ male and female mice as they aged [348].

5.4.7. Saccharomyces cerevisiae Ntg1 and Ntg2 proteins

In *S. cerevisiae*, two genes *ntg1* and *ntg2* encode two proteins named Ntg1 and Ntg2, respectively, which are closely related to each other with 47% identity and 63% similarity, and possess 399 and 380 amino acids with an average molecular mass of 45.6 kDa and 43.9 kDa, respectively [270,276,357–360]. Both proteins are DNA glycosylases with AP-lyase activity and possess a significant sequence homology to *E. coli* Nth with a HhH DNA-binding motif containing a Lys residue involved in catalysis, but only Ntg2 contains the iron-sulfur center near the C-terminus. In addition, Ntg1 possesses a positively charged N-terminus as a putative mitochondrial transit sequence, indicating that this protein may be involved in the repair of DNA damage in mitochondria [358,359,361]. Indeed, Ntg1 has been shown to primarily localize to mitochondria with some localization in the nucleus [361]. The reason may be that this protein lacks the iron-sulfur cluster [362,363]. In contrast, Ntg2 has been shown to be exclusively located in the nucleus because proteins containing the iron-sulfur cluster in mitochondria may lose the iron that can be used to generate free radicals [361]. Moreover, the subcellular localization of Ntg1 and Ntg2 caused different sensitivities to alkylating agents in *S. cerevisiae*, perhaps due to the more vulnerability of mitochondrial DNA to damaging agents. On the other hand, the *ntg1*, *ntg2*, *ntg1*/*ntg2* mutants of *S. cerevisiae* exhibited no more sensitivity to DNA-damaging agents than the wild-type *S. cerevisiae* [361]. Moreover, cells lacking both Ntg1 and Ntg2 were generally not sensitive to DNA-damaging agents, and did not exhibit a spontaneous mutator phenotype, suggesting that alternative mechanisms are involved in the repair of DNA lesions and AP sites in yeast [360,364].

Ntg1 and Ntg2 removed 5,6-diHUra, 5,6-diHThy, Thy glycol, Ura glycol and Me-FapyGua from oligodeoxynucleotides; however, no activity on 8-OH-Gua was detected, although Ntg1 removed this lesion at low efficiency, when paired with non-cognate Gua only [361,365,366]. Both proteins have been shown to possess a cross-activity and to remove the pyrimidine-derived lesions 5-OH-Cyt, 5-OH-Ura, 5-OH-6-HUra, Thy glycol, 5-OH-6-HThy and 5-OH-5-MeHyd, and the purine-derived lesions FapyAde and FapyGua, but not 8-OH-Gua, from DNA with multiple lesions [361,366]. The lack of 8-OH-Gua excision from DNA is on a par with that from oligodeoxynucleotides. 5-OH-6-HThy and 5-OH-6-HUra were excised by both Ntg1 and Ntg2 with the highest k_{cat}/K_M values. Other lesions exhibited lower excision kinetics, but their k_{cat}/K_M values were roughly similar to one another. Taken together, these findings showed that the cross-activities of Ntg1 and Ntg2 for purine- and pyrimidine-derived lesions differ from those of *E. coli* Nth and Nei in that Ntg1 and Ntg2 efficiently remove FapyGua in addition to FapyAde from DNA with multiple lesions.

Recent studies showed that Ntg1 and Ntg2 are post-translationally modified by Small Ubiquitin-like Modifier (SUMO), and Ntg1 is modified as a result of oxidative stress and DNA damage [367,368]. Sites of SUMO modification in Ntg1 have been identified [369]. hNTH1 has also been shown to be modified by SUMO in response to DNA damage. The results suggested that SUMO modification of DNA glycosylases might be an evolutionarily conserved mechanism to respond to oxidatively induced DNA damage in cells.

5.4.8. NEIL1 protein

In 2002, a novel DNA glycosylase was discovered in human cells using the human genome database and named human NEIL1 (hNEIL1) because of its sequence homology to *E. coli* Nei (Nei-like) [370–372]. This enzyme belongs to the Fpg/Nei family, consists of 390 amino acids with an average molecular mass of 43.7 kDa and possesses an additional β,δ-elimination activity. The activation of hNEIL1 depends on cell cycle and it is expressed in cells

predominantly in the S phase, suggesting that its repair function is likely to be associated with replication [112,373–378]. The N-terminal Pro-2 is utilized to catalyze sequential glycosylase activity, and β- and δ-eliminations, and mutations at this site compromise the enzymatic activity [371,373]. hNEIL1 is located in both the nucleus and mitochondria, lending credence to its importance in maintaining genetic stability [347]. The expression of hNEIL1 is tissue-dependent with the highest expression in liver, pancreas and thymus, and with moderate expression in brain, spleen, prostate and ovary [372–374]. The structure of hNEIL1 has been solved using X-ray crystallography, revealing that it does not contain a zinc-finger motif presented in *E. coli* Fpg and Nei, but maintains a similar overall fold termed "zinc-less finger" motif [379]. Mouse NEIL1 (mNEIL1) consisting of 389 amino acids with an average molecular mass of 43.6 kDa has also been found, isolated and characterized [380,381]. Both hNEIL1 and mNEIL1 excised Me-FapyGua and a number of pyrimidine-derived lesions from oligodeoxynucleotides with one single lesion, but not 8-OH-Gua paired with Cyt [370,371,373,380,381]. Although the excision of 8-OH-Gua by hNEIL1 has been reported in an early study [372], this activity has not been confirmed by many other studies *in vitro* and *in vivo* [261,347,348,370,382–385]. On the other hand, oxidation products of 8-OH-Gua, i.e., Gh and two diastereomers of Sp have been shown to be excellent substrates of both NEIL1 proteins [22,386,387]. When DNA with multiple lesions was used, both hNEIL1 and mNEIL1 mainly removed FapyAde and FapyGua, and also exhibited a lesser activity on Thy glycol and 5-OH-5-MeHyd [370,382]. In this case, too, no activity on 8-OH-Gua was detected in agreement with the previous studies that used 8-OH-Gua–containing oligodeoxynucleotides as substrates. Measurement of excision kinetics of mNEIL1 for FapyAde and FapyGua under identical conditions showed that the efficiency of mNEIL1 is similar to or greater than those of other prokaryotic and eukaryotic DNA glycosylases that act on these lesions [382]. The k_{cat}/K_M values for excision of FapyGua and FapyAde were $9.3 \pm 0.6 \times 10^{-5}$ min^{-1} mmol^{-1} L and $7.1 \pm 0.1 \times 10^{-5}$ min^{-1} mmol^{-1} L, respectively, indicating somewhat greater preference of mNEIL1 for FapyGua than for FapyAde.

The contribution of NEIL1 to the excision of FapyAde and FapyGua in cell extracts has been demonstrated, when synthetic oligodeoxynucleotides containing FapyAde or FapyGua were used [347]. In agreement with the *in vitro* studies discussed above, FapyAde and FapyGua, but not 8-OH-Gua, significantly accumulated in three different organs of *neil1*$^{-/-}$ mice and in *neil1*-knockdown cells, providing the evidence that FapyAde and FapyGua are the main physiological substrates of NEIL1 *in vivo* [348,384,385]. Fig. 6 illustrates the greater accumulation of FapyAde and FapyGua, but not 8-OH-Gua, in livers of male and female *neil1*$^{-/-}$ mice than in wild-type mice [348]. This was also the case for two other organs of *neil1*$^{-/-}$ mice, which developed pulmonary and hepatocellular tumors in the second half of their lives [348]. Even a dramatic increase in tumor development has been observed in *nth1*$^{-/-}$/*neil1*$^{-/-}$ mice. Another study demonstrated the accumulation of FapyGua in both *neil1*$^{-/-}$ and *ogg1*$^{-/-}$ mice, and that of 8-OH-Gua in *ogg1*$^{-/-}$ mice, but not in *neil1*$^{-/-}$ mice [385]. These results confirmed that FapyGua is a physiological substrate of both NEIL1 and OGG1, and that NEIL1 does not act on 8-OH-Gua *in vivo*. NEIL1 has been shown to remove some DNA lesions from quadruplex DNA, and to exhibit preference for lesions such as Gh, but not for Thy glycol in the telomeric sequence context [388,389]. However, no activity on 8-OH-Gua in quadruplex DNA has been detected in agreement with previous results that NEIL1 does recognize this lesion (see above). These findings suggested that both NEIL1 may play a role in protecting the integrity of telomeres and in gene regulation. Psoralen-induced interstrand DNA cross-links have also been shown to be the substrates of NEIL1 [390,391].

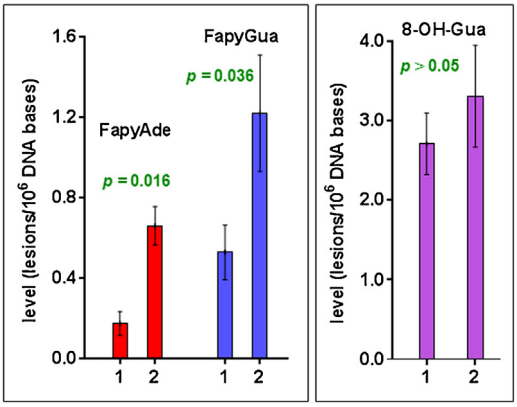

Fig. 6. Levels of FapyAde, FapyGua and 8-OH-Gua in livers of wild-type mice (1) and *neil1*$^{-/-}$ mice (2). Uncertainties are standard deviations. (Redrawn from the data in [348]).

Various polymorphic variants of hNEIL1, i.e., NEIL1-Ser82Cys, NEIL1-Gly83Asp, NEIL1-Cys136Arg, NEIL1-Asp252Asn and NEIL1-Pro208Ser, and NEIL1ΔGlu28 have been cloned, expressed and purified [383,392]. The reason for this effort was that the National Institute of Environmental and Health Sciences Environmental Genome Project identified some of these variants by sequencing the *neil1* gene in a set of people representative of the US population. Single nucleotide polymorphisms occurred at approximately 1% within this set of individuals. NEIL1-Ser82Cys, NEIL1-Gly83Asp and NEIL1-Asp252Asn have been shown to retain near wild-type activity on abasic site-containing oligodeoxynucleotides, although NEIL1-Gly83Asp exhibited the β-elimination reaction, but not the β,δ-elimination reaction. NEIL1-Cys136Arg had significantly reduced activity. Using Thy glycol–containing oligodeoxynucleotides, NEIL1-Ser82Cys and NEIL1-Asp252Asn exhibited DNA glycosylase activity similar to the wild-type NEIL1. In contrast, NEIL1-Gly83Asp and NEIL1-Cys136Arg were completely devoid of this activity. NEIL1-Pro208Ser, which was found in patients with colorectal carcinoma [393], exhibited wild-type activity, whereas NEIL1ΔGlu28 efficiently acted on Sp and Gh, and on Thy glycol to a lesser extent [392]. The use of DNA with multiple lesions showed efficient excision of FapyAde and FapyGua by wild-type NEIL1, NEIL1-Ser82Cys and NEIL1-Asp252Asn with similar excision kinetics. Consistent with the lack of activity on Thy glycol–containing oligodeoxynucleotides, NEIL1-Gly83Asp, which was found in patients with cholangiocarcinoma [394], exhibited no activity for FapyAde and FapyGua, and pyrimidine-derived lesions [383]. This is in agreement with the results obtained with double-stranded oligodeoxynucleotides [392]. RNA editing of hNEIL1 from Lys-242 to Arg-242 significantly reduced its DNA glycosylase activity for Thy glycol in oligodeoxynucleotides, although the removal of Gh was enhanced [392,395]. If mouse models can be extrapolated to humans, it may be speculated that individuals carrying these variants may be at greater risk for developing diseases such as metabolic syndrome and cancer as observed in *neil1*$^{-/-}$ mice [85,348,396–398]. In support of this notion, several NEIL1 variants have been associated with several types of cancers, and cancer-associated NEIL1 variants have been identified in the *neil1* gene [393,394,399,400].

In addition to its action as a DNA glycosylase in BER, NEIL1 may be involved in NER of 8,5′-cyclopurine-2′-deoxynucleosides, as evidenced from the accumulation of *R*-cdA and *S*-cdA in liver DNA of *neil1*$^{-/-}$ mice [385]. These lesions are repaired by NER, not by BER [63–66]. It may well be that NEIL1 interacts with the proteins of the NER complex. For example, Cockayne syndrome complementation group B (CSB) protein plays a role in the repair of *S*-cdA [401], and cooperates with NEIL1 in the repair of FapyAde and FapyGua [384].

Other NER proteins may also be involved in the action of NEIL1 on *R*-cdA and *S*-cdA, since it cannot itself initiate BER at these lesions. To this end, the importance of interaction of hNEIL1 with other DNA repair proteins has been shown to be critical for efficient repair of oxidatively induced DNA damage including prereplicative repair [376,402–407].

5.4.9. NEIL2 protein

Another human Nei-like DNA glycosylase/AP-lyase with β,δ-elimination has been discovered and named NEIL2 [370,373,408]. This protein is comprised of 332 amino acids with an average molecular mass of 36.8 kDa and shows no significant sequence homology to NEIL1. On the other hand, NEIL2 possesses an N-terminal Pro at its active site in analogy to NEIL1. It is highly expressed in skeletal muscle and testis without any change during cell cycle [373], in contrast to the preferential expression of NEIL1 in liver, thymus and pancreas, and during the S-phase [370]. NEIL2 has been found both in the nucleus and mitochondria [347,409]. The overall identity of NEIL2 to *E. coli* Fpg and Nei is 32% and 27%, respectively, sharing an H2TH and a zinc finger motif with them. NEIL2 showed a unique preference for excision from single-stranded oligodeoxynucleotides and bubble structures generated during transcription and/or replication [370]. Thus, NEIL2 has been suggested to act in transcription-coupled repair of DNA damage [410]. NEIL2 efficiently excised 5-OH-Ura from oligodeoxynucleotides when paired with Gua, but exhibited a lower activity for 5,6-diHUra and 5-OH-Cyt, and a very weak activity for Thy glycol and 8-OH-Gua. Removal of Sp and Gh from double-stranded oligodeoxynucleotides has also been observed [22]. Thus far, however, the excision by NEIL2 of any DNA base lesions from DNA with multiple lesions has not been studied. This was mainly due to the fact that NEIL2 is highly unstable and loses its activity very quickly after storage at low temperature or by incubation at 37 °C [373]. The importance of NEIL2 for the long term maintenance of genomic maintenance has been demonstrated by the fact that *neil2*$^{-/-}$ mice, which had accumulated DNA lesions in the transcriptionally active sequences, were susceptible to inflammation and exhibited age-dependent increase in oxidatively induced DNA damage [411]. Furthermore, telomere loss and genetic instability have been observed in embryonic fibroblasts from these mice. Several polymorphic variants of NEIL2 such as NEIL2-Arg103Gln, NEIL2-Arg103Trp, NEIL2-Pro123Thr, NEIL2-His12Leu, NEIL2-Glu77Lys and NEIL2-Arg257Leu have been frequently found in several cancers [400,412]. NEIL2-Arg257Leu and NEIL2-Arg103Gln found in lung cancer patients have been overexpressed and purified [400,412]. NEIL2-Arg257Leu exhibited significantly less repair capacity than wild-type NEIL2 and NEIL2-Arg103Gln. The activity of the latter was comparable to that of wild-type NEIL2. In human cells expressing NEIL2-Arg257Leu, higher level of accumulation of DNA damage has been observed than in cells expressing wild-type NEIL2. The data suggested that individuals carrying the NEIL2-Arg257Leu variant of NEIL2 might be at risk for lung carcinogenesis.

5.4.10. NEIL3 protein

Another protein has been identified in human cells as a Nei-like DNA glycosylase and named NEIL3 [372]. This protein lacks the catalytic N-terminal Pro, but has a Val instead. Human NEIL3 (hNEIL3) is a large protein with 605 amino acids and an average molecular mass of 67.8 kDa. The full-length mouse Neil3 (MmuNeil3), its glycosylase domain (MmuNeil3Δ324), the full-length hNEIL3, a truncated human core-NEIL3 and the glycosylase domain of NEIL3 (hNEIL3Δ324) have been overexpressed and purified [98,261,413–416]. First, NEIL3 has been found to recognize Me-FapyGua; however, subsequent studies failed to detect any DNA glycosylase activity of either the full-length protein or its glycosylase domain [417,418]. Mice lacking the *neil3* gene have been generated, which were viable and did not exhibit any adverse phenotype [417]. On the other hand, loss of NEIL3 has been shown to reduce cellular proliferation and sensitize cells to genotoxic stress [419]. The expression of NEIL3 has been observed in the S phase, and in thymus and testis, in some tumor tissues and during embryonic development and in areas of the brain containing stem cells, suggesting that NEIL3 might be important for stem cell differentiation [85,294,417–422]. NEIL3 appears to be localized in the nucleus, and has not been found in mitochondria thus far [415,417]. A weak lyase activity of NEIL3 for single-stranded oligodeoxynucleotides has been detected, and a partial rescue of an *E. coli nth nei* mutant from H_2O_2 sensitivity has been observed [418]. However, the DNA glycosylase activity of NEIL3 has remained undetermined and controversial. Subsequently, full-length MmuNEIL3 and MmuNEIL3Δ324 have been purified and characterized as a functional DNA glycosylase [261]. MmuNEIL3Δ324 has been shown to possess a conserved N-terminus, the H2TH motif and the Fpg/Nei family zinc finger motif. Both MmuNEIL3 and MmuNEIL3Δ324 efficiently excised Gh and the two diastereomers of Sp, but not 8-OH-Gua, from double-stranded oligodeoxynucleotides. This was accompanied with β-elimination and very low β,δ-elimination in contrast to NEIL1 and NEIL2. MmuNEIL3 and MmuNEIL3Δ324 preferred bubble and fork structures of single-stranded oligodeoxynucleotides containing 5-OH-Ura, 5-OH-Cyt, 5,6-diHThy and 5,6-diHUra. The glycosylase domain of human NEIL3 has been purified and shown to remove Sp and Gh from single- and double-stranded oligodeoxynucleotides with β-elimination only, and, with less efficiency, 5-OH-Ura and 5-OH-Cyt from single-stranded oligodeoxynucleotides [416]. When DNA with multiple lesions was used, MmuNEIL3Δ324 efficiently excised FapyAde and FapyGua, but also exhibited a significantly broader specificity for 5-OH-Ura, 5-OH-Cyt, 5-OH-5-MeHyd, Thy glycol and 8-OH-Ade than hNEIL1 and mNEIL1 [261]. No excision of 8-OH-Gua was observed in agreement with the results on 8-OH-Gua–containing oligodeoxynucleotides. MmuNEIL3 formed the Schiff base intermediate with its catalytic N-terminal Val in contrast to other members of the Fpg/Nei family that use the N-terminal Pro. The crystal structure of NEIL3 has been elucidated and shown to possess the same fold as that of other Fpg/Nei proteins, but to lack the recognition loop, also called αF-β9/10 loop, which has been found to be required for the recognition of 8-OH-Gua [94,96,423]. This indicates as to why this protein is unable to recognize 8-OH-Gua [414,415]. Moreover, NEIL3 has been shown to remove DNA lesions such as Thy glycol, Sp and Gh from quadruplex DNA, but not 8-OH-Gua, and to play an important role in telomere maintenance [388]. Unlike NEIL1, however, NEIL3 preferred Thy glycol, but not Sp or Gh, in the telomeric sequence context. The inactivity toward 8-OH-Gua agrees with the previous results that NEIL3 does not act on this lesion in DNA or oligodeoxynucleotides [261].

To test the role of MmuNEIL3 *in vivo*, MmuNEIL3Δ324 and NEIL1Δ56 were expressed in an *E. coli fpg nei mutY* mutant strain, which exhibits a much greater spontaneous G→T transversion mutation frequency than the wild-type *E. coli* strain [252,253]. The expression of both MmuNEIL3Δ324 and NEIL1Δ56 significantly reduced the mutation frequency in the *E. coli fpg nei mutY* mutant strain [252,261]. This finding suggested that MmuNEIL3 recognizes guanine-derived lesions *in vivo*. To prove this observation further, the level of FapyGua was measured in DNA of both strains and found to be significantly elevated in the mutant strain when compared to wild-type *E. coli* due to the absence of Fpg, which specifically acts on FapyGua (see above). The expression of MmuNEIL3Δ324 or NEIL1Δ56 in the mutant strain caused a significant reduction of the level of FapyGua. In contrast, the expression of *E. coli* Nei did not reduce the level of FapyGua,

agreeing with the lack of *in vitro* recognition of this lesion by *E. coli* Nei (see above). Taken together, these findings proved that, in analogy to NEIL1, NEIL3 recognizes FapyGua *in vivo* and that the reduction of the mutation frequency by the expression of MmuNEIL3Δ324 mainly results from the activity of NEIL3 on FapyGua. The recognition of FapyGua by NEIL3 *in vivo* agrees with the findings of *in vitro* studies (see above). Furthermore, the extreme elevation of the G→T transversions in the *fpg nei mutY* mutant strain are likely to result mainly from elevated levels of FapyGua, which is well known to cause such mutations [195,261–263]. In another related case to NEIL proteins, abnormal expressions of NEIL1, NEIL2 and NEIL3 have been found to be associated with somatic mutations in cancer [424]. No observable phenotype in *neil3*$^{-/-}$ mice has been observed [417]. Later, however, a homozygous missense mutation in *neil3* that abolishes the enzymatic activity has been identified in patients with severe recurrent respiratory infections, impaired B cell function and peripheral B cell tolerance, and sever autoimmunity [425]. Moreover, *neil3*$^{-/-}$ mice exhibited elevated serum levels of antibodies, kidney inflammation, and apoptosis and cell death in T and B cells. This study demonstrated that NEIL3 deficiency may lead to increased lymphocyte apoptosis, autoantibodies and predisposition to autoimmunity.

Finally, it should be mentioned that prokaryotic and eukaryotic bifunctional DNA glycosylases/lyases such as Fpg, Nei, Nth, NEIL1 and NTH1 have been shown to act on oxidatively induced guanine (C8)-thymine(N3) intrastrand cross-links (Gua[8,3]Thy) and those separated by a cytosine in double-stranded oligodeoxynucleotides [426]. DNA glycosylases removed guanine by hydrolyzing the *N*-glycosidic bond between the sugar moiety and guanine in these cross-links and cleaved the DNA strands on the 3′-side of the resulting AP site *via* either β-elimination or β,δ-elimination. These tandem cross-links and others (Gua[8,5-Me]Thy and Gua[8,5]Cyt) have been identified *in vitro*, and in mouse and human cells [46,69,427–429].

5.5. Fungal and plant DNA glycosylases

As in bacteria, formamidopyrimidine DNA glycosylases have been found in fungi and plants. Among fungi, *Candida albicans* (*C. albicans*) is a human fungal pathogen that grows as yeast and filamentous cells, and can cause complications including mortality in immunocompromised patients due to rapid development of antifungal drugs [430–432]. Since the immune system generates reactive species such as free radicals to fight pathogens [1,433], *C. albicans* must deal with the effects of reactive species for survival by various mechanisms including BER and NER [432]. Formamidopyrimidine DNA glycosylase of *C. albicans* (*Cal*Fpg) has been expressed, purified and characterized [434]. The alignment of the amino acid sequence of *Cal*Fpg with those of other DNA glycosylases showed that it belongs the Fpg/Nei family, but is more similar to *E. coli* Fpg than *E. coli* Nei. With the use of double-stranded oligodeoxynucleotides with one single lesion, modified pyrimidines have been shown to be excellent substrates for *Cal*Fpg with some discrimination against mispairs. 8-OH-Gua was not a substrate; however, its oxidation products Sp and Gh paired with Cyt were the best substrates. Furthermore, *Cal*Fpg has been shown to also possess a β,δ-elimination activity in analogy to *E. coli* Fpg and Nei, and act on single-stranded oligodeoxynucleotides with a single lesion. The use of DNA with multiple lesions showed that FapyAde and FapyGua were excellent substrates, although *Cal*Fpg exhibited a better preference for the latter than the former. 8-OH-Ade, 5-OH-5-MeHyd and 5-OH-Cyt were also released to some extent. A very low activity for 8-OH-Gua has been observed in excellent agreement with the results on oligodeoxynucleotides. These findings clearly indicated the distinction between *E. coli* Fpg and *Cal*Fpg in terms of 8-OH-Gua excision.

A bifunctional formamidopyrimidine DNA glycosylase of *Arabidopsis thaliana* Fpg (*Ath*Fpg) has been expressed, purified and characterized, and found to have structural similarity to bacterial Fpg and Nei proteins [434,435]. In double-stranded oligodeoxynucleotides, the preferred substrates of *Ath*Fpg were Gh, two diastereomers of Sp, Me-FapyGua and AP sites with β,δ-elimination; however, no activity on 8-OH-Gua was detected [96,435]. 5-OH-Ura and 5,6-diHUra were preferred pyrimidine-derived lesions. *Ath*Fpg efficiently removed FapyAde and FapyGua from DNA with multiple lesions, but did not recognize 8-OH-Gua in agreement with the observation using oligodeoxynucleotides [435]. 5-OH-5-MeHyd was a good substrate, but 5-OH-Cyt and Thy glycol were not excised. These findings show that *Ath*Fpg is more similar to mammalian NEIL1 than to *E. coli* Fpg. The crystal structure of a functional C-terminal deletion form of *Ath*Fpg (*Ath*FpgΔ88) has been determined, and found to be similar to that of other members of the Fpg/Nei family [435]. This protein possesses a zincless finger as NEIL1 and, in contrast to bacterial Fpg proteins, it harbors a very short αF-β9/10 loop, which is required for the recognition of 8-OH-Gua. Efficient removal of FapyAde and FapyGua, and other lesions by *Ath*Fpg revealed that the absence of the αF–β9/10 loop does not affect the removal of DNA lesions other than 8-OH-Gua. To prove this fact further, some amino acid residues corresponding to the αF-β9/10 loop have been deleted from *E. coli* Fpg (*E. coli* FpgΔ213-229) [435]. Indeed, *E. coli* FpgΔ213-229 did not recognize 8-OH-Gua in oligodeoxynucleotides, whereas Me-FapyGua, Gh, Sp and 5,6-diHUra were efficiently excised, and the lyase activity was retained. Similarly, when DNA with multiple lesions was used, *E. coli* FpgΔ213-229 exhibited no activity on 8-OH-Gua whatsoever, but recognized FapyGua, FapyAde and 8-OH-Ade as well as wild-type *E. coli* Fpg. Fig. 7 illustrates these results [435], which revealed as to why eukaryotic Fpg glycosylases do not excise 8-OH-Gua, and that the αF–β9/10 loop is essential and specific for the recognition of this lesion.

5.6. Viral DNA glycosylases

In UV radiation-resistant organisms such as *Micrococcus luteus* and phage T4-infected *E. coli*, a DNA glycosylase has been discovered and named T4 endonuclease V (T4-pyrimidine dimer glycosylase) (T4-pdg) [140,436–438]. This protein is comprised of 138 amino acids with an average molecular mass of 16.1 kDa. T4-pdg hydrolyzes the glycosidic bond of the 5′-pyrimidine of the UV radiation-induced pyrimidine dimers, followed by the

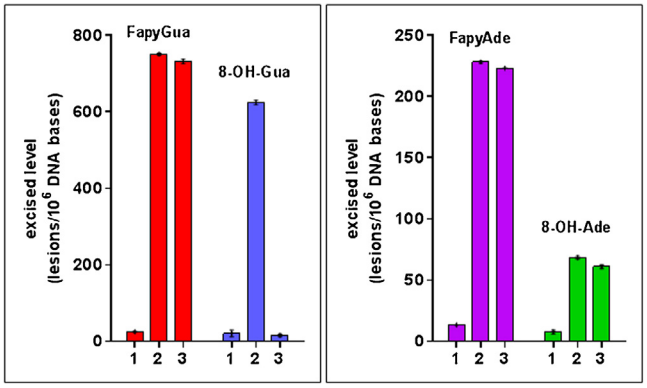

Fig. 7. Activities of *E. coli* Fpg and *E. coli* FpgΔ213-229 on purine-derived lesions in high-molecular weight DNA with multiple lesions. 1: no enzyme; 2: *E. coli* Fpg; 3: *E. coli* FpgΔ213-229. Uncertainties are standard deviations. (Redrawn from the data in [435]).

hydrolysis of the phosphodiester bond at the 3′-side of the generated AP site (AP-lyase activity). For catalysis, the N-terminal α-amino group of the enzyme is used as the nucleophile in combination with Glu-23 near the active site [140,439]. First, the enzyme has been strictly recognized as a pyrimidine dimer-specific DNA glycosylase. However, T4-pdg has been later shown to recognize and efficiently remove FapyAde from γ- or UV-irradiated DNA with multiple lesions [440]. The rate of this excision was about 1% to 3% that of the excision of UV radiation-induced pyrimidine dimers. Other lesions present in DNA were not recognized. Interestingly, in addition to being a typical •OH radical-induced product, FapyAde along with FapyGua have been shown to be formed in DNA by UV-irradiation as well [441]. Efficient excision of FapyAde from γ-irradiated DNA as well as from UV-irradiated DNA unequivocally showed that T4-pdg acts not only on pyrimidine dimers, but also on an •OH- and UV radiation-induced monomeric product in DNA.

A DNA glycosylase has been discovered in Chlorella virus PBCV-1 that infects single-celled Chlorella-like green algea [442]. This enzyme has been shown to be specific for UV radiation-induced pyrimidine dimers with a concomitant lyase activity, and thus named Chlorella virus pyrimidine dimer glycosylase (cv-pdg) [140,443–445]. This DNA glycosylase possesses 139 amino acids with an average molecular mass of 16.3 kDa and is a true sequence homolog of T4-pdg with 41% amino acid identity. However, cv-pdg exhibits a higher catalytic activity and broader substrate specificity than T4-pdg [140,442]. Similar to T4-pdg, Glu-23 is involved in the catalytic mechanism of cv-pdg for both glycosylase and lyase activities [443–445]. Using DNA with multiple lesions, cv-pdg has been shown to efficiently excise FapyAde and FapyGua, but not 8-OH-Gua or 8-OH-Ade [446]. When T4-pdg and cv-pdg were tested under identical conditions, T4-pdg excised FapyAde, but not FapyGua. The amount of FapyAde excised by cv-pdg was approximately 7-fold greater than that by T4-pdg. The measurement of excision kinetics showed that cv-pdg excises FapyAde with 4-fold greater activity than FapyGua. This indicates the greater specificity of the enzyme for the excision of the former than the latter. These findings show that cv-pdg possesses an activity for two •OH- and UV radiation-induced monomeric products in DNA in addition to its activity for pyrimidine dimers. Taken together, T4-pdg and cv-pdg exhibit different substrate specificities despite significant structural similarities, and are not only specific for pyrimidine dimers, but also act on UV radiation-induced monomeric formamidopyrimidines.

Two Nei-like proteins have been discovered in the giant *Acanthamoeba polyphaga mimivirus* (Mimivirus) [447]. These proteins named *Mv*Nei1 and *Mv*Nei2 have been cloned, expressed and purified, and shown to exhibit activities similar to those of human NEIL1, NEIL2 and NEIL3 [448–451]. The crystal structures of *Mv*Nei1 and *Mv*Nei2 showed that *Mv*Nei1 possesses a zinc-less-finger β-hairpin motif similar to human NEIL1, whereas there exists a C—H—C—C type zinc-finger in *Mv*Nei2 similar to that in human NEIL2, and a N-terminal catalytic Val-2 as in NEIL3 [449–451]. Both enzymes exhibited robust activity on AP sites, Gh, Sp, Thy glycol, 5,6-diHUra and 5-OH-Ura in single- and double-stranded oligodeoxynucleotides when paired with the cognate base. Substrate specificities of these enzymes have not been determined using DNA with multiple lesions.

6. Comments on excision kinetics and substrate differences

Table 1 summarizes the substrate specificities of DNA glycosylases discussed in this article. The results obtained with both oligodeoxynucleotides with one single lesion, and high-molecular weight DNA containing multiple lesions are presented together in a single column. The differences between the substrate specificities of DNA glycosylases are clearly seen in this table. In general, the substrate specificities obtained with oligodeoxynucleotides and high-molecular weight DNA were somewhat similar, although some significant differences were observed. Thus, some lesions excised by a DNA glycosylase from an oligodeoxynucleotide were not recognized and removed by the same enzyme from DNA. Moreover, some of the kinetic parameters such as the K_M values of DNA glycosylases obtained with DNA have been shown to be significantly greater than those obtained with oligodeoxynucleotides, whereas the k_{cat} values were similar for both substrate types (for examples, see [301,322]). There may be several reasons for these phenomena. When oligodeoxynucleotides are used, a DNA glycosylase would encounter only one lesion without competition, and the effective concentration of the single lesion would be extremely high such as 1 lesion per 20 to 40 deoxynucleotides. Assuming the level of a lesion in a damaged DNA substrate being approximately 200 lesions/10^6 DNA bases among multiple other lesions and normal DNA bases, the difference between the concentrations of the lesion in two different substrates would be at least 200-fold. In addition, a DNA glycosylase would simultaneously encounter numerous lesions in DNA, and then would search for its substrates and distinguish them from non-substrates and normal DNA bases. As discussed above, DNA glycosylases scan and slide along DNA, and recognize a substrate lesion before insertion into the substrate-binding pocket of the enzyme with the involvement of a “nucleotide flipping” mechanism [85,86,92–100,106]. The binding lifetimes of DNA glycosylases increase and the mean diffusion constants decrease with the increase in the number of DNA lesions [97–99,106]. Therefore, the use of short oligodeoxynucleotides with a single lesion may underemphasize or completely ignore the role of scanning, sliding and lesion recognition. This is supported by the fact that the action of DNA glycosylases on short oligodeoxynucleotides exhibits faster kinetics [452]. The greater K_M values for lesions in DNA than those in oligodeoxynucleotides are consistent with the one-dimensional diffusion model for proteins searching for a specific lesion or element in DNA [453–456]. The size of the high-molecular weight DNA molecule and the associated long distances between substrate lesions will increase the translocation time for the search of a lesion, and therefore the K_M value [322,456]. This will lead to the lack of recognition of nonspecific substrates in DNA, whereas specific and physiological substrates will be efficiently acted upon and removed as shown by many studies, including those done with *E. coli* mutants. For example, the mutation spectrum of the *nth nei fpg* triple mutants showed no significant increase in C → T transitions over those exclusively found in the *nth nei* double mutants [246,252,268]. Cytosine-derived lesions such as 5-OH-Cyt and 5-OH-Ura lead to C → T transitions, and *E. coli* Fpg recognizes these lesions in oligodeoxynucleotides only [268], but not in high-molecular weight DNA [30,223]. Therefore, 5-OH-Cyt and 5-OH-Ura, and other pyrimidine-derived lesions such as 5,6-diHUra are non-specific substrates of *E. coli* Fpg, whereas 8-OH-Gua, FapyGua and FapyAde, which are efficiently recognized in high-molecular weight DNA [30,223], constitute specific and physiological substrates of this enzyme [268,456]. Extensive discussions of the search of DNA glycosylases for DNA lesions can be found elsewhere [86,95,97–100,103,104,106,140,456–458].

7. DNA glycosylases as biomarkers and therapy targets

Malignant tumors possess increased levels of oxidatively induced DNA damage [459–476]. Elevated levels of DNA damage in tumors may lead to overexpression of DNA repair proteins including DNA glycosylases. This may provide tumors an evolutionary advantage for survival and increase their repair capacity in comparison to normal tissues. Increased DNA repair

Table 1
Substrate specificities of DNA glycosylases for oxidatively induced DNA base lesions. Symbols: X^a, determined using DNA with multiple lesions; X^b, determined using oligodeoxynucleotides with a single lesion; $X^{a,b}$, determined using DNA with multiple lesions as well as oligodeoxynucleotides with a single lesion.

DNA lesions	UNG	SMUG1	TDG	MBD4	*E. coli* Fpg	*Dr*Fpg	OGG1 proteins	Nth proteins	NTH1 proteins	Ntg1 Ntg2	*E. coli* Nei	NEIL1	NEIL2	NEIL3	dS3	*Mtu*Fpg1	*Mtu*Nei1	*Mtu*Nth	*Cal*Fpg	*Ath*Fpg	T4-pdg	cv-pdg	*Mv*Nei1 *Mv*Nei2
FapyAde					$X^{a,b}$	X^a		$X^{a,b}$	$X^{a,b}$	$X^{a,b}$	$X^{a,b}$	$X^{a,b}$		X^a		X^a	X^a	X^a	X^a	X^a	X^a	X^a	
8-OH-Ade					X^a									X^a		X^a		X^a	X^a				
FapyGua					$X^{a,b}$	X^a	$X^{a,b}$			$X^{a,b}$		$X^{a,b}$		X^a	X^a	X^a	X^a	X^a	X^a	X^a		X^a	
8-OH-Gua					$X^{a,b}$	X^a	$X^{a,b}$								X^a	X^a							
Sp					X^b						X^b	X^b	X^b	X^b		X^b	X^b		X^b	X^b			X^b
Gh												X^b	X^b	X^b		X^b	X^b		X^b	X^b			X^b
5-OH-Cyt					X^b			$X^{a,b}$	X^a	X^a	$X^{a,b}$		X^b	$X^{a,b}$			$X^{a,b}$	$X^{a,b}$	X^a				
Cyt glycol					X^b			$X^{a,b}$															
5-OH-6-HCyt								X^a															
5,6-diOH-Cyt								X^a	X^a		X^a												
5-formylCyt			X^b																				
5-carboxylCyt			X^b																				
5-OH-Ura	X^a	X^a			X^b			$X^{a,b}$	X^a	X^a	$X^{a,b}$	X^b	X^b	$X^{a,b}$			X^a	X^a		X^b			X^b
Ura gly								$X^{a,b}$		X^b	$X^{a,b}$												
5,6-diOH-Ura	X^a	X^a						X^a			X^a												
5-OH-6-HUra								X^a		X^a	X^a												
alloxan	X^a	X^a						X^a															
5,6-diHUra								$X^{a,b}$	X^b	X^b	X^a	X^b	X^b	X^b			X^b	X^b		X^b			X^b
Thy glycol								$X^{a,b}$	$X^{a,b}$	$X^{a,b}$	$X^{a,b}$	$X^{a,b}$		$X^{a,b}$			$X^{a,b}$	$X^{a,b}$					X^b
5-OH-6-HThy								X^a	X^a	X^a	$X^{a,b}$												
5-OH-5-MeHyd								$X^{a,b}$		X^a	X^a	X^a		X^a		X^a	X^a	X^a	X^a	X^a			
5,6-diHThy								$X^{a,b}$		X^b	$X^{a,b}$			X^b									
5-OHMeUra		X^b	X^b	X^b																			
5-formylUra		X^b																					

that removes DNA lesions generated by DNA-damaging therapeutic agents before they become toxic is a major mechanism for resistance to therapy (reviewed in [477,478]). DNA repair capacity might be a predictive biomarker of patient response to therapy [478–480]. Therefore, DNA repair proteins have been emerging as biomarkers for patient response to therapy, and thus may help predict and guide treatments [477–487]. To this end, the accurate measurement of the overexpression or underexpression of DNA repair proteins in tissues will become critical for the use of these proteins as biomarkers [478,479]. Recent advances made with the application of mass spectrometric techniques for this purpose are promising for achieving this goal [156,488–493].

DNA repair proteins are therapy targets for the development of novel therapeutic agents in cancer therapy (for extensive collections of reviews see [478,479,494]). Success with the inhibitors of PARP1 and other proteins of the BER pathway paved the way for the acceptance of the inhibition of these proteins in tumors as a novel concept for cancer therapy. Intense efforts are underway worldwide to find inhibitors of DNA repair proteins (https://clinicaltrials.gov/ct2/results/map?term=DNA+repair+inhibitors) (for an extensive collection of recent reviews see [478]). Such compounds might become anticancer drugs for combination therapy or as single agents for monotherapy that exploits the "synthetic lethality" concept, eventually leading to personalized cancer therapy [478,480,494]. Despite the successes with some BER proteins, DNA glycosylases have received much less attention and the development of inhibitors has been lagging. Recently, DNA glycosylases such as NEIL1, OGG1 and NTH1 have been identified as potential targets in combination chemotherapeutic strategies [495,496]. To find inhibitors of these proteins, a high-throughput assay has been developed that uses double-stranded oligodeoxynucleotides with a single DNA base lesion to screen small molecule libraries and thus to detect small molecule inhibitors of DNA glycosylases with an associated AP-lyase activity [157,158]. A number of purine analogs have been found to be efficient inhibitors of NEIL1 and NTH1; however, these compounds did not inhibit OGG1 [157]. Further search resulted in finding various hydrazide derivatives as efficient inhibitors of OGG1 [158]. High-molecular weight DNA substrates have also been used to identify the inhibition of excision of known physiological substrates of NEIL1, NTH1 and OGG1 [157,158]. In terms of the efficiency of individual inhibitors, these results were in excellent agreement with those obtained using the high-throughput assay with double-stranded oligodeoxynucleotides. It is concluded that the combined use of high-throughput assays with double-stranded oligodeoxynucleotides and the GC–MS methodology with DNA substrates with multiple lesions will be necessary to find effective inhibitors of the entire family of DNA glycosylases. This concept that uses two different types of assays may achieve the goal of discovering suitable drugs for inhibition of DNA glycosylases in cancer therapy.

8. Conclusions

DNA glycosylases exist in all organisms with various substrate specificities and lyase activities to initiate the cellular repair of DNA base lesions. Prokaryotic DNA glycosylases possess broader specificities than their eukaryotic counterparts. Eukaryotes possess additional DNA glycosylases to deal with a large variety of oxidatively induced DNA base lesions derived from purines and pyrimidines. There is a redundancy in activities among these enzymes, some of which possess cross-activities for both purine- and pyrimidine-derived DNA lesions. Great strides have been made in understanding the mechanism of action of DNA glycosylases for recognition and excision of a multiplicity of modified DNA bases among millions of intact DNA bases. Methodologies have been developed for the measurement of substrate specificities and excision kinetics. Thus, the combined use of oligodeoxynucleotide substrates with a single DNA lesion and damaged DNA substrates with multiple lesions led to great advances in the elucidation of the properties of DNA glycosylases. The crystal structures of DNA glycosylases have been elucidated, greatly contributing to the understanding of mechanisms of action. The role of DNA glycosylases in prevention of the diseases such as cancer has largely been demonstrated, although the modulation of disease risk by these enzymes remains quite complex. This is in part due to the fact that there are multiple DNA glycosylases with multiple isoforms and different cellular localization to remove the same lesions. Although much is known about DNA glycosylases and their substrates, the broad understanding of their roles and mechanistic aspects in human cells remains elusive. To this end, the detection of additional mutant human DNA glycosylases and the elucidation of their roles in disease processes will be one of the ultimate goals of the efforts in this field. In recent years, promising advances have been made in the efforts of the development of inhibitors of human DNA glycosylases as novel anti-cancer drugs. This field is still in its infancy when compared to the development of inhibitors of other enzymes of the BER pathway. Highly challenging accurate measurement of cellular levels of DNA glycosylases in normal and tumor tissues will be of fundamental importance for the determination of DNA repair capacity for the application of inhibitors. More efforts will have to be invested for the discovery of inhibitors of human DNA glycosylases as a future challenge to greatly benefit from the knowledge that has accumulated since the first discovery of a DNA glycosylase over four decades ago.

Conflict of interest

The authors declare that there are no conflicts of interest.

Acknowledgements

The contributions of our collaborators to the studies in our laboratory reviewed in this article are greatly acknowledged. Their names can be found in the list of References

References

[1] B. Halliwell, J.M.C. Gutteridge, Free Radicals in Biology and Medicine, fifth edition, Oxford University Press, Oxford, 2015.
[2] R.A. Beckman, L.A. Loeb, Genetic instability in cancer: theory and experiment, Semin. Cancer Biol. 15 (2005) 423–435.
[3] L.A. Loeb, Human cancers express mutator phenotypes: origin, consequences and targeting, Nature Rev. Cancer 11 (2011) 450–457.
[4] D. Hanahan, R.A. Weinberg, The hallmarks of cancer, Cell 100 (2000) 57–70.
[5] L.M. Coussens, Z. Werb, Inflammation and cancer, Nature 420 (2002) 860–867.
[6] A. Mantovani, P. Allavena, A. Sica, F. Balkwill, Cancer-related inflammation, Nature 454 (2008) 436–444.
[7] R.E. Huie, S. Padmaja, The reaction of NO with superoxide, Free Radic. Res. Commun. 18 (1993) 195–199.
[8] C. von Sonntag, Free-Radical-Induced DNA Damage and Its Repair, Springer, Hiedelberg, 2006.
[9] A.B. Ross, W.G. Mallard, W.P. Helman, B.H.J. Bielski, G.V. Buxton, D.E. Cabelli, C.L. Greenstock, R.E. Huie, P. Neta, NDRL-NIST Solution Kinetics Database, National Institute of Standards and Technology, Gaithersburg, 1992.
[10] M. Dizdaroglu, P. Jaruga, Mechanisms of free radical-induced damage to DNA, Free Radic. Res. 46 (2012) 382–419.
[11] P. O'Neill, Pulse radiolytic study of the interaction of thiols and ascorbate with OH adducts of dGMP and dG: implications for DNA repair processes, Radiat. Res. 96 (1983) 198–210.
[12] A.J.S.C. Vieira, S. Steenken, Pattern of OH radical reactions with N6,N6-dimethyladenosine. Production of three isomeric OH adducts and their dehydration and ring-opening reactions, J. Am. Chem. Soc. 109 (1987) 7441–7448.
[13] S. Steenken, Purine bases, nucleosides, and nucleotides: aqueous solution redox chemistry and transformation reactions of their radical cations and e^- and OH adducts, Chem. Rev. 89 (1989) 503–520.
[14] A.J.S.C. Vieira, S. Steenken, Pattern of OH radical reaction with adenine and its nucleosides and nucleotides. Characterization of two types of isomeric OH

adduct and their unimolecular transformation reactions, J. Am. Chem. Soc. 112 (1990) 6986–6994.
[15] L.P. Candeias, S. Steenken, Reaction of HO• with guanine derivatives in aqueous solution: formation of two different redox-active OH-adduct radicals and their unimolecular transformation reactions. Properties of G(-H)•, Chem. Eur. J. 6 (2000) 475–484.
[16] S. Steenken, S.V. Jovanovic, M. Bietti, K. Bernhard, The trap depth (in DNA) of 8-oxo-7,8-dihydro-2'-deoxyguanosine as derived from electron-transfer equilibria in aqeous solution, J. Am. Chem. Soc. 122 (2000) 2373–2384.
[17] W. Luo, J.G. Muller, E.M. Rachlin, C.J. Burrows, Characterization of spiroiminodihydantoin as a product of one-electron oxidation of 8-Oxo-7,8-dihydroguanosine, Org. Lett. 2 (2000) 613–616.
[18] W. Luo, J.G. Muller, E.M. Rachlin, C.J. Burrows, Characterization of hydantoin products from one-electron oxidation of 8-oxo-7,8-dihydroguanosine in a nucleoside model, Chem. Res. Toxicol. 14 (2001) 927–938.
[19] J.C. Niles, J.S. Wishnok, S.R. Tannenbaum, Spiroiminodihydantoin is the major product of the 8-oxo-7,8-dihydroguanosine reaction with peroxynitrite in the presence of thiols and guanosine photooxidation by methylene blue, Org. Lett. 3 (2001) 963–966.
[20] C.J. Burrows, J.G. Muller, O. Kornyushyna, W. Luo, V. Duarte, M.D. Leipold, S.S. David, Structure and potential mutagenicity of new hydantoin products from guanosine and 8-oxo-7, 8-dihydroguanine oxidation by transition metals, Environ. Health Perspect. 110 (Suppl 5) (2002) 713–717.
[21] W. Adam, M.A. Arnold, M. Grune, W.M. Nau, U. Pischel, C.R. Saha-Moller, Spiroiminodihydantoin is a major product in the photooxidation of 2'-deoxyguanosine by the triplet states and oxyl radicals generated from hydroxyacetophenone photolysis and dioxetane thermolysis, Org. Lett. 4 (2002) 537–540.
[22] M.K. Hailer, P.G. Slade, B.D. Martin, T.A. Rosenquist, K.D. Sugden, Recognition of the oxidized lesions spiroiminodihydantoin and guanidinohydantoin in DNA by the mammalian base excision repair glycosylases NEIL1 and NEIL2, DNA Repair (Amst.) 4 (2005) 41–50.
[23] W.L. Neeley, J.M. Essigmann, Mechanisms of formation, genotoxicity, and mutation of guanine oxidation products, Chem. Res. Toxicol. 19 (2006) 491–505.
[24] R.P. Hickerson, F. Prat, C.E. Muller, C.S. Foote, C.J. Burrows, Sequence and stacking dependence of 8-oxoguanine oxidation: comparison of one-electron vs singlet oxygen mechanism, J. Am. Chem. Soc. 121 (1999) 9423–9428.
[25] V. Duarte, D. Gasparutto, L.F. Yamaguchi, J.-L. avanat, G.R. artinez, M.H.G. edeiros, P. di Mascio, J. Cadet, Oxaluric acid as the major product of singlet oxygen-mediated oxidation of 8-oxo-7,8-dihydroguanine in DNA, J. Am. Chem. Soc. 122 (2000) 12622–12628.
[26] G.V. Buxton, C.L. Greenstock, W.P. Helman, A.B. Ross, Critical review of rate constants for reactions of hydrated electrons, hydrogen atoms, and hydroxyl radicals (•OH/•O−) in aqueous solution, J. Phys. Chem. Ref. Data 17 (1988) 513–886.
[27] L.P. Candeias, P. Wolf, P. O'Neill, S. Steenken, Reaction of hydrated electrons with guanine nucleosides: fast protonation on carbon of the electron adduct, J. Phys. Chem. 96 (1992) 10302–10307.
[28] M. D'Angelantonio, M. Russo, P. Kaloudis, Q.G. Mulazzani, P. Wardman, M. Guerra, C. Chatgilialoglu, Reaction of hydrated electrons with guanine derivatives: tautomerism of intermediate species, J. Phys. Chem. B 113 (2009) 2170–2176.
[29] M.C.R. Symons, Apllication of electron spin resonance spectroscopy to the study of the effects of ionising radiation on DNA and DNA complexes, J. Chem. Soc. Faraday Trans 83 (1987) 1–11.
[30] S. Boiteux, E. Gajewski, J. Laval, M. Dizdaroglu, Substrate specificity of the *Escherichia coli* Fpg protein (formamidopyrimidine-DNA glycosylase): excision of purine lesions in DNA produced by ionizing radiation or photosensitization, Biochemistry 31 (1992) 106–110.
[31] H. Kasai, Z. Yamaizumi, M. Berger, J. Cadet, Photosensitized formation of 7,8-dihydro-8-oxo-2'-deoxyguanosine (8-hydroxy-2'-deoxyguanosine) in DNA by riboflavin: a non singlet oxygen mediated reaction, J. Am. Chem. Soc. 114 (1992) 9692–9694.
[32] S.G. Swarts, D. Becker, M. Sevilla, K.T. Wheeler, Radiation-induced DNA damage as a function of hydration. II. Base damage from electron-loss centers, Radiat. Res. 145 (1996) 304–314.
[33] L.I. Shukla, A. Adhikary, R. Pazdro, D. Becker, M.D. Sevilla, Formation of 8-oxo-7,8-dihydroguanine-radicals in gamma-irradiated DNA by multiple one-electron oxidations, Nucleic Acids Res. 32 (2004) 6565–6574.
[34] J. Cadet, T. Douki, J.L. Ravanat, Oxidatively generated damage to the guanine moiety of DNA: mechanistic aspects and formation in cells, Acc. Chem. Res. 41 (2008) 1075–1083.
[35] Y. Rokhlenko, J. Cadet, N.E. Geacintov, V. Shafirovich, Mechanistic aspects of hydration of guanine radical cations in DNA, J. Am. Chem. Soc. 136 (2014) 5956–5962.
[36] K. Miaskiewicz, R. Osman, Theoretical study on the deoxyribose radicals formed by hydrogen abstraction, J. Am. Chem. Soc. 116 (1994) 232–238.
[37] B. Balasubramanian, W.K. Pogozelski, T.D. Tullius, DNA strand breaking by the hydroxyl radical is governed by the accessible surface areas of the hydrogen atoms of the DNA backbone, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 9738–9743.
[38] W.K. Pogozelski, T.D. Tullius, Oxidative strand scission of nucleic acids: routes initiated by hydrogen abstraction from the sugar moiety, Chem. Rev. 98 (1998) 1089–1108.
[39] M. Dizdaroglu, Clemens von Sonntag and the early history of radiation-induced sugar damage in DNA, Int. J. Radiat. Biol. 90 (2014) 446–458.
[40] K. Keck, Bildung von Cyclonucleotiden bei Betrahlung wässriger Lösungen von Purinnucleotiden, Z. Naturforsch. B 23 (1968) 1034–1043.
[41] P. Jaruga, M. Dizdaroglu, 8,5'-Cyclopurine-2'-deoxynucleosides in DNA: mechanisms of formation, measurement, repair and biological effects, DNA Repair (Amst.) 7 (2008) 1413–1425.
[42] Y. Wang, Bulky DNA lesions induced by reactive oxygen species, Chem. Res. Toxicol. 21 (2008) 276–281.
[43] M. Dizdaroglu, E. Coskun, P. Jaruga, Measurement of oxidatively induced DNA damage and its repair, by mass spectrometric techniques, Free Radic. Res. 49 (2015) 525–548.
[44] N. Belmadoui, F. Boussicault, M. Guerra, J.L. Ravanat, C. Chatgilialoglu, J. Cadet, Radiation-induced formation of purine 5',8-cyclonucleosides in isolated and cellular DNA: high stereospecificity and modulating effect of oxygen, Org. Biomol. Chem. 8 (2010) 3211–3219.
[45] H.C. Box, J.B. Dawidzik, E.E. Budzinski, Free radical-induced double lesions in DNA, Free Radic. Biol. Med. 31 (2001) 856–868.
[46] C. Crean, Y. Uvaydov, N.E. Geacintov, V. Shafirovich, Oxidation of single-stranded oligonucleotides by carbonate radical anions: generating intrastrand cross-links between guanine and thymine bases separated by cytosines, Nucleic Acids Res. 36 (2008) 742–755.
[47] A.G. Georgakilas, Processing of DNA damage clusters in human cells: current status of knowledge, Mol. Biosyst. 4 (2008) 30–35.
[48] J. Cadet, T. Douki, J.L. Ravanat, Oxidatively generated base damage to cellular DNA, Free Radic. Biol. Med. 49 (2010) 9–21.
[49] J. Cadet, J.R. Wagner, Oxidatively generated base damage to cellular DNA by hydroxyl radical and one-electron oxidants: similarities and differences, Arch Biochem. Biophys. 557 (2014) 47–54.
[50] J.H. Hoeijmakers, Genome maintenance mechanisms for preventing cancer, Nature 411 (2001) 366–374.
[51] R.D. Wood, M. Mitchell, T. Lindahl, Human DNA repair genes, Mutat. Res. 577 (2005) 275–283.
[52] E.C. Friedberg, G.C. Walker, W. Siede, R.D. Wood, R.A. Schultz, T. Ellenberger, DNA Repair and Mutagenesis, ASM Press, Washington, D.C, 2006.
[53] A.L. Jackson, L.A. Loeb, The contribution of endogenous sources of DNA damage to the multiple mutations in cancer, Mutat. Res. 477 (2001) 7–21.
[54] J.F. Davidson, H.H. Guo, L.A. Loeb, Endogenous mutagenesis and cancer, Mutat. Res. 509 (2002) 17–21.
[55] L.A. Loeb, Mutator phenotype in cancer: origin and consequences, Semin. Cancer Biol. 20 (2010) 279–280.
[56] M. Sekiguchi, T. Tsuzuki, Oxidative nucleotide damage: consequences and prevention, Oncogene 21 (2002) 8895–8904.
[57] J.J. Lin, A. Sancar, A new mechanism for repairing oxidative damage to DNA: (A)BC excinuclease removes AP sites and thymine glycols from DNA, Biochemistry 28 (1989) 7979–7984.
[58] Y.W. Kow, S.S. Wallace, B. Van Houten, UvrABC nuclease complex repairs thymine glycol, an oxidative DNA base damage, Mutat. Res. 235 (1990) 147–156.
[59] J.T. Reardon, T. Bessho, H.C. Kung, P.H. Bolton, A. Sancar, In vitro repair of oxidative DNA damage by human nucleotide excision repair system: possible explanation for neurodegeneration in Xeroderma pigmentosum patients, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 9463–9468.
[60] V. Shafirovich, K. Kropachev, T. Anderson, Z. Liu, M. Kolbanovskiy, B.D. Martin, K. Sugden, Y. Shim, X. Chen, J.H. Min, N.E. Geacintov, Base and nucleotide excision repair of oxidatively generated guanine lesions in DNA, J. Biol. Chem. 291 (2016) 5309–5319.
[61] M. Dizdaroglu, Free-radical-induced formation of an 8, 5'-cyclo-2'-deoxyguanosine moiety in deoxyribonucleic acid, Biochem. J. 238 (1986) 247–254.
[62] M. Dizdaroglu, M.L. Dirksen, H.X. Jiang, J.H. Robbins, Ionizing-radiation-induced damage in the DNA of cultured human cells. Identification of 8,5'-cyclo-2'-deoxyguanosine, Biochem. J. 241 (1987) 929–932.
[63] I. Kuraoka, C. Bender, A. Romieu, J. Cadet, R.D. Wood, T. Lindahl, Removal of oxygen free-radical-induced 5',8-purine cyclodeoxynucleosides from DNA by the nucleotide excision-repair pathway in human cells, Proc, Natl. Acad. Sci. U. S. A. 97 (2000) 3832–3837.
[64] P.J. Brooks, D.S. Wise, D.A. Berry, J.V. Kosmoski, M.J. Smerdon, R.L. Somers, H. Mackie, A.Y. Spoonde, E.J. Ackerman, K. Coleman, R.E. Tarone, J.H. Robbins, The oxidative DNA lesion 8,5'-(*S*)-cyclo-2'-deoxyadenosine is repaired by the nucleotide excision repair pathway and blocks gene expression in mammalian cells, J. Biol. Chem. 275 (2000) 22355–22362.
[65] P. Pande, R.S. Das, C. Sheppard, Y.W. Kow, A.K. Basu, Repair efficiency of (5'S)-8,5'-cyclo-2'-deoxyguanosine and (5'S)-8,5'-cyclo-2'-deoxyadenosine depends on the complementary base, DNA Repair (Amst.) 11 (2012) 926–931.
[66] K. Kropachev, S. Ding, M.A. Terzidis, A. Masi, Z. Liu, Y. Cai, M. Kolbanovskiy, C. Chatgilialoglu, S. Broyde, N.E. Geacintov, V. Shafirovich, Structural basis for the recognition of diastereomeric 5',8-cyclo-2'-deoxypurine lesions by the human nucleotide excision repair system, Nucleic Acids Res. 42 (2014) 5020–5032.
[67] Z. Yang, L.C. Colis, A.K. Basu, Y. Zou, Recognition and incision of gamma-radiation-induced cross-linked guanine-thymine tandem lesion G[8,5-Me]T by UvrABC nuclease, Chem. Res. Toxicol. 18 (2005) 1339–1346.
[68] S. Ding, K. Kropachev, Y. Cai, M. Kolbanovskiy, S.A. Durandina, Z. Liu, V. Shafirovich, S. Broyde, N.E. Geacintov, Structural, energetic and dynamic properties of guanine(C8)-thymine(N3) cross-links in DNA provide insights on susceptibility to nucleotide excision repair, Nucleic Acids Res. 40 (2012) 2506–2517.

[69] J. Wang, H. Cao, C. You, B. Yuan, R. Bahde, S. Gupta, C. Nishigori, L.J. Niedernhofer, P.J. Brooks, Y. Wang, Endogenous formation and repair of oxidatively induced G[8–5 m]T intrastrand cross-link lesion, Nucleic Acids Res. 40 (2012) 7368–7374.
[70] B. Demple, T. Herman, D.S. Chen, Cloning and expression of APE, the cDNA encoding the major human apurinic endonuclease: definition of a family of DNA repair enzymes, Proc. Natl. Acad. Sci. U. S. A. 88 (1991) 11450–11454.
[71] D.M. Wilson III, D. Barsky, The major human abasic endonuclease: formation, consequences and repair of abasic lesions in DNA, Mutat. Res. 485 (2001) 283–307.
[72] B. Demple, L. Harrison, Repair of oxidative damage to DNA: enzymology and biology, Annu. Rev. Biochem. 63 (1994) 915–948.
[73] J.S. Sung, B. Demple, Roles of base excision repair subpathways in correcting oxidized abasic sites in DNA, FEBS J. 273 (2006) 1620–1629.
[74] H. Fung, B. Demple, Distinct roles of Ape1 protein in the repair of DNA damage induced by ionizing radiation or bleomycin, J. Biol. Chem. 286 (2011) 4968–4977.
[75] M.M. Greenberg, Abasic and oxidized abasic site reactivity in DNA: enzyme inhibition, cross-linking, and nucleosome catalyzed reactions, Acc. Chem. Res. 47 (2014) 646–655.
[76] M. Dizdaroglu, Oxidatively induced DNA damage and its repair in cancer, Mutat. Res. Rev. Mutat. Res. 763 (2015) 212–245.
[77] J. Rouse, S.P. Jackson, Interfaces between the detection, signaling, and repair of DNA damage, Science 297 (2002) 547–551.
[78] S.P. Jackson, Sensing and repairing DNA double-strand breaks, Carcinogenesis 23 (2002) 687–696.
[79] T. Lindahl, An N-glycosidase from Escherichia coli that releases free uracil from DNA containing deaminated cytosine residues, Proc. Natl. Acad. Sci. U. S. A. 71 (1974) 3649–3653.
[80] G. Frosina, P. Fortini, O. Rossi, F. Carrozzino, G. Raspaglio, L.S. Cox, D.P. Lane, A. Abbondandolo, E. Dogliotti, Two pathways for base excision repair in mammalian cells, J. Biol. Chem. 271 (1996) 9573–9578.
[81] S. Mitra, T.K. Hazra, R. Roy, S. Ikeda, T. Biswas, J. Lock, I. Boldogh, T. Izumi, Complexities of DNA base excision repair in mammalian cells, Mol. Cells 7 (1997) 305–312.
[82] R.D. Wood, M. Mitchell, J. Sgouros, T. Lindahl, Human DNA repair genes, Science 291 (2001) 1284–1289.
[83] D.E. Barnes, T. Lindahl, Repair and genetic consequences of endogenous DNA base damage in mammalian cells, Annu. Rev. Genet. 38 (2004) 445–476.
[84] S.S. David, V.L. O'Shea, S. Kundu, Base-excision repair of oxidative DNA damage, Nature 447 (2007) 941–950.
[85] H. Sampath, A.K. McCullough, R.S. Lloyd, Regulation of DNA glycosylases and their role in limiting disease, Free Radic. Res. 46 (2012) 460–478.
[86] A. Prakash, S. Doublie, S.S. Wallace, The Fpg/Nei family of DNA glycosylases: substrates, structures, and search for damage, Prog. Mol. Biol. Transl. Sci. 110 (2012) 71–91.
[87] S.S. Wallace, D.L. Murphy, J.B. Sweasy, Base excision repair and cancer, Cancer Lett. 327 (2012) 73–89.
[88] S.S. Wallace, Base excision repair: a critical player in many games, DNA Repair (Amst.) 19 (2014) 14–26.
[89] N.C. Bauer, A.H. Corbett, P.W. Doetsch, The current state of eukaryotic DNA base damage and repair, Nucleic Acids Res. 43 (2015) 10083–10101.
[90] A.C. Drohat, C.T. Coey, Role of base excision repair enzymes in erasing epigenetic marks from DNA, Chem. Rev. 116 (2016) 12711–12729.
[91] A. Prakash, S. Doublie, Base excision repair in the mitochondria, J. Cell Biochem. 116 (2015) 1490–1499.
[92] J.C. Fromme, G.L. Verdine, Structural insights into lesion recognition and repair by the bacterial 8-oxoguanine DNA glycosylase MutM, Nat. Struct. Biol. 9 (2002) 544–552.
[93] M.L. Dodson, R.S. Lloyd, Mechanistic comparisons among base excision repair glycosylases, Free Radic. Biol. Med. 32 (2002) 678–682.
[94] J.C. Fromme, G.L. Verdine, DNA lesion recognition by the bacterial repair enzyme MutM, J. Biol. Chem. 278 (2003) 51543–51548.
[95] A. Banerjee, W.L. Santos, G.L. Verdine, Structure of a DNA glycosylase searching for lesions, Science 311 (2006) 1153–1157.
[96] Y. Qi, M.C. Spong, K. Nam, A. Banerjee, S. Jiralerspong, M. Karplus, G.L. Verdine, Encounter and extrusion of an intrahelical lesion by a DNA repair enzyme, Nature 462 (2009) 762–766.
[97] A.R. Dunn, N.M. Kad, S.R. Nelson, D.M. Warshaw, S.S. Wallace, Single Qdot-labeled glycosylase molecules use a wedge amino acid to probe for lesions while scanning along DNA, Nucleic Acids Res. 39 (2011) 7487–7498.
[98] S.S. Wallace, DNA glycosylases search for and remove oxidized DNA bases, Environ. Mol. Mutagen 54 (2013) 691–704.
[99] A.J. Lee, D.M. Warshaw, S.S. Wallace, Insights into the glycosylase search for damage from single-molecule fluorescence microscopy, DNA Repair (Amst.) 19 (2014) 23–31.
[100] S.R. Nelson, A.R. Dunn, S.D. Kathe, D.M. Warshaw, S.S. Wallace, Two glycosylase families diffusively scan DNA using a wedge residue to probe for and identify oxidatively damaged bases, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) E2091–2099.
[101] E.A. Mullins, R. Shi, Z.D. Parsons, P.K. Yuen, S.S. David, Y. Igarashi, B.F. Eichman, The DNA glycosylase AlkD uses a non-base-flipping mechanism to excise bulky lesions, Nature 527 (2015) 254–258.
[102] D.O. Zharkov, A.P. Grollman, The DNA trackwalkers: principles of lesion search and recognition by DNA glycosylases, Mutat. Res. 577 (2005) 24–54.
[103] P.C. Blainey, A.M. van Oijen, A. Banerjee, G.L. Verdine, X.S. Xie, A base-excision DNA-repair protein finds intrahelical lesion bases by fast sliding in contact with DNA, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 5752–5757.
[104] P.C. Blainey, G. Luo, S.C. Kou, W.F. Mangel, G.L. Verdine, B. Bagchi, X.S. Xie, Nonspecifically bound proteins spin while diffusing along DNA, Nat. Struct. Mol. Biol. 16 (2009) 1224–1229.
[105] S.L. Cravens, J.T. Stivers, Comparative effects of ions, molecular crowding, and bulk DNA on the damage search mechanisms of hOGG1 and hUNG, Biochemistry 55 (2016) 5230–5242.
[106] A.J. Lee, S.S. Wallace, Visualizing the search for radiation-damaged DNA bases in real time, Radiat. Phys. Chem. Oxf. Engl. 128 (2016) (1993) 126–133.
[107] S.R. Rajski, B.A. Jackson, J.K. Barton, DNA repair: models for damage and mismatch recognition, Mutat. Res. 447 (2000) 49–72.
[108] J.C. Genereux, J.K. Barton, Mechanisms for DNA charge transport, Chem. Rev. 110 (2010) 1642–1662.
[109] J.C. Genereux, A.K. Boal, J.K. Barton, DNA-mediated charge transport in redox sensing and signaling, J. Am. Chem. Soc. 132 (2010) 891–905.
[110] P. Fortini, E. Parlanti, O.M. Sidorkina, J. Laval, E. Dogliotti, The type of DNA glycosylase determines the base excision repair pathway in mammalian cells, J. Biol. Chem. 274 (1999) 15230–15236.
[111] D.S. Chen, T. Herman, B. Demple, Two distinct human DNA diesterases that hydrolyze 3'-blocking deoxyribose fragments from oxidized DNA, Nucleic Acids Res. 19 (1991) 5907–5914.
[112] L. Wiederhold, J.B. Leppard, P. Kedar, F. Karimi-Busheri, A. Rasouli-Nia, M. Weinfeld, A.E. Tomkinson, T. Izumi, R. Prasad, S.H. Wilson, S. Mitra, T.K. Hazra, AP endonuclease-independent DNA base excision repair in human cells, Mol. Cell 15 (2004) 209–220.
[113] Y. Matsumoto, K. Kim, Excision of deoxyribose phosphate residues by DNA polymerase β during DNA repair, Science 269 (1995) 699–702.
[114] D.K. Srivastava, B.J. Berg, R. Prasad, J.T. Molina, W.A. Beard, A.E. Tomkinson, S. H. Wilson, Mammalian abasic site base excision repair. Identification of the reaction sequence and rate-determining steps, J. Biol. Chem. 273 (1998) 21203–21209.
[115] W.A. Beard, S.H. Wilson, Structural design of a eukaryotic DNA repair polymerase: DNA polymerase beta, Mutat. Res. 460 (2000) 231–244.
[116] W.A. Beard, R. Prasad, S.H. Wilson, Activities and mechanism of DNA polymerase beta, Methods Enzymol. 408 (2006) 91–107.
[117] L.R. Hiraoka, J.J. Harrington, D.S. Gerhard, M.R. Lieber, C.L. Hsieh, Sequence of human FEN-1, a structure-specific endonuclease, and chromosomal localization of the gene (FEN1) in mouse and human, Genomics 25 (1995) 220–225.
[118] A. Klungland, T. Lindahl, Second pathway for completion of human DNA base excision-repair: reconstitution with purified proteins and requirement for DNase IV (FEN1), EMBO J. 16 (1997) 3341–3348.
[119] M.R. Lieber, The FEN-1 family of structure-specific nucleases in eukaryotic DNA replication, recombination and repair, Bioessays 19 (1997) 233–240.
[120] B.I. Lee, D.M. Wilson, III, The RAD2 domain of human exonuclease 1 Exhibits 5' to 3' exonuclease and flap structure-specific endonuclease activities, J. Biol. Chem. 274 (1999) 37763–37769.
[121] R.S. Williams, T.A. Kunkel, FEN nucleases: bind, bend, fray, cut, Cell 145 (2011) 171–172.
[122] S.E. Tsutakawa, S. Classen, B.R. Chapados, A.S. Arvai, L.D. Finger, G. Guenther, C.G. Tomlinson, P. Thompson, A.H. Sarker, B. Shen, P.K. Cooper, J.A. Grasby, J.A. Tainer, Human flap endonuclease structures, DNA double-base flipping, and a unified understanding of the FEN1 superfamily, Cell 145 (2011) 198–211.
[123] E.K. Braithwaite, P.S. Kedar, L. Lan, Y.Y. Polosina, K. Asagoshi, V.P. Poltoratsky, J.K. Horton, H. Miller, G.W. Teebor, A. Yasui, S.H. Wilson, DNA polymerase lambda protects mouse fibroblasts against oxidative DNA damage and is recruited to sites of DNA damage/repair, J Biol. Chem. 280 (2005) 31641–31647.
[124] J.K. Horton, S.H. Wilson, Hypersensitivity phenotypes associated with genetic and synthetic inhibitor-induced base excision repair deficiency, DNA Repair (Amst.) 6 (2007) 530–543.
[125] R. Prasad, N. Dyrkheeva, J. Williams, S.H. Wilson, Mammalian base excision repair: functional partnership between PARP-1 and APE1 in AP-Site repair, PLoS One 10 (2015) e0124269.
[126] A. Bird, DNA methylation patterns and epigenetic memory, Genes Dev. 16 (2002) 6–21.
[127] S.J. Cokus, S. Feng, X. Zhang, Z. Chen, B. Merriman, C.D. Haudenschild, S. Pradhan, S.F. Nelson, M. Pellegrini, S.E. Jacobsen, Shotgun bisulphite sequencing of the Arabidopsis genome reveals DNA methylation patterning, Nature 452 (2008) 215–219.
[128] M.J. Bauer, R.L. Fischer, Genome demethylation and imprinting in the endosperm, Curr. Opin. Plant Biol. 14 (2011) 162–167.
[129] A.M. Deaton, S. Webb, A.R. Kerr, R.S. Illingworth, J. Guy, R. Andrews, A. Bird, Cell type-specific DNA methylation at intragenic CpG islands in the immune system, Genome Res. 21 (2011) 1074–1086.
[130] A.M. Deaton, A. Bird, CpG islands and the regulation of transcription, Genes Dev. 25 (2011) 1010–1022.
[131] M.D. Wyatt, Advances in understanding the coupling of DNA base modifying enzymes to processes involving base excision repair, Adv. Cancer Res. 119 (2013) 63–106.
[132] R.M. Kohli, Y. Zhang, TET enzymes, TDG and the dynamics of DNA demethylation, Nature 502 (2013) 472–479.
[133] B. Kinde, H.W. Gabel, C.S. Gilbert, E.C. Griffith, M.E. Greenberg, Reading the unique DNA methylation landscape of the brain: non-CpG methylation,

hydroxymethylation, and MeCP2, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) 6800–6806.
[134] R. Savva, K. McAuley-Hecht, T. Brown, L. Pearl, The structural basis of specific base-excision repair by uracil-DNA glycosylase, Nature 373 (1995) 487–493.
[135] C.D. Mol, A.S. Arvai, G. Slupphaug, B. Kavli, I. Alseth, H.E. Krokan, J.A. Tainer, Crystal structure and mutational analysis of human uracil-DNA glycosylase: structural basis for specificity and catalysis, Cell 80 (1995) 869–878.
[136] L.H. Pearl, Structure and function in the uracil-DNA glycosylase superfamily, Mutat. Res. 460 (2000) 165–181.
[137] J.I. Friedman, J.T. Stivers, Detection of damaged DNA bases by DNA glycosylase enzymes, Biochemistry 49 (2010) 4957–4967.
[138] J.A. Eisen, P.C. Hanawalt, A phylogenomic study of DNA repair genes, proteins, and processes, Mutat. Res. 435 (1999) 171–213.
[139] L. Aravind, D.R. Walker, E.V. Koonin, Conserved domains in DNA repair proteins and evolution of repair systems, Nucleic Acids Res. 27 (1999) 1223–1242.
[140] A.K. McCullough, M.L. Dodson, R.S. Lloyd, Initiation of base excision repair: glycosylase mechanisms and structures, Annu. Rev. Biochem. 68 (1999) 255–285.
[141] D.O. Zharkov, G. Shoham, A.P. Grollman, Structural characterization of the Fpg family of DNA glycosylases, DNA Repair 2 (2003) 839–862.
[142] C.F. Kuo, D.E. McRee, C.L. Fisher, S.F. O'Handley, R.P. Cunningham, J.A. Tainer, Atomic structure of the DNA repair [4Fe-4S] enzyme endonuclease III, Science 258 (1992) 434–440.
[143] M.M. Thayer, H. Ahern, D.X. Xing, R.P. Cunningham, J.A. Tainer, Novel DNA binding motifs in the DNA repair enzyme endonuclease III crystal structure, EMBO J. 14 (1995) 4108–4120.
[144] M.L. Dodson, M.L. Michaels, R.S. Lloyd, Unified catalytic mechanism for DNA glycosylases, J. Biol. Chem. 269 (1994) 32709–32712.
[145] H.M. Nash, S.D. Bruner, O.D. Schärer, T. Kawate, T.A. Addona, E. Sponner, W.S. Lane, G.L. Verdine, Cloning of a yeast 8-oxoguanine DNA glycosylase reveals the existence of a base-excision DNA-repair protein superfamily, Curr. Biol. 6 (1996) 968–980.
[146] H.M. Nash, R. Lu, W.S. Lane, G.L. Verdine, The critical active-site amine of the human 8-oxoguanine DNA glycosylase, hOgg1: direct identification, ablation and chemical reconstitution, Chem. Biol. 4 (1997) 693–702.
[147] S.D. Bruner, D.P. Norman, G.L. Verdine, Structural basis for recognition and repair of the endogenous mutagen 8-oxoguanine in DNA, Nature 403 (2000) 859–866.
[148] J.C. Fromme, S.D. Bruner, W. Yang, M. Karplus, G.L. Verdine, Product-assisted catalysis in base-excision DNA repair, Nat. Struct. Biol. 10 (2003) 204–211.
[149] J.T. Stivers, Y.L. Jiang, A mechanistic perspective on the chemistry of DNA repair glycosylases, Chem. Rev. 103 (2003) 2729–2759.
[150] S.J. Chung, G.L. Verdine, Structures of end products resulting from lesion processing by a DNA glycosylase/lyase, Chem. Biol. 11 (2004) 1643–1649.
[151] P.J. Berti, J.A. McCann, Toward a detailed understanding of base excision repair enzymes: transition state and mechanistic analyses of N-glycoside hydrolysis and N-glycoside transfer, Chem. Rev. 106 (2006) 506–555.
[152] A.C. Drohat, A. Maiti, Mechanisms for enzymatic cleavage of the N-glycosidic bond in DNA, Org. Biomol. Chem. 12 (2014) 8367–8378.
[153] R.J. Sung, M. Zhang, Y. Qi, G.L. Verdine, Structural and biochemical analysis of DNA helix invasion by the bacterial 8-oxoguanine DNA glycosylase MutM, J. Biol. Chem. 288 (2013) 10012–10023.
[154] M. Dizdaroglu, Application of capillary gas chromatography-mass spectrometry to chemical characterization of radiation-induced base damage of DNA; implications for assessing DNA repair processes, Anal. Biochem. 144 (1985) 593–603.
[155] M. Dizdaroglu, Quantitative determination of oxidative base damage in DNA by stable isotope-dilution mass spectrometry, FEBS Lett. 315 (1993) 1–6.
[156] P.T. Reddy, P. Jaruga, G. Kirkali, G. Tuna, B.C. Nelson, M. Dizdaroglu, Identification and quantification of human DNA repair protein NEIL1 by liquid chromatography/isotope-dilution tandem mass spectrometry, J. Proteome Res. 12 (2013) 1049–1061.
[157] A.C. Jacobs, M.J. Calkins, A. Jadhav, D. Dorjsuren, D. Maloney, A. Simeonov, P. Jaruga, M. Dizdaroglu, A.K. McCullough, R.S. Lloyd, Inhibition of DNA glycosylases via small molecule purine analogs, PLoS One 8 (2013) e81667.
[158] N. Donley, P. Jaruga, E. Coskun, M. Dizdaroglu, A.K. McCullough, R.S. Lloyd, Small molecule inhibitors of 8-Oxoguanine DNA glycosylase-1 (OGG1), ACS Chem. Biol. 10 (2015) 2334–2343.
[159] K. Wiebauer, J. Jiricny, In vitro correction of G:T mispairs to G:C pairs in nuclear extracts from human cells, Nature 339 (1989) 234–236.
[160] P. Neddermann, J. Jiricny, The purification of a mismatch-specific thymine-DNA glycosylase from HeLa cells, J. Biol. Chem. 268 (1993) 21218–21224.
[161] P. Neddermann, J. Jiricny, Efficient removal of uracil from G:U mispairs by the mismatch-specific thymine DNA glycosylase from HeLa cells, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 1642–1646.
[162] H. Nilsen, M. Otterlei, T. Haug, K. Solum, T.A. Nagelhus, F. Skorpen, H.E. Krokan, Nuclear and mitochondrial uracil-DNA glycosylases are generated by alternative splicing and transcription from different positions in the UNG gene, Nucleic Acids Res. 25 (1997) 750–755.
[163] H.E. Krokan, F. Drablos, G. Slupphaug, Uracil in DNA?occurrence, consequences and repair, Oncogene 21 (2002) 8935–8948.
[164] B. Kavli, O. Sundheim, M. Akbari, M. Otterlei, H. Nilsen, F. Skorpen, P.A. Aas, L. Hagen, H.E. Krokan, G. Slupphaug, hUNG2 is the major repair enzyme for removal of uracil from U:A matches, U:G mismatches, and U in single-stranded DNA, with hSMUG1 as a broad specificity backup, J. Biol. Chem. 277 (2002) 39926–39936.
[165] J.E. Wibley, T.R. Waters, K. Haushalter, G.L. Verdine, L.H. Pearl, Structure and specificity of the vertebrate anti-mutator uracil-DNA glycosylase SMUG1, Mol. Cell 11 (2003) 1647–1659.
[166] M. Akbari, M. Otterlei, J. Pena-Diaz, P.A. Aas, B. Kavli, N.B. Liabakk, L. Hagen, K. Imai, A. Durandy, G. Slupphaug, H.E. Krokan, Repair of U/G and U/A in DNA by UNG2-associated repair complexes takes place predominantly by short-patch repair both in proliferating and growth-arrested cells, Nucleic Acids Res. 32 (2004) 5486–5498.
[167] L. Hagen, B. Kavli, M.M. Sousa, K. Torseth, N.B. Liabakk, O. Sundheim, J. Pena-Diaz, M. Otterlei, O. Horning, O.N. Jensen, H.E. Krokan, G. Slupphaug, Cell cycle-specific UNG2 phosphorylations regulate protein turnover, activity and association with RPA, EMBO J. 27 (2008) 51–61.
[168] B. Doseth, T. Visnes, A. Wallenius, I. Ericsson, A. Sarno, H.S. Pettersen, A. Flatberg, T. Catterall, G. Slupphaug, H.E. Krokan, B. Kavli, Uracil-DNA glycosylase in base excision repair and adaptive immunity: species differences between man and mouse, J. Biol. Chem. 286 (2011) 16669–16680.
[169] H.E. Krokan, M. Bjoras, Base excision repair, Cold Spring Harb. Perspect. Biol. 5 (2013) a012583.
[170] A.B. Sjolund, A.G. Senejani, J.B. Sweasy, MBD4 and TDG: multifaceted DNA glycosylases with ever expanding biological roles, Mutat. Res. 743-744 (2013) 12–25.
[171] J.H. Xue, G.F. Xu, T.P. Gu, G.D. Chen, B.B. Han, Z.M. Xu, M. Bjoras, H.E. Krokan, G. L. Xu, Y.R. Du, Uracil-DNA glycosylase UNG promotes tet-mediated DNA demethylation, J. Biol. Chem. 291 (2016) 731–738.
[172] L.S. Pidugu, J.W. Flowers, C.T. Coey, E. Pozharski, M.M. Greenberg, A.C. Drohat, Structural basis for excision of 5-Formylcytosine by thymine DNA glycosylase, Biochemistry (2016).
[173] L. Aravind, E.V. Koonin, The alpha/beta fold uracil DNA glycosylases: a common origin with diverse fates, Genome Biol. 1 (2000) (RESEARCH0007).
[174] T.H. Zastawny, P.W. Doetsch, M. Dizdaroglu, A novel activity of E. coli uracil DNA N-glycosylase excision of isodialuric acid (5,6-dihydroxyuracil), a major product of oxidative DNA damage, from DNA, FEBS Lett. 364 (1995) 255–258.
[175] M. Dizdaroglu, A. Karakaya, P. Jaruga, G. Slupphaug, H.E. Krokan, Novel activities of human uracil DNA N-glycosylase for cytosine-derived products of oxidative DNA damage, Nucleic Acids Res. 24 (1996) 418–422.
[176] Q. An, P. Robins, T. Lindahl, D.E. Barnes, C −>T mutagenesis and gamma-radiation sensitivity due to deficiency in the Smug1 and Ung DNA glycosylases, EMBO J. 24 (2005) 2205–2213.
[177] R.J. Boorstein, A. Cummings Jr., D.R. Marenstein, M.K. Chan, Y. Ma, T.A. Neubert, S.M. Brown, G.W. Teebor, Definitive identification of mammalian 5-hydroxymethyluracil DNA N-glycosylase activity as SMUG1, J. Biol. Chem. 276 (2001) 41991–41997.
[178] A. Masaoka, M. Matsubara, R. Hasegawa, T. Tanaka, S. Kurisu, H. Terato, Y. Ohyama, N. Karino, A. Matsuda, H. Ide, Mammalian 5-formyluracil-DNA glycosylase. 2. Role of SMUG1 uracil-DNA glycosylase in repair of 5-formyluracil and other oxidized and deaminated base lesions, Biochemistry 42 (2003) 5003–5012.
[179] M. Matsubara, A. Masaoka, T. Tanaka, T. Miyano, N. Kato, H. Terato, Y. Ohyama, S. Iwai, H. Ide, Mammalian 5-formyluracil-DNA glycosylase. 1. Identification and characterization of a novel activity that releases 5-formyluracil from DNA, Biochemistry 42 (2003) 4993–5002.
[180] A. Maiti, A.C. Drohat, Thymine DNA glycosylase can rapidly excise 5-formylcytosine and 5-carboxylcytosine: potential implications for active demethylation of CpG sites, J. Biol. Chem. 286 (2011) 35334–35338.
[181] M.T. Bennett, M.T. Rodgers, A.S. Hebert, L.E. Ruslander, L. Eisele, A.C. Drohat, Specificity of human thymine DNA glycosylase depends on N-glycosidic bond stability, J. Am. Chem. Soc. 128 (2006) 12510–12519.
[182] M.T. Morgan, M.T. Bennett, A.C. Drohat, Excision of 5-halogenated uracils by human thymine DNA glycosylase. Robust activity for DNA contexts other than CpG, J. Biol. Chem. 282 (2007) 27578–27586.
[183] B. Hendrich, U. Hardeland, H.H. Ng, J. Jiricny, A. Bird, The thymine glycosylase MBD4 can bind to the product of deamination at methylated CpG sites, Nature 401 (1999) 301–304.
[184] H. Hashimoto, Y. Liu, A.K. Upadhyay, Y. Chang, S.B. Howerton, P.M. Vertino, X. Zhang, X. Cheng, Recognition and potential mechanisms for replication and erasure of cytosine hydroxymethylation, Nucleic Acids Res. 40 (2012) 4841–4849.
[185] F. Petronzelli, A. Riccio, G.D. Markham, S.H. Seeholzer, M. Genuardi, M. Karbowski, A.T. Yeung, Y. Matsumoto, A. Bellacosa, Investigation of the substrate spectrum of the human mismatch-specific DNA N-glycosylase MED1 (MBD4): fundamental role of the catalytic domain, J. Cell. Physiol. 185 (2000) 473–480.
[186] F. Petronzelli, A. Riccio, G.D. Markham, S.H. Seeholzer, J. Stoerker, M. Genuardi, A.T. Yeung, Y. Matsumoto, A. Bellacosa, Biphasic kinetics of the human DNA repair protein MED1 (MBD4), a mismatch-specific DNA N-glycosylase, J. Biol. Chem. 275 (2000) 32422–32429.
[187] V. Valinluck, P. Liu, J.I. Kang Jr., A. Burdzy, L.C. Sowers, 5-halogenated pyrimidine lesions within a CpG sequence context mimic 5-methylcytosine by enhancing the binding of the methyl-CpG-binding domain of methyl-CpG-binding protein 2 (MeCP2), Nucleic Acids Res. 33 (2005) 3057–3064.
[188] D.P. Turner, S. Cortellino, J.E. Schupp, E. Caretti, T. Loh, T.J. Kinsella, A. Bellacosa, The DNA N-glycosylase MED1 exhibits preference for halogenated pyrimidines and is involved in the cytotoxicity of 5-iododeoxyuridine, Cancer Res. 66 (2006) 7686–7693.
[189] C.D. Mol, A.S. Arvai, T.J. Begley, R.P. Cunningham, J.A. Tainer, Structure and activity of a thermostable thymine-DNA glycosylase: evidence for base

twisting to remove mismatched normal DNA bases, J Mol. Biol. 315 (2002) 373–384.
[190] K.G. Au, M. Cabrera, J.H. Miller, P. Modrich, Escherichia coli mutY gene product is required for specific A-G—C. G mismatch correction, Proc. Natl. Acad. Sci. U. S. A. 85 (1988) 9163–9166.
[191] J.P. McGoldrick, Y.-C. Yeh, M. Solomon, J.M. Essigmann, A.-L. Lu, Characterization of a mammalian homolog of the Escherichia coli MutY mismatch repair protein, Mol. Cell. Biol. 15 (1995) 989–996.
[192] Y. Guan, R.C. Manuel, A.S. Arvai, S.S. Parikh, C.D. Mol, J.H. Miller, S. Lloyd, J.A. Tainer, MutY catalytic core, mutant and bound adenine structures define specificity for DNA repair enzyme superfamily, Nat. Struct. Biol. 5 (1998) 1058–1064.
[193] M.M. Slupska, W.M. Luther, J.H. Chiang, H. Yang, J.H. Miller, Functional expression of hMYH, a human homolog of the Escherichia coli MutY protein, J. Bacteriol. 181 (1999) 6210–6213.
[194] C.J. Wiederholt, M.O. Delaney, M.A. Pope, S.S. David, M.M. Greenberg, Repair of DNA containing Fapy.dG and its beta-C-nucleoside analogue by formamidopyrimidine DNA glycosylase and MutY, Biochemistry 42 (2003) 9755–9760.
[195] M.M. Greenberg, The formamidopyrimidines: purine lesions formed in competition with 8-oxopurines from oxidative stress, Acc. Chem. Res. 45 (2012) 588–597.
[196] T. Ohtsubo, K. Nishioka, Y. Imaiso, S. Iwai, H. Shimokawa, H. Oda, T. Fujiwara, Y. Nakabeppu, Identification of human MutY homolog (hMYH) as a repair enzyme for 2-hydroxyadenine in DNA and detection of multiple forms of hMYH located in nuclei and mitochondria, Nucleic Acids Res. 28 (2000) 1355–1364.
[197] T.R. O'Connor, J. Laval, Human cDNA expressing a functional DNA glycosylase excising 3-methyladenine and 7-methylguanine, Biochem. Biophys. Res. Commun. 176 (1991) 1170–1177.
[198] T.R. O'Connor, Purification and characterization of human 3-methyladenine-DNA glycosylase, Nucleic Acids Res. 21 (1993) 5561–5569.
[199] T. Bessho, R. Roy, K. Yamamoto, H. Kasai, S. Nishimura, K. Tano, S. Mitra, Repair of 8-hydroxyguanine in DNA by mammalian N-methylpurine- DNA glycosylase, Proc. Natl. Acad. Sci. U. S. A. 90 (1993) 8901–8904.
[200] M. Saparbaev, J. Laval, Excision of hypoxanthine from DNA containing dIMP residues by the Escherichia coli, yeast, rat, and human alkylpurine DNA glycosylases, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 5873–5877.
[201] M. Saparbaev, K. Kleibl, J. Laval, Escherichia coli, Saccharomyces cerevisiae, rat and human 3-methyladenine DNA glycosylases repair 1,N^6-ethenoadenine when present in DNA, Nucleic Acids Res. 23 (1995) 3750–3755.
[202] C.Y. Lee, J.C. Delaney, M. Kartalou, G.M. Lingaraju, A. Maor-Shoshani, J.M. Essigmann, L.D. Samson, Recognition and processing of a new repertoire of DNA substrates by human 3-methyladenine DNA glycosylase (AAG), Biochemistry 48 (2009) 1850–1861.
[203] A.Y. Lau, O.D. Scharer, L. Samson, G.L. Verdine, T. Ellenberger, Crystal structure of a human alkylbase-DNA repair enzyme complexed to DNA: mechanisms for nucleotide flipping and base excision, Cell 95 (1998) 249–258.
[204] C.J. Chetsanga, T. Lindahl, Release of 7-methylguanine residues whose imidazole rings have been opened from damaged DNA by a DNA glycosylase from Escherichia coli, Nucleic Acids Res. 6 (1979) 3673–3684.
[205] C.J. Chetsanga, M. Lozon, C. Makaroff, L. Savage, Purification and characterization of Escherichia coli formamidopyrimidine-DNA glycosylase that excises damaged 7-methylguanine from deoxyribonucleic acid, Biochemistry 20 (1981) 5201–5207.
[206] S. Boiteux, T.R. O'Connor, J. Laval, Formamidopyrimidine-DNA glycosylase of Escherichia coli: cloning and sequencing of the fpg structural gene and overproduction of the protein, EMBO J. 6 (1987) 3177–3183.
[207] S. Boiteux, T.R. O'Connor, F. Lederer, A. Gouyette, J. Laval, Homogeneous Escherichia coli FPG protein. A DNA glycosylase which excises imidazole ring-opened purines and nicks DNA at apurinic/apyrimidinic sites, J. Biol. Chem. 265 (1990) 3916–3922.
[208] T.R. O'Connor, R.J. Graves, G. De Murcia, B. Castaing, J. Laval, Fpg protein of Escherichia coli is a zinc finger protein whose cysteine residues have a structural and/or functional role, J. Biol. Chem. 268 (1993) 9063–9070.
[209] J. Tchou, A.P. Grollman, The catalytic mechanism of Fpg protein. Evidence for a Schiff base intermediate and amino terminus localization of the catalytic site, J. Biol. Chem. 270 (1995) 11671–11677.
[210] T.R. O'Connor, J. Laval, Physical association of the 2,6-diamino-4-hydroxy-5N-formamidopyrimidine-DNA glycosylase of Escherichia coli and an activity nicking DNA at apurinic/apyrimidinic sites, Proc, Natl. Acad. Sci. U. S. A. 86 (1989) 5222–5226.
[211] V. Bailly, W.G. Verly, T. O'Connor, J. Laval, Mechanism of DNA strand nicking at apurinic/apyrimidinic sites by Escherichia coli [formamidopyrimidine]DNA glycosylase, Biochem. J. 262 (1989) 581–589.
[212] R.J. Graves, I. Felzenszwalb, J. Laval, T.R. O'Connor, Excision of 5'-terminal deoxyribose phosphate from damaged DNA is catalyzed by the Fpg protein of Escherichia coli, J. Biol. Chem. 267 (1992) 14429–14435.
[213] R. Gilboa, D.O. Zharkov, G. Golan, A.S. Fernandes, S.E. Gerchman, E. Matz, J.H. Kycia, A.P. Grollman, G. Shoham, Structure of formamidopyrimidine-DNA glycosylase covalently complexed to DNA, J. Biol. Chem. 277 (2002) 19811–19816.
[214] L. Breimer, T. Lindahl, A DNA glycosylase from Escherichia coli that releases free urea from a polydeoxyribonucleotide containing fragments of base residues, Nucleic Acids Res. 8 (1980) 6199–6211.
[215] L. Breimer, Enzymatic excision form gamma-irradiated polydeoxyribonucleotides of adenine residues whose imidazole rings have been ruptured, Nucleic Acids Res. 12 (1984) 6359–6367.
[216] J. Tchou, H. Kasai, S. Shibutani, M.-H. Chung, J. Laval, A.P. Grollman, S. Nishimura, 8-oxoguanine (8-hydroxyguanine) DNA glycosylase and its substrate specificity, Proc. Natl. Acad. Sci. U. S. A. 88 (1991) 4690–4694.
[217] S.S. Wallace, Enzymatic processing of radiation-induced free radical damage in DNA, Radiat. Res. 150 (1998) S60–S79.
[218] Y. Guo, V. Bandaru, P. Jaruga, X. Zhao, C.J. Burrows, S. Iwai, M. Dizdaroglu, J.P. Bond, S.S. Wallace, The oxidative DNA glycosylases of Mycobacterium tuberculosis exhibit different substrate preferences from their Escherichia coli counterparts, DNA Repair (Amst.) 9 (2010) 177–190.
[219] J. Tchou, V. Bodepudi, S. Shibutani, I. Antoshechkin, J. Miller, A.P. Grollman, F. Johnson, Substrate specificity of Fpg protein. Recognition and cleavage of oxidatively damaged DNA, J. Biol. Chem. 269 (1994) 15318–15324.
[220] P. Jaruga, M. Dizdaroglu, Repair of products of oxidative DNA base damage in human cells, Nucleic Acids Res. 24 (1996) 1389–1394.
[221] J. Tuo, P. Jaruga, H. Rodriguez, M. Dizdaroglu, V.A. Bohr, The Cockayne syndrome group B gene product is involved in cellular repair of 8-hydroxyadenine in DNA, J. Biol. Chem. 277 (2002) 30832–30837.
[222] J. Tuo, P. Jaruga, H. Rodriguez, V.A. Bohr, M. Dizdaroglu, Primary fibroblasts of Cockayne syndrome patients are defective in cellular repair of 8-hydroxyguanine and 8-hydroxyadenine resulting from oxidative stress, FASEB J. 17 (2003) 668–674.
[223] A. Karakaya, P. Jaruga, V.A. Bohr, A.P. Grollman, M. Dizdaroglu, Kinetics of excision of purine lesions from DNA by Escherichia coli Fpg protein, Nucleic Acids Res. 25 (1997) 474–479.
[224] B. Castaing, A. Geiger, H. Seliger, P. Nehls, J. Laval, C. Zelwer, S. Boiteux, Cleavage and binding of a DNA fragment containing a single 8-oxoguanine by wild type and mutant FPG proteins, Nucleic Acids Res. 21 (1993) 2899–2905.
[225] O. Sidorkina, M. Dizdaroglu, J. Laval, Effect of single mutations on the specificity of Escherichia coli FPG protein for excision of purine lesions from DNA damaged by free radicals, Free Radic. Biol. Med. 31 (2001) 816–823.
[226] K. Haraguchi, M.O. Delaney, C.J. Wiederholt, A. Sambandam, Z. Hantosi, M.M. Greenberg, Synthesis and characterization of oligonucleotides containing formamidopyrimidine lesions (Fapy. dA, Fapy. dG) at defined sites, Nucleic Acids Res. (Suppl) (2001) 129–130.
[227] K. Haraguchi, M.O. Delaney, C.J. Wiederholt, A. Sambandam, Z. Hantosi, M.M. Greenberg, Synthesis and characterization of oligodeoxynucleotides containing formamidopyrimidine lesions and nonhydrolyzable analogues, J. Am. Chem. Soc. 124 (2002) 3263–3269.
[228] L.T. Burgdorf, T. Carell, Synthesis, stability, and conformation of the formamidopyrimidine G DNA lesion, Chem. Eur. J. 8 (2002) 293–301.
[229] Y.L. Jiang, C.J. Wiederholt, J.N. Patro, K. Haraguchi, M.M. Greenberg, Synthesis of oligonucleotides containing Fapy. dG (N(6)-(2-deoxy-alpha,beta-D-erythropentofuranosyl)-2,6-diamino-4-hydroxy-5–formamidopyrimidine) using a 5'-dimethoxytrityl dinucleotide phosphoramidite, J. Org. Chem. 70 (2005) 141–149.
[230] C.J. Wiederholt, M.O. Delaney, M.M. Greenberg, Interaction of DNA containing Fapy.dA or its C-nucleoside analogues with base excision repair enzymes. Implications for mutagenesis and enzyme inhibition, Biochemistry 41 (2002) 15838–15844.
[231] J.R. Battista, Against all odds: the survival strategies of Deinococcus radiodurans, Annu. Rev. Microbiol 51 (1997) 203–224.
[232] C. Bauche, J. Laval, Repair of oxidized bases in the extremely radiation-resistant bacterium Deinococcus radiodurans, J. Bacteriol. 181 (1999) 262–269.
[233] M.S. Lipton, L. Pasa-Tolic', G.A. Anderson, D.J. Anderson, D.L. Auberry, J.R. Battista, M.J. Daly, J. Fredrickson, K.K. Hixson, H. Kostandarithes, C. Masselon, L.M. Markillie, R.J. Moore, M.F. Romine, Y. Shen, E. Stritmatter, N. Tolic', H.R. Udseth, A. Venkateswaran, K.K. Wong, R. Zhao, R.D. Smith, Global analysis of the Deinococcus radiodurans proteome by using accurate mass tags, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 11049–11054.
[234] S. Sentürker, C. Bauche, J. Laval, M. Dizdaroglu, Substrate specificity of Deinococcus radiodurans Fpg protein, Biochemistry 38 (1999) 9435–9439.
[235] M. Radman, An endonuclease from Escherichia coli that introduces single polynucleotide chain scissions in ultraviolet-irradiated DNA, J. Biol. Chem. 251 (1976) 1438–1445.
[236] R.P. Cunningham, B. Weiss, Endonuclease III (nth) mutants of escherichia coli, Proc. Natl. Acad. Sci. U. S. A. 82 (1985) 474–478.
[237] H. Asahara, P.M. Wistort, J.F. Bank, R.H. Bakerian, R.P. Cunningham, Purification and characterization of Escherichia coli endonuclease III from the cloned nth gene, Biochemistry 28 (1989) 4444–4449.
[238] R.P. Cunningham, H. Asahara, J.F. Bank, C.P. Scholes, J.C. Salerno, K. Surerus, E. Munck, J. McCracken, J. Peisach, M.H. Emptage, Endonuclease III is an iron-sulfur protein, Biochemistry 28 (1989) 4450–4455.
[239] A.A. Purmal, G.W. Lampman, J.P. Bond, Z. Hatahet, S.S. Wallace, Enzymatic processing of uracil glycol, a major oxidative product of DNA cytosine, J. Biol. Chem. 273 (1998) 10026–10035.
[240] L. Gros, M.K. Saparbaev, J. Laval, Enzymology of the repair of free radicals-induced DNA damage, Oncogene 21 (2002) 8905–8925.
[241] C. D'Ham, A. Romieu, M. Jaquinod, D. Gasparutto, J. Cadet, Excision of 5,6-dihydroxy-5,6-dihydrothymine, 5,6-dihydrothymine, and 5-hydroxycytosine from defined sequence oligonucleotides by Escherichia coli endonuclease III and Fpg proteins: kinetic and mechanistic aspects, Biochemistry 38 (1999) 3335–3344.

[242] M. Dizdaroglu, J. Laval, S. Boiteux, Substrate specificity of Escherischia coli endonuclease III: excision of thymine- and cytosine-derived lesions in DNA produced by ionizing radiation-generated free radicals, Biochemistry 32 (1993) 12105–12111.
[243] M. Dizdaroglu, C. Bauche, H. Rodriguez, J. Laval, Novel substrates of Escherichia coli Nth protein and its kinetics for excision of modified bases from DNA damaged by free radicals, Biochemistry 39 (2000) 5586–5592.
[244] C.J. Wiederholt, J.N. Patro, Y.L. Jiang, K. Haraguchi, M.M. Greenberg, Excision of formamidopyrimidine lesions by endonucleases III and VIII is not a major DNA repair pathway in Escherichia coli, Nucleic Acids Res. 33 (2005) 3331–3338.
[245] R.J. Melamede, Z. Hatahet, Y.W. Kow, H. Ide, S.S. Wallace, Isolation and characterization of endonuclease VIII from Escherichia coli, Biochemistry 33 (1994) 1255–1264.
[246] D. Jiang, Z. Hatahet, J.O. Blaisdell, R.J. Melamede, S.S. Wallace, Escherichia coli endonuclease VIII: cloning, sequencing, and overexpression of the nei structural gene and characterization of nei and nei nth mutants, J. Bacteriol. 179 (1997) 3773–3782.
[247] D. Jiang, Z. Hatahet, R.J. Melamede, Y.W. Kow, S.S. Wallace, Characterization of escherichia coli endonuclease VIII, J. Biol. Chem. 272 (1997) 32230–32239.
[248] Y. Saito, F. Uraki, S. Nakajima, A. Asaeda, K. Ono, K. Kubo, K. Yamamoto, Characterization of endonuclease III (nth) and endonuclease VIII (nei) mutants of escherichia coli K-12, J. Bacteriol. 179 (1997) 3783–3785.
[249] K.Y. Kropachev, D.O. Zharkov, A.P. Grollman, Catalytic mechanism of Escherichia coli endonuclease VIII: roles of the intercalation loop and the zinc finger, Biochemistry 45 (2006) 12039–12049.
[250] S. Burgess, P. Jaruga, M.L. Dodson, M. Dizdaroglu, R.S. Lloyd, Determination of active site residues in Escherichia coli endonuclease VIII, J. Biol. Chem. 277 (2002) 2938–2944.
[251] D.O. Zharkov, G. Golan, R. Gilboa, A.S. Fernandes, S.E. Gerchman, J.H. Kycia, R. A. Rieger, A.P. Grollman, G. Shoham, Structural analysis of an Escherichia coli endonuclease VIII covalent reaction intermediate, EMBO J. 21 (2002) 789–800.
[252] J.O. Blaisdell, Z. Hatahet, S.S. Wallace, A novel role for Escherichia coli endonuclease VIII in prevention of spontaneous G–> T transversions, J. Bacteriol. 181 (1999) 6396–6402.
[253] T.K. Hazra, T. Izumi, R. Venkataraman, Y.W. Kow, M. Dizdaroglu, S. Mitra, Characterization of a novel 8-oxoguanine-DNA glycosylase activity in Escherichia coli and identification of the enzyme as endonuclease VIII, J. Biol. Chem. 275 (2000) 27762–27767.
[254] M. Dizdaroglu, S.M. Burgess, P. Jaruga, T.K. Hazra, H. Rodriguez, R.S. Lloyd, Substrate specificity and excision kinetics of Escherichia coli endonuclease VIII (Nei) for modified bases in DNA damaged by free radicals, Biochemistry 40 (2001) 12150–12156.
[255] S.T. Cole, R. Brosch, J. Parkhill, T. Garnier, C. Churcher, D. Harris, S.V. Gordon, K. Eiglmeier, S. Gas, C.E. Barry III, F. Tekaia, K. Badcock, D. Basham, D. Brown, T. Chillingworth, R. Connor, R. Davies, K. Devlin, T. Feltwell, S. Gentles, N. Hamlin, S. Holroyd, T. Hornsby, K. Jagels, A. Krogh, J. McLean, S. Moule, L. Murphy, K. Oliver, J. Osborne, M.A. Quail, M.A. Rajandream, J. Rogers, S. Rutter, K. Seeger, J. Skelton, R. Squares, S. Squares, J.E. Sulston, K. Taylor, S. Whitehead, B.G. Barrell, Deciphering the biology of Mycobacterium tuberculosis from the complete genome sequence, Nature 393 (1998) 537–544.
[256] V.S. Sidorenko, M.A. Rot, M.L. Filipenko, G.A. Nevinsky, D.O. Zharkov, Novel DNA glycosylases from mycobacterium tuberculosis, Biochemistry (Mosc.) 73 (2008) 442–450.
[257] I. Olsen, S.V. Balasingham, T. Davidsen, E. Debebe, E.A. Rodland, S.D. van, K. Kremer, I. Alseth, T. Tonjum, Characterization of the major formamidopyrimidine-DNA glycosylase homolog in Mycobacterium tuberculosis and its linkage to variable tandem repeats, FEMS Immunol. Med. Microbiol. 56 (2009) 151–161.
[258] Y. Guo, S.S. Wallace, V. Bandaru, A novel bicistronic vector for overexpressing Mycobacterium tuberculosis proteins in Escherichia coli, Protein Expr. Purif. 65 (2009) 230–237.
[259] D.O. Zharkov, R.A. Rieger, C.R. Iden, A.P. Grollman, NH_2-terminal proline acts as a nucleophile in the glycosylase/AP- lyase reaction catalyzed by Escherichia coli formamidopyrimidine- DNA glycosylase (Fpg) protein, J. Biol. Chem. 272 (1997) 5335–5341.
[260] O.V. Lavrukhin, R.S. Lloyd, Involvement of phylogenetically conserved acidic amino acid residues in catalysis by an oxidative DNA damage enzyme formamidopyrimidine glycosylase, Biochemistry 39 (2000) 15266–15271.
[261] M. Liu, V. Bandaru, J.P. Bond, P. Jaruga, X. Zhao, P.P. Christov, C.J. Burrows, C.J. Rizzo, M. Dizdaroglu, S.S. Wallace, The mouse ortholog of NEIL3 is a functional DNA glycosylase in vitro and in vivo, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 4925–4930.
[262] C.J. Wiederholt, M.M. Greenberg, Fapy.dG instructs Klenow exo$^-$ to misincorporate deoxyadenosine, J. Am. Chem. Soc. 124 (2002) 7278–7679.
[263] M.A. Kalam, K. Haraguchi, S. Chandani, E.L. Loechler, M. Moriya, M.M. Greenberg, A.K. Basu, Genetic effects of oxidative DNA damages: comparative mutagenesis of the imidazole ring-opened formamidopyrimidines (Fapy lesions) and 8-oxo-purines in simian kidney cells, Nucleic Acids Res. 34 (2006) 2305–2315.
[264] A.A. Purmal, G.W. Lampman, Y.W. Kow, S.S. Wallace, The sequence context-dependent mispairing of 5-hydroxycytosine and 5-hydroxyuridine in vitro, Ann. N. Y. Acad. Sci. 726 (1994) 361–363.
[265] D.I. Feig, L.C. Sowers, L.A. Loeb, Reverse chemical mutagenesis: identification of the mutagenic lesions resulting from reactive oxygen species-mediated damage to DNA, Proc. Natl. Acad. Sci. U. S. A. 91 (1994) 6609–6613.
[266] D.A. Kreutzer, J.M. Essigmann, Oxidized, deaminated cytosines are a source of C –> T transitions in vivo, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 3578–3582.
[267] D. Wang, D.A. Kreutzer, J.M. Essigmann, Mutagenicity and repair of oxidative DNA damage: insights from studies using defined lesions, Mutat. Res. Fundam. Mol. Mech. Mutagen 400 (1998) 99–115.
[268] S.S. Wallace, Biological consequences of free radical-damaged DNA bases, Free Radic. Biol. Med. 33 (2002) 1–14.
[269] P. Auffret van der Kemp, D. Thomas, R. Barbey, R. De Oliveira, S. Boiteux, Cloning and expression in *Escherichia coli* of the OGG1 gene of Saccharomyces cerevisiae, which codes for a DNA glycosylase that excises 7,8-dihydro-8-oxoguanine and 2, 6-diamino-4-hydroxy-5-N-methylformamidopyrimidine, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 5197–5202.
[270] P.M. Girard, S. Boiteux, Repair of oxidized DNA bases in the yeast Saccharomyces cerevisiae, Biochimie 79 (1997) 559–566.
[271] P.M. Girard, N. Guibourt, S. Boiteux, The Ogg1 protein of Saccharomyces cerevisiae: a 7,8-dihydro-8-oxoguanine DNA glycosylase/AP lyase whose lysine 241 is a critical residue for catalytic activity, Nucleic Acids Res. 25 (1997) 3204–3211.
[272] P.M. Girard, C. D'Ham, J. Cadet, S. Boiteux, Opposite base-dependent excision of 7,8-dihydro-8-oxoadenine by the Ogg1 protein of Saccharomyces cerevisiae, Carcinogenesis 19 (1998) 1299–1305.
[273] K.K. Singh, B. Sigala, H.A. Sikder, C. Schwimmer, Inactivation of Saccharomyces cerevisiae OGG1 DNA repair gene leads to an increased frequency of mitochondrial mutants, Nucleic Acids Res. 29 (2001) 1381–1388.
[274] R. Vongsamphanh, J.R. Wagner, D. Ramotar, Saccharomyces cerevisiae Ogg1 prevents poly(GT) tract instability in the mitochondrial genome, DNA Repair (Amst.) 5 (2006) 235–242.
[275] B. Karahalil, P.M. Girard, S. Boiteux, M. Dizdaroglu, Substrate specificity of the Ogg1 protein of *Saccharomyces cerevisiae*: excision of guanine lesions produced in DNA by ionizing radiation- or hydrogen peroxide/metal ion-generated free radicals, Nucleic Acids Res. 26 (1998) 1228–1233.
[276] S.D. Bruner, H.M. Nash, W.S. Lane, G.L. Verdine, Repair of oxidatively damaged guanine in Saccharomyces cerevisiae by an alternative pathway, Curr. Biol. 8 (1998) 393–403.
[277] J.P. Radicella, C. Dherin, C. Desmaze, M.S. Fox, S. Boiteux, Cloning and characterization of hOGG1, a human homolog of the OGG1 gene of Saccharomyces cerevisiae, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 8010–8015.
[278] H. Aburatani, Y. Hippo, T. Ishida, R. Takashima, C. Matsuba, T. Kodama, M. Takao, A. Yasui, K. Yamamoto, M. Asano, K. Fukasawa, T. Yoshinari, H. Inoue, E. Ohtsuka, S. Nishimura, Cloning and characterization of mammalian 8-hydroxyguanine- specific DNA glycosylase/apurinic, apyrimidinic lyase, a functional mutM homologue, Cancer Res. 57 (1997) 2151–2156.
[279] K. Arai, K. Morishita, K. Shinmura, T. Kohno, S.R. Kim, T. Nohmi, M. Taniwaki, S. Ohwada, J. Yokota, Cloning of a human homolog of the yeast *OGG1* gene that is involved in the repair of oxidative DNA damage, Oncogene 14 (1997) 2857–2861.
[280] T. Roldán-Arjona, Y.F. Wei, K.C. Carter, A. Klungland, C. Anselmino, R.P. Wang, M. Augustus, T. Lindahl, Molecular cloning and functional expression of a human cDNA encoding the antimutator enzyme 8-hydroxyguanine-DNA glycosylase, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 8016–8020.
[281] T.A. Rosenquist, D.O. Zharkov, A.P. Grollman, Cloning and characterization of a mammalian 8-oxoguanine DNA glycosylase, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 7429–7434.
[282] K. Shinmura, H. Kasai, A. Sasaki, H. Sugimura, J. Yokota, 8-hydroxyguanine (7, 8-dihydro-8-oxoguanine) DNA glycosylase and AP lyase activities of hOGG1 protein and their substrate specificity, Mutat. Res. DNA Repair 385 (1997) 75–82.
[283] M. Bjorås, L. Luna, B. Johnson, E. Hoff, T. Haug, T. Rognes, E. Seeberg, Opposite base-dependent reactions of a human base excision repair enzyme on DNA containing 7,8-dihydro-8-oxoguanine and abasic sites, EMBO J. 16 (1997) 6314–6322.
[284] F.C. Kuo, J. Sklar, Augmented expression of a human gene for 8-oxoguanine DNA glycosylase (MutM) in B lymphocytes of the dark zone in lymph node germinal centers, J. Exp. Med. 186 (1997) 1547–1556.
[285] T. Ishida, Y. Hippo, Y. Nakahori, I. Matsushita, T. Kodama, S. Nishimura, H. Aburatani, Structure and chromosome location of human OGG1, Cytogenet. Cell Genet. 85 (1999) 232–236.
[286] S. Boiteux, J.P. Radicella, Base excision repair of 8-hydroxyguanine protects DNA from endogenous oxidative stress, Biochimie 81 (1999) 59–67.
[287] M. Takao, H. Aburatani, K. Kobayashi, A. Yasui, Mitochondrial targeting of human DNA glycosylases for repair of oxidative DNA damage, Nucleic Acids Res. 26 (1998) 2917–2922.
[288] K. Nishioka, T. Ohtsubo, H. Oda, T. Fujiwara, D. Kang, K. Sugimachi, Y. Nakabeppu, Expression and differential intracellular localization of two major forms of human 8-oxoguanine DNA glycosylase encoded by alternatively spliced OGG1 mRNAs, Mol. Biol. Cell 10 (1999) 1637–1652.
[289] E. Seeberg, L. Luna, I. Morland, L. Eide, B. Johnsen, E. Larsen, I. Alseth, F. Dantzer, K. Baynton, R. Aamodt, K.I. Kristiansen, T. Rognes, A. Klungland, M. Bjoras, Base removers and strand scissors: different strategies employed in base excision and strand incision at modified base residues in DNA, Cold Spring Harb. Symp. Quant. Biol. 65 (2000) 135–142.

[290] A. Klungland, I. Rosewell, S. Hollenbach, E. Larsen, G. Daly, B. Epe, E. Seeberg, T. Lindahl, D.E. Barnes, Accumulation of premutagenic DNA lesions in mice defective in removal of oxidative base damage, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 13300–13305.
[291] N.C. Souza-Pinto, B.A. Hogue, V.A. Bohr, DNA repair and aging in mouse liver: 8-oxodG glycosylase activity increase in mitochondrial but not in nuclear extracts, Free Radic. Biol. Med. 30 (2001) 916–923.
[292] N.C. Souza-Pinto, L. Eide, B.A. Hogue, T. Thybo, T. Stevnsner, E. Seeberg, A. Klungland, V.A. Bohr, Repair of 8-oxodeoxyguanosine lesions in mitochondrial DNA depends on the oxoguanine DNA glycosylase (OGG1) gene and 8-oxoguanine accumulates in the mitochondrial dna of OGG1-defective mice, Cancer Res. 61 (2001) 5378–5381.
[293] V.A. Bohr, Repair of oxidative DNA damage in nuclear and mitochondrial DNA, and some changes with aging in mammalian cells, Free Radic. Biol. Med. 32 (2002) 804–812.
[294] V. Rolseth, E. Runden-Pran, L. Luna, C. McMurray, M. Bjoras, O.P. Ottersen, Widespread distribution of DNA glycosylases removing oxidative DNA lesions in human and rodent brains, DNA Repair (Amst.) 7 (2008) 1578–1588.
[295] D.P. Norman, S.J. Chung, G.L. Verdine, Structural and biochemical exploration of a critical amino acid in human 8-oxoguanine glycosylase, Biochemistry 42 (2003) 1564–1572.
[296] C.T. Radom, A. Banerjee, G.L. Verdine, Structural characterization of human 8-oxoguanine DNA glycosylase variants bearing active site mutations, J. Biol. Chem. 282 (2007) 9182–9194.
[297] M. Bjoras, E. Seeberg, L. Luna, L.H. Pearl, T.E. Barrett, Reciprocal flipping underlies substrate recognition and catalytic activation by the human 8-oxo-guanine DNA glycosylase, J. Mol. Biol. 317 (2002) 171–177.
[298] C.M. Crenshaw, K. Nam, K. Oo, P.S. Kutchukian, B.R. Bowman, M. Karplus, G.L. Verdine, Enforced presentation of an extrahelical guanine to the lesion recognition pocket of human 8-oxoguanine glycosylase, hOGG1, J. Biol. Chem. 287 (2012) 24916–24928.
[299] B. Dalhus, M. Forsbring, I.H. Helle, E.S. Vik, R.J. Forstrom, P.H. Backe, I. Alseth, M. Bjoras, Separation-of-function mutants unravel the dual-reaction mode of human 8-oxoguanine DNA glycosylase, Structure 19 (2011) 117–127.
[300] R. Lu, H.M. Nash, G.L. Verdine, A mammalian DNA repair enzyme that excises oxidatively damaged guanines maps to a locus frequently lost in lung cancer, Curr. Biol. 7 (1997) 397–407.
[301] C. Dherin, J.P. Radicella, M. Dizdaroglu, S. Boiteux, Excision of oxidatively damaged DNA bases by the human alpha-hOgg1 protein and the polymorphic alpha-hOgg1(Ser326Cys) protein which is frequently found in human populations, Nucleic Acids Res. 27 (1999) 4001–4007.
[302] N. Krishnamurthy, K. Haraguchi, M.M. Greenberg, S.S. David, Efficient removal of formamidopyrimidines by 8-oxoguanine glycosylases, Biochemistry 47 (2008) 1043–1050.
[303] T. Kohno, K. Shinmura, M. Tosaka, M. Tani, S.R. Kim, H. Sugimura, T. Nohmi, H. Kasai, J. Yokota, Genetic polymorphisms and alternative splicing of the *hOGG1* gene, that is involved in the repair of 8-hydroxyguanine in damaged DNA, Oncogene 16 (1998) 3219–3225.
[304] R.J. Hung, J. Hall, P. Brennan, P. Boffetta, Genetic polymorphisms in the base excision repair pathway and cancer risk: a HuGE review, Am. J. Epidemiol. 162 (2005) 925–942.
[305] H. Blons, J.P. Radicella, O. Laccourreye, D. Brasnu, P. Beaune, S. Boiteux, P. Laurent-Puig, Frequent allelic loss at chromosome 3p distinct from genetic alterations of the 8-oxoguanine DNA glycosylase 1 gene in head and neck cancer, Mol. Carcinog. 26 (1999) 254–260.
[306] S. Chevillard, J.P. Radicella, C. Levalois, J. Lebeau, M.F. Poupon, S. Oudard, B. Dutrillaux, S. Boiteux, Mutations in OGG1, a gene involved in the repair of oxidative DNA damage, are found in human lung and kidney tumours, Oncogene 16 (1998) 3083–3086.
[307] M. Daimon, T. Oizumi, S. Toriyama, S. Karasawa, Y. Jimbu, K. Wada, W. Kameda, S. Susa, M. Muramatsu, I. Kubota, S. Kawata, T. Kato, Association of the Ser326Cys polymorphism in the OGG1 gene with type 2 DM, Biochem. Biophys. Res. Commun. 386 (2009) 26–29.
[308] F. Thameem, S. Puppala, D.M. Lehman, M.P. Stern, J. Blangero, H.E. Abboud, R. Duggirala, S.L. Habib, The Ser(326)Cys polymorphism of 8-oxoguanine glycosylase 1 (OGG1) is associated with type 2 diabetes in Mexican Americans, Hum. Hered. 70 (2010) 97–101.
[309] W.X. Duan, R.X. Hua, W. Yi, L.J. Shen, Z.X. Jin, Y.H. Zhao, D.H. Yi, W.S. Chen, S.Q. Yu, The association between OGG1 Ser326Cys polymorphism and lung cancer susceptibility: a meta-analysis of 27 studies, PLoS One 7 (2012) e35970.
[310] P.T. Zhou, B. Li, J. Ji, M.M. Wang, C.F. Gao, A systematic review and meta-analysis of the association between OGG1 Ser326Cys polymorphism and cancers, Med. Oncol. 32 (2015) 472.
[311] K. Shinmura, T. Kohno, H. Kasai, K. Koda, H. Sugimura, J. Yokota, Infrequent mutations of the hOGG1 gene, that is involved in the excision of 8-hydroxyguanine in damaged DNA, in human gastric cancer, Jpn. J. Cancer Res. 89 (1998) 825–828.
[312] M. Audebert, S. Chevillard, C. Levalois, G. Gyapay, A. Vieillefond, J. Klijanienko, P. Vielh, A.K. El Naggar, S. Oudard, S. Boiteux, J.P. Radicella, Alterations of the DNA repair gene OGG1 in human clear cell carcinomas of the kidney, Cancer Res. 60 (2000) 4740–4744.
[313] M. Audebert, J.P. Radicella, M. Dizdaroglu, Effect of single mutations in the OGG1 gene found in human tumors on the substrate specificity of the ogg1 protein, Nucleic Acids Res. 28 (2000) 2672–2678.
[314] J.G. Mabley, P. Pacher, A. Deb, R. Wallace, R.H. Elder, C. Szabo, Potential role for 8-oxoguanine DNA glycosylase in regulating inflammation, FASEB J. 19 (2005) 290–292.
[315] M. Kunisada, K. Sakumi, Y. Tominaga, A. Budiyanto, M. Ueda, M. Ichihashi, Y. Nakabeppu, C. Nishigori, 8-Oxoguanine formation induced by chronic UVB exposure makes Ogg1 knockout mice susceptible to skin carcinogenesis, Cancer Res. 65 (2005) 6006–6010.
[316] E. Touati, V. Michel, J.M. Thiberge, P. Ave, M. Huerre, F. Bourgade, A. Klungland, A. Labigne, Deficiency in OGG1 protects against inflammation and mutagenic effects associated with H. pylori infection in mouse, Helicobacter 11 (2006) 494–505.
[317] Z. Wang, D.B. Rhee, J. Lu, C.T. Bohr, F. Zhou, H. Vallabhaneni, N.C. de Souza-Pinto, Y. Liu, Characterization of oxidative guanine damage and repair in mammalian telomeres, PLoS Genet. 6 (2010) e1000951.
[318] H. Sampath, V. Vartanian, M.R. Rollins, K. Sakumi, Y. Nakabeppu, R.S. Lloyd, 8-Oxoguanine DNA glycosylase (OGG1) deficiency increases susceptibility to obesity and metabolic dysfunction, PLoS One 7 (2012) e51697.
[319] L. Aguilera-Aguirre, K. Hosoki, A. Bacsi, Z. Radak, T.G. Wood, S.G. Widen, S. Sur, B.T. Ameredes, A. Saavedra-Molina, A.R. Brasier, X. Ba, I. Boldogh, Whole transcriptome analysis reveals an 8-oxoguanine DNA glycosylase-1-driven DNA repair-dependent gene expression linked to essential biological processes, Free Radic. Biol. Med. 81 (2015) 107–118.
[320] T. Arai, V.P. Kelly, O. Minowa, T. Noda, S. Nishimura, High accumulation of oxidative DNA damage, 8-hydroxyguanine, in Mmh/Ogg1 deficient mice by chronic oxidative stress, Carcinogenesis 23 (2002) 2005–2010.
[321] T. Arai, V.P. Kelly, O. Minowa, T. Noda, S. Nishimura, The study using wild-type and Ogg1 knockout mice exposed to potassium bromate shows no tumor induction despite an extensive accumulation of 8-hydroxyguanine in kidney DNA, Toxicology 221 (2006) 179–186.
[322] V.S. Sidorenko, A.P. Grollman, P. Jaruga, M. Dizdaroglu, D.O. Zharkov, Substrate specificity and excision kinetics of natural polymorphic variants and phosphomimetic mutants of human 8-oxoguanine-DNA glycosylase, FEBS J. 276 (2009) 5149–5162.
[323] G. Mao, X. Pan, B.B. Zhu, Y. Zhang, F. Yuan, J. Huang, M.A. Lovell, M.P. Lee, W.R. Markesbery, G.M. Li, L. Gu, Identification and characterization of OGG1 mutations in patients with Alzheimer's disease, Nucleic Acids Res. 35 (2007) 2759–2766.
[324] J.W. Hill, T.K. Hazra, T. Izumi, S. Mitra, Stimulation of human 8-oxoguanine-DNA glycosylase by AP-endonuclease: potential coordination of the initial steps in base excision repair, Nucleic Acids Res. 29 (2001) 430–438.
[325] A.E. Vidal, I.D. Hickson, S. Boiteux, J.P. Radicella, Mechanism of stimulation of the DNA glycosylase activity of hOGG1 by the major human AP endonuclease: bypass of the AP lyase activity step, Nucleic Acids Res. 29 (2001) 1285–1292.
[326] T. Saitoh, K. Shinmura, S. Yamaguchi, M. Tani, S. Seki, H. Murakami, Y. Nojima, J. Yokota, Enhancement of OGG1 protein AP lyase activity by increase of APEX protein, Mutat. Res. 486 (2001) 31–40.
[327] V.S. Sidorenko, G.A. Nevinsky, D.O. Zharkov, Mechanism of interaction between human 8-oxoguanine-DNA glycosylase and AP endonuclease, DNA Repair (Amst.) 6 (2007) 317–328.
[328] T. Pawson, J.D. Scott, Protein phosphorylation in signaling–50 years and counting, Trends Biochem. Sci. 30 (2005) 286–290.
[329] T.K. Hazra, T. Izumi, L. Maidt, R.A. Floyd, S. Mitra, The presence of two distinct 8-oxoguanine repair enzymes in human cells: their potential complementary roles in preventing mutation, Nucleic Acids Res. 26 (1998) 5116–5122.
[330] C. Dherin, M. Dizdaroglu, H. Doerflinger, S. Boiteux, J.P. Radicella, Repair of oxidative DNA damage in *Drosophila melanogaster*: identification and characterization of dOgg1 a second DNA glycosylase activity for 8-hydroxyguanine and formamidopyrimidines, Nucleic Acids Res. 28 (2000) 4583–4592.
[331] D.M. Wilson III, W.A. Deutsch, M.R. Kelley, Cloning of the Drosophila ribosomal protein S3: another multifunctional ribosomal protein with AP endonuclease DNA repair activity, Nucleic Acids Res. 21 (1993) 2516.
[332] D.M. Wilson III, W.A. Deutsch, M.R. Kelley, Drosophila ribosomal protein S3 contains an activity that cleaves DNA at apurinic/apyrimidinic sites, J. Biol. Chem. 269 (1994) 25359–25364.
[333] A. Yacoub, L. Augeri, M.R. Kelley, P.W. Doetsch, W.A. Deutsch, A Drosophila ribosomal protein contains 8-oxoguanine and abasic site DNA repair activities, EMBO J. 15 (1996) 2306–2312.
[334] W.A. Deutsch, A. Yacoub, P. Jaruga, T.H. Zastawny, M. Dizdaroglu, Characterization and mechanism of action of Drosophila ribosomal protein S3 DNA glycosylase activity for the removal of oxidatively damaged DNA bases, J. Biol. Chem. 272 (1997) 32857–32860.
[335] J. Kim, L.S. Chubatsu, A. Admon, J. Stahl, R. Fellous, S. Linn, Implication of mammalian ribosomal protein S3 in the processing of DNA damage, J. Biol. Chem. 270 (1995) 13620–13629.
[336] V. Hegde, M.R. Kelley, Y. Xu, I.S. Mian, W.A. Deutsch, Conversion of the bifunctional 8-oxoguanine/beta-delta apurinic/apyrimidinic DNA repair activities of Drosophila ribosomal protein S3 into the human S3 monofunctional beta-elimination catalyst through a single amino acid change, J. Biol. Chem. 276 (2001) 27591–27596.
[337] V. Hegde, M. Wang, W.A. Deutsch, Characterization of human ribosomal protein S3 binding to 7,8-dihydro-8-oxoguanine and abasic sites by surface plasmon resonance, DNA Repair (Amst.) 3 (2004) 121–126.
[338] V. Hegde, S. Yadavilli, W.A. Deutsch, Knockdown of ribosomal protein S3 protects human cells from genotoxic stress, DNA Repair (Amst.) 6 (2007) 94–99.

[339] M.V. Garcia-Ortiz, R.R. Ariza, T. Roldan-Arjona, An OGG1 orthologue encoding a functional 8-oxoguanine DNA glycosylase/lyase in Arabidopsis thaliana, Plant Mol. Biol. 47 (2001) 795–804.
[340] S. Boiteux, J.P. Radicella, Excision repair of 8-oxoguanine in eukaryotes, in: M. Dizdaroglu, A.E. Karakaya (Eds.), Advances in DNA Damage and Repair: Oxygen Radical Effects, Cellular Protection, and Bilogical Consequences, Kluwer Academic/Plenum Publishers, New York, 1999, pp. 35–45.
[341] S. Boiteux, J.P. Radicella, The human OGG1 gene: structure, functions, and its implication in the process of carcinogenesis, Arch. Biochem. Biophys. 377 (2000) 1–8.
[342] S. Boiteux, L. Gellon, N. Guibourt, Repair of 8-oxoguanine in *Saccharomyces cerevisiae*: interplay of DNA repair and replication mechanisms, Free Radic. Biol. Med. 32 (2002) 1244–1253.
[343] T. Roldán-Arjona, C. Anselmino, T. Lindahl, Molecular cloning and functional analysis of a *Schizosaccharomyces pombe* homologue of *Escherichia coli* endonuclease III, Nucleic Acids Res. 24 (1996) 3307–3312.
[344] B. Karahalil, T. Roldan-Arjona, M. Dizdaroglu, Substrate specificity of *Schizosaccharomyces pombe* Nth protein for products of oxidative DNA damage, Biochemistry 37 (1998) 590–595.
[345] R. Aspinwall, D.G. Rothwell, T. Roldan-Arjona, C. Anselmino, C.J. Ward, J.P. Cheadle, J.R. Sampson, T. Lindahl, P.C. Harris, I.D. Hickson, Cloning and characterization of a functional human homolog of *Escherichia coli* endonuclease III, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 109–114.
[346] M. Dizdaroglu, B. Karahalil, S. Sentürker, T.J. Buckley, T. Roldan-Arjona, Excision of products of oxidative DNA base damage by human NTH1 protein, Biochemistry 38 (1999) 243–246.
[347] J. Hu, N.C. de Souza-Pinto, K. Haraguchi, B.A. Hogue, P. Jaruga, M.M. Greenberg, M. Dizdaroglu, V.A. Bohr, Repair of formamidopyrimidines in DNA involves different glycosylases: role of the OGG1, NTH1, and NEIL1 enzymes, J. Biol. Chem. 280 (2005) 40544–40551.
[348] M.K. Chan, M.T. Ocampo-Hafalla, V. Vartanian, P. Jaruga, G. Kirkali, K.L. Koenig, S. Brown, R.S. Lloyd, M. Dizdaroglu, G.W. Teebor, Targeted deletion of the genes encoding NTH1 and NEIL1 DNA N-glycosylases reveals the existence of novel carcinogenic oxidative damage to DNA, DNA Repair (Amst.) 8 (2009) 786–794.
[349] K. Imai, A.H. Sarker, K. Akiyama, S. Ikeda, M. Yao, K. Tsutsui, T. Shohmori, S. Seki, Genomic structure and sequence of a human homologue (NTHL1/NTH1) of Escherichia coli endonuclease III with those of the adjacent parts of TSC2 and SLC9A3R2 genes, Gene 222 (1998) 287–295.
[350] B. Karahalil, B.A. Hogue, N.C. Souza-Pinto, V.A. Bohr, Base excision repair capacity in mitochondria and nuclei: tissue-specific variations, FASEB J. 16 (2002) 1895–1902.
[351] H.A. Galick, S. Kathe, M. Liu, S. Robey-Bond, D. Kidane, S.S. Wallace, J.B. Sweasy, Germ-line variant of human NTH1 DNA glycosylase induces genomic instability and cellular transformation, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 14314–14319.
[352] S. Koketsu, T. Watanabe, H. Nagawa, Expression of DNA repair protein: MYH, NTH1 and MTH1 in colorectal cancer, Hepatogastroenterology 51 (2004) 638–642.
[353] M. Goto, K. Shinmura, H. Igarashi, M. Kobayashi, H. Konno, H. Yamada, M. Iwaizumi, S. Kageyama, T. Tsuneyoshi, S. Tsugane, H. Sugimura, Altered expression of the human base excision repair gene NTH1 in gastric cancer, Carcinogenesis 30 (2009) 1345–1352.
[354] E. Short, L.E. Thomas, J. Hurley, S. Jose, J.R. Sampson, Inherited predisposition to colorectal cancer: towards a more complete picture, J. Med. Genet. 52 (2015) 791–796.
[355] B. Rivera, E. Castellsague, I. Bah, L.C. van Kempen, W.D. Foulkes, Biallelic NTHL1 mutations in a woman with multiple primary tumors, N. Engl. J. Med. 373 (2015) 1985–1986.
[356] R.D. Weren, M.J. Ligtenberg, C.M. Kets, R.M. de Voer, E.T. Verwiel, L. Spruijt, W. A. van Zelst-Stams, M.C. Jongmans, C. Gilissen, J.Y. Hehir-Kwa, A. Hoischen, J. Shendure, E.A. Boyle, E.J. Kamping, I.D. Nagtegaal, B.B. Tops, F.M. Nagengast, A. Geurts van Kessel, J.H. van Krieken, R.P. Kuiper, N. Hoogerbrugge, A germline homozygous mutation in the base-excision repair gene NTHL1 causes adenomatous polyposis and colorectal cancer, Nat. Genet. 47 (2015) 668–671.
[357] L.G. Eide, C. Sander, H. Prydz, Sequencing and analysis of a 35.4 kb region on the right arm of chromosome IV from Saccharomyces cerevisiae reveal 23 open reading frames, Yeast 12 (1996) 1085–1090.
[358] L. Augeri, Y.M. Lee, A.B. Barton, P.W. Doetsch, Purification, characterization, gene cloning, and expression of Saccharomyces cerevisiae redoxyendonuclease a homolog of Escherichia coli endonuclease III, Biochemistry 36 (1997) 721–729.
[359] H.J. You, R.L. Swanson, P.W. Doetsch, Saccharomyces cerevisiae possesses two functional homologues of Escherichia coli endonuclease III, Biochemistry 37 (1998) 6033–6040.
[360] S. Boiteux, S. Jinks-Robertson, DNA repair mechanisms and the bypass of DNA damage in Saccharomyces cerevisiae, Genetics 193 (2013) 1025–1064.
[361] H.J. You, R.L. Swanson, C. Harrington, A.H. Corbett, S. Jinks-Robertson, S. Senturker, S.S. Wallace, S. Boiteux, M. Dizdaroglu, P.W. Doetsch, Saccharomyces cerevisiae Ntg1p and Ntg2p: broad specificity N- glycosylases for the repair of oxidative DNA damage in the nucleus and mitochondria, Biochemistry 38 (1999) 11298–11306.
[362] S.I. Liochev, I. Fridovich, How does superoxide dismutase protect against tumor necrosis factor: a hypothesis informed by effect of superoxide on free iron, Free Radic. Biol. Med. 23 (1997) 668–671.
[363] P.R. Gardner, Superoxide-driven aconitase FE-S center cycling, Biosci. Rep. 17 (1997) 33–42.
[364] L. Gellon, R. Barbey, P. Auffret van der Kemp, D. Thomas, S. Boiteux, Synergism between base excision repair, mediated by the DNA glycosylases Ntg1 and Ntg2, and nucleotide excision repair in the removal of oxidatively damaged DNA bases in Saccharomyces cerevisiae, Mol. Genet. Genom. 265 (2001) 1087–1096.
[365] L. Eide, M. Bjorås, M. Pirovano, I. Alseth, K.G. Berdal, E. Seeberg, Base excision of oxidative purine and pyrimidine DNA damage in Saccharomyces cerevisiae by a DNA glycosylase with sequence similarity to endonuclease III from Escherichia coli, Proc. Natl. Acad. Sci. U. S. A. 93 (1996) 10735–10740.
[366] S. Sentürker, P. Auffret van der Kemp, H.J. You, P.W. Doetsch, M. Dizdaroglu, S. Boiteux, Substrate specificities of the Ntg1 and Ntg2 proteins of *Saccharomyces cerevisiae* for oxidized DNA bases are not identical, Nucleic Acids Res. 26 (1998) 5270–5276.
[367] J.T. Hannich, A. Lewis, M.B. Kroetz, S.J. Li, H. Heide, A. Emili, M. Hochstrasser, Defining the SUMO-modified proteome by multiple approaches in Saccharomyces cerevisiae, J. Biol. Chem. 280 (2005) 4102–4110.
[368] L.M. Griffiths, D. Swartzlander, K.L. Meadows, K.D. Wilkinson, A.H. Corbett, P. W. Doetsch, Dynamic compartmentalization of base excision repair proteins in response to nuclear and mitochondrial oxidative stress, Mol. Cell. Biol. 29 (2009) 794–807.
[369] D.B. Swartzlander, A.J. McPherson, H.R. Powers, K.L. Limpose, E.G. Kuiper, N.P. Degtyareva, A.H. Corbett, P.W. Doetsch, Identification of SUMO modification sites in the base excision repair protein, Ntg1, DNA Repair (Amst.) 48 (2016) 51–62.
[370] T.K. Hazra, T. Izumi, I. Boldogh, B. Imhoff, Y.W. Kow, P. Jaruga, M. Dizdaroglu, S. Mitra, Identification and characterization of a human DNA glycosylase for repair of modified bases in oxidatively damaged DNA, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 3523–3528.
[371] V. Bandaru, S. Sunkara, S.S. Wallace, J.P. Bond, A novel human DNA glycosylase that removes oxidative DNA damage and is homologous to Escherichia coli endonuclease VIII, DNA Repair (Amst.) 1 (2002) 517–529.
[372] I. Morland, V. Rolseth, L. Luna, T. Rognes, M. Bjoras, E. Seeberg, Human DNA glycosylases of the bacterial Fpg/MutM superfamily: an alternative pathway for the repair of 8-oxoguanine and other oxidation products in DNA, Nucleic Acids Res. 30 (2002) 4926–4936.
[373] T.K. Hazra, Y.W. Kow, Z. Hatahet, B. Imhoff, I. Boldogh, S.K. Mokkapati, S. Mitra, T. Izumi, Identification and characterization of a novel human DNA glycosylase for repair of cytosine-derived lesions, J. Biol. Chem. 277 (2002) 30417–30420.
[374] T. Izumi, L.R. Wiederhold, G. Roy, R. Roy, A. Jaiswal, K.K. Bhakat, S. Mitra, T.K. Hazra, Mammalian DNA base excision repair proteins: their interactions and role in repair of oxidative DNA damage, Toxicology 193 (2003) 43–65.
[375] H. Dou, C.A. Theriot, A. Das, M.L. Hegde, Y. Matsumoto, I. Boldogh, T.K. Hazra, K.K. Bhakat, S. Mitra, Interaction of the human DNA glycosylase NEIL1 with proliferating cell nuclear antigen. The potential for replication-associated repair of oxidized bases in mammalian genomes, J. Biol. Chem. 283 (2008) 3130–3140.
[376] M.L. Hegde, C.A. Theriot, A. Das, P.M. Hegde, Z. Guo, R.K. Gary, T.K. Hazra, B. Shen, S. Mitra, Physical and functional interaction between human oxidized base-specific DNA glycosylase NEIL1 and flap endonuclease 1, J. Biol. Chem. 283 (2008) 27028–27037.
[377] A.K. Maiti, I. Boldogh, H. Spratt, S. Mitra, T.K. Hazra, Mutator phenotype of mammalian cells due to deficiency of NEIL1 DNA glycosylase, an oxidized base-specific repair enzyme, DNA Repair (Amst.) 7 (2008) 1213–1220.
[378] C.A. Theriot, M.L. Hegde, T.K. Hazra, S. Mitra, RPA physically interacts with the human DNA glycosylase NEIL1 to regulate excision of oxidative DNA base damage in primer-template structures, DNA Repair (Amst.) 9 (2010) 643–652.
[379] S. Doublie, V. Bandaru, J.P. Bond, S.S. Wallace, The crystal structure of human endonuclease VIII-like 1 (NEIL1) reveals a zincless finger motif required for glycosylase activity, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 10284–10289.
[380] M. Takao, S. Kanno, K. Kobayashi, Q.M. Zhang, S. Yonei, G.T. van der Horst, A. Yasui, A back-up glycosylase in Nth1 knock-out mice is a functional Nei (endonuclease VIII) homologue, J. Biol. Chem. 277 (2002) 42205–42213.
[381] T.A. Rosenquist, E. zaika, A.S. Fernandes, D.O. Zharkov, H. Miller, A.P. Grollman, The novel DNA glycosylase, NEIL1, protects mammalian cells from radiation-mediated cell death, DNA Repair (Amst.) 2 (2003) 581–591.
[382] P. Jaruga, M. Birincioglu, T.A. Rosenquist, M. Dizdaroglu, Mouse NEIL1 protein is specific for excision of 2,6-diamino-4-hydroxy-5-formamidopyrimidine and 4,6-diamino-5-formamidopyrimidine from oxidatively damaged DNA, Biochemistry 43 (2004) 15909–15914.
[383] L.M. Roy, P. Jaruga, T.G. Wood, A.K. McCullough, M. Dizdaroglu, R.S. Lloyd, Human polymorphic variants of the NEIL1 DNA glycosylase, J. Biol. Chem. 282 (2007) 15790–15798.
[384] M. Muftuoglu, N.C. de Souza-Pinto, A. Dogan, M. Aamann, T. Stevnsner, I. Rybanska, G. Kirkali, M. Dizdaroglu, V.A. Bohr, Cockayne syndrome group B protein stimulates repair of formamidopyrimidines by NEIL1 DNA glycosylase, J. Biol. Chem. 284 (2009) 9270–9279.
[385] P. Jaruga, Y. Xiao, V. Vartanian, R.S. Lloyd, M. Dizdaroglu, Evidence for the involvement of DNA repair enzyme NEIL1 in nucleotide excision repair of (5'R)- and (5'S)-8, 5'-cyclo-2'-deoxyadenosines, Biochemistry 49 (2010) 1053–1055.
[386] N. Krishnamurthy, X. Zhao, C.J. Burrows, S.S. David, Superior removal of hydantoin lesions relative to other oxidized bases by the human DNA glycosylase hNEIL1, Biochemistry 47 (2008) 7137–7146.

[387] X. Zhao, N. Krishnamurthy, C.J. Burrows, S.S. David, Mutation versus repair: NEIL1 removal of hydantoin lesions in single-stranded, bulge, bubble, and duplex DNA contexts, Biochemistry 49 (2010) 1658–1666.
[388] J. Zhou, M. Liu, A.M. Fleming, C.J. Burrows, S.S. Wallace, Neil3 and NEIL1 DNA glycosylases remove oxidative damages from quadruplex DNA and exhibit preferences for lesions in the telomeric sequence context, J. Biol. Chem. 288 (2013) 27263–27272.
[389] J. Zhou, A.M. Fleming, A.M. Averill, C.J. Burrows, S.S. Wallace, The NEIL glycosylases remove oxidized guanine lesions from telomeric and promoter quadruplex DNA structures, Nucleic Acids Res. 43 (2015) 7171.
[390] S. Couve-Privat, G. Mace, F. Rosselli, M.K. Saparbaev, Psoralen-induced DNA adducts are substrates for the base excision repair pathway in human cells, Nucleic Acids Res. 35 (2007) 5672–5682.
[391] S. Couve, G. Mace-Aime, F. Rosselli, M.K. Saparbaev, The human oxidative DNA glycosylase NEIL1 excises psoralen-induced interstrand DNA cross-links in a three-stranded DNA structure, J. Biol. Chem. 284 (2009) 11963–11970.
[392] A. Prakash, B.L. Carroll, J.B. Sweasy, S.S. Wallace, S. Doublie, Genome and cancer single nucleotide polymorphisms of the human NEIL1 DNA glycosylase: activity, structure, and the effect of editing, DNA Repair (Amst.) 14 (2014) 17–26.
[393] A.R. Dallosso, S. Dolwani, N. Jones, S. Jones, J. Colley, J. Maynard, S. Idziaszczyk, V. Humphreys, J. Arnold, A. Donaldson, D. Eccles, A. Ellis, D.G. Evans, I.M. Frayling, F.J. Hes, R.S. Houlston, E.R. Maher, M. Nielsen, S. Parry, E. Tyler, V. Moskvina, J.P. Cheadle, J.R. Sampson, Inherited predisposition to colorectal adenomas caused by multiple rare alleles of MUTYH but not OGG1, NUDT1, NTH1 or NEIL 1, 2 or 3, Gut 57 (2008) 1252–1255.
[394] M. Forsbring, E.S. Vik, B. Dalhus, T.H. Karlsen, A. Bergquist, E. Schrumpf, M. Bjoras, K.M. Boberg, I. Alseth, Catalytically impaired hMYH and NEIL1 mutant proteins identified in patients with primary sclerosing cholangitis and cholangiocarcinoma, Carcinogenesis 30 (2009) 1147–1154.
[395] J. Yeo, R.A. Goodman, N.T. Schirle, S.S. David, P.A. Beal, RNA editing changes the lesion specificity for the DNA repair enzyme NEIL1, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 20715–20719.
[396] V. Vartanian, B. Lowell, I.G. Minko, T.G. Wood, J.D. Ceci, S. George, S.W. Ballinger, C.L. Corless, A.K. McCullough, R.S. Lloyd, The metabolic syndrome resulting from a knockout of the NEIL1 DNA glycosylase, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 1864–1869.
[397] H. Mori, R. Ouchida, A. Hijikata, H. Kitamura, O. Ohara, Y. Li, X. Gao, A. Yasui, R. S. Lloyd, J.Y. Wang, Deficiency of the oxidative damage-specific DNA glycosylase NEIL1 leads to reduced germinal center B cell expansion, DNA Repair (Amst.) 8 (2009) 1328–1332.
[398] H. Sampath, A.K. Batra, V. Vartanian, J.R. Carmical, D. Prusak, I.B. King, B. Lowell, L.F. Earley, T.G. Wood, D.L. Marks, A.K. McCullough, R.S. Lloyd, Variable penetrance of metabolic phenotypes and development of high-fat diet-induced adiposity in NEIL1-deficient mice, Am. J. Physiol. Endocrinol. Metab. 300 (2011) E724–E734.
[399] K. Shinmura, H. Tao, M. Goto, H. Igarashi, T. Taniguchi, M. Maekawa, T. Takezaki, H. Sugimura, Inactivating mutations of the human base excision repair gene NEIL1 in gastric cancer, Carcinogenesis 25 (2004) 2311–2317.
[400] P. Broderick, T. Bagratuni, J. Vijayakrishnan, S. Lubbe, I. Chandler, R.S. Houlston, Evaluation of NTHL1, NEIL1, NEIL2, MPG, TDG, UNG and SMUG1 genes in familial colorectal cancer predisposition, BMC Cancer 6 (243) (2006).
[401] G. Kirkali, N.C. de Souza-Pinto, P. Jaruga, V.A. Bohr, M. Dizdaroglu, Accumulation of (5'S)-8,5'-cyclo-2'-deoxyadenosine in organs of Cockayne syndrome complementation group B gene knockout mice, DNA Repair (Amst.) 8 (2009) 274–278.
[402] S.K. Mokkapati, L. Wiederhold, T.K. Hazra, S. Mitra, Stimulation of DNA glycosylase activity of OGG1 by NEIL1: functional collaboration between two human DNA glycosylases, Biochemistry 43 (2004) 11596–11604.
[403] A. Das, I. Boldogh, J.W. Lee, J.A. Harrigan, M.L. Hegde, J. Piotrowski, P.N. de Souza, W. Ramos, M.M. Greenberg, T.K. Hazra, S. Mitra, V.A. Bohr, The human Werner syndrome protein stimulates repair of oxidative DNA base damage by the DNA glycosylase NEIL1, J. Biol. Chem. 282 (2007) 26591–26602.
[404] M.L. Hegde, P.M. Hegde, D. Arijit, I. Boldogh, S. Mitra, Human DNA glycosylase NEIL1's interactions with downstream repair proteins is critical for efficient repair of oxidized DNA base damage and enhanced cell survival, Biomolecules 2 (2012) 564–578.
[405] M.L. Hegde, S. Banerjee, P.M. Hegde, L.J. Bellot, T.K. Hazra, I. Boldogh, S. Mitra, Enhancement of NEIL1 protein-initiated oxidized DNA base excision repair by heterogeneous nuclear ribonucleoprotein U (hnRNP-U) via direct interaction, J. Biol. Chem. 287 (2012) 34202–34211.
[406] M.L. Hegde, P.M. Hegde, L.J. Bellot, S.M. Mandal, T.K. Hazra, G.M. Li, I. Boldogh, A.E. Tomkinson, S. Mitra, Prereplicative repair of oxidized bases in the human genome is mediated by NEIL1 DNA glycosylase together with replication proteins, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) E3090–3099.
[407] P.M. Hegde, A. Dutta, S. Sengupta, J. Mitra, S. Adhikari, A.E. Tomkinson, G.M. Li, I. Boldogh, T.K. Hazra, S. Mitra, M.L. Hegde, The C-terminal domain (CTD) of human DNA glycosylase NEIL1 is required for forming BERosome repair complex with DNA replication proteins at the replicating genome: DOMINANT NEGATIVE FUNCTION OF THE CTD, J. Biol. Chem. 290 (2015) 20919–20933.
[408] H. Dou, S. Mitra, T.K. Hazra, Repair of oxidized bases in DNA bubble structures by human DNA glycosylases NEIL1 and NEIL2, J. Biol. Chem. 278 (2003) 49679–49684.
[409] S.M. Mandal, M.L. Hegde, A. Chatterjee, P.M. Hegde, B. Szczesny, D. Banerjee, I. Boldogh, R. Gao, M. Falkenberg, C.M. Gustafsson, P.S. Sarkar, T.K. Hazra, Role of human DNA glycosylase Nei-like 2 (NEIL2) and single strand break repair protein polynucleotide kinase 3'-phosphatase in maintenance of mitochondrial genome, J. Biol. Chem. 287 (2012) 2819–2829.
[410] D. Banerjee, S.M. Mandal, A. Das, M.L. Hegde, S. Das, K.K. Bhakat, I. Boldogh, P. S. Sarkar, S. Mitra, T.K. Hazra, Preferential repair of oxidized base damage in the transcribed genes of mammalian cells, J. Biol. Chem. 286 (2011) 6006–6016.
[411] A. Chakraborty, M. Wakamiya, T. Venkova-Canova, R.K. Pandita, L. Aguilera-Aguirre, A.H. Sarker, D.K. Singh, K. Hosoki, T.G. Wood, G. Sharma, V. Cardenas, P.S. Sarkar, S. Sur, T.K. Pandita, I. Boldogh, T.K. Hazra, Neil2-null mice accumulate oxidized DNA bases in the transcriptionally active sequences of the genome and are susceptible to innate inflammation, J. Biol. Chem. 290 (2015) 24636–24648.
[412] S. Dey, A.K. Maiti, M.L. Hegde, P.M. Hegde, I. Boldogh, P.S. Sarkar, S.Z. Abdel-Rahman, A.H. Sarker, B. Hang, J. Xie, A.E. Tomkinson, M. Zhou, B. Shen, G. Wang, C. Wu, D. Yu, D. Lin, V. Cardenas, T.K. Hazra, Increased risk of lung cancer associated with a functionally impaired polymorphic variant of the human DNA glycosylase NEIL2, DNA Repair (Amst.) 11 (2012) 570–578.
[413] S.Z. Krokeide, N. Bolstad, J.K. Laerdahl, M. Bjoras, L. Luna, Expression and purification of NEIL3, a human DNA glycosylase homolog, Protein Expr. Purif. 65 (2009) 160–164.
[414] M. Liu, V. Bandaru, A. Holmes, A.M. Averill, W. Cannan, S.S. Wallace, Expression and purification of active mouse and human NEIL3 proteins, Protein Expr. Purif. 84 (2012) 130–139.
[415] M. Liu, K. Imamura, A.M. Averill, S.S. Wallace, S. Doublie, Structural characterization of a mouse ortholog of human NEIL3 with a marked preference for single-stranded DNA, Structure 21 (2013) 247–256.
[416] S.Z. Krokeide, J.K. Laerdahl, M. Salah, L. Luna, F.H. Cederkvist, A.M. Fleming, C. J. Burrows, B. Dalhus, M. Bjoras, Human NEIL3 is mainly a monofunctional DNA glycosylase removing spiroimindiohydantoin and guanidinohydantoin, DNA Repair (Amst.) 12 (2013) 1159–1164.
[417] K. Torisu, D. Tsuchimoto, Y. Ohnishi, Y. Nakabeppu, Hematopoietic tissue-specific expression of mouse Neil3 for endonuclease VIII-like protein, J. Biochem. 138 (2005) 763–772.
[418] M. Takao, Y. Oohata, K. Kitadokoro, K. Kobayashi, S. Iwai, A. Yasui, S. Yonei, Q. M. Zhang, Human Nei-like protein NEIL3 has AP lyase activity specific for single-stranded DNA and confers oxidative stress resistance in Escherichia coli mutant, Genes Cells 14 (2009) 261–270.
[419] V. Rolseth, S.Z. Krokeide, D. Kunke, C.G. Neurauter, R. Suganthan, Y. Sejersted, G.A. Hildrestrand, M. Bjoras, L. Luna, Loss of Neil3, the major DNA glycosylase activity for removal of hydantoins in single stranded DNA, reduces cellular proliferation and sensitizes cells to genotoxic stress, Biochim. Biophys. Acta 1833 (2013) 1157–1164.
[420] A. Kauffmann, F. Rosselli, V. Lazar, V. Winnepenninckx, A. Mansuet-Lupo, P. Dessen, J.J. Van den Oord, A. Spatz, A. Sarasin, High expression of DNA repair pathways is associated with metastasis in melanoma patients, Oncogene 27 (2008) 565–573.
[421] C.G. Neurauter, L. Luna, M. Bjoras, Release from quiescence stimulates the expression of human NEIL3 under the control of the Ras dependent ERK-MAP kinase pathway, DNA Repair (Amst.) 11 (2012) 401–409.
[422] G.A. Hildrestrand, C.G. Neurauter, D.B. Diep, C.G. Castellanos, S. Krauss, M. Bjoras, L. Luna, Expression patterns of Neil3 during embryonic brain development and neoplasia, BMC. Neurosci. 10 (2009) 45.
[423] L. Serre, S. d.J. Pereira, Boiteux, C. Zelwer, B. Castaing, Crystal structure of the Lactococcus lactis formamidopyrimidine-DNA glycosylase bound to an abasic site analogue-containing DNA, EMBO J. 21 (2002) 2854–2865.
[424] K. Shinmura, H. Kato, Y. Kawanishi, H. Igarashi, M. Goto, H. Tao, Y. Inoue, S. Nakamura, K. Misawa, H. Mineta, H. Sugimura, Abnormal expressions of DNA glycosylase genes NEIL1, NEIL2, and NEIL3 are associated with somatic mutation loads in human cancer, Oxid. Med. Cell Longev. 2016 (1546392) (2016).
[425] M.J. Massaad, J. Zhou, D. Tsuchimoto, J. Chou, H. Jabara, E. Janssen, S. Glauzy, B. G. Olson, H. Morbach, T.K. Ohsumi, K. Schmitz, M. Kyriacos, J. Kane, K. Torisu, Y. Nakabeppu, L.D. Notarangelo, E. Chouery, A. Megarbane, P.B. Kang, E. Al-Idrissi, H. Aldhekri, E. Meffre, M. Mizui, G.C. Tsokos, J.P. Manis, W. Al-Herz, S.S. Wallace, R.S. Geha, Deficiency of base excision repair enzyme NEIL3 drives increased predisposition to autoimmunity, J. Clin. Invest. 126 (2016) 4219–4236.
[426] I. Talhaoui, V. Shafirovich, Z. Liu, C. Saint-Pierre, Z. Akishev, B.T. Matkarimov, D. Gasparutto, N.E. Geacintov, M. Saparbaev, Oxidatively generated guanine (C8)-Thymine(N3) intrastrand cross-links in double-stranded DNA are repaired by base excision repair pathways, J. Biol. Chem. 290 (2015) 14610–14617.
[427] Y. Jiang, H. Hong, H. Cao, Y. Wang, In vivo formation and in vitro replication of a guanine-thymine intrastrand cross-link lesion, Biochemistry 46 (2007) 12757–12763.
[428] H. Hong, H. Cao, Y. Wang, Formation and genotoxicity of a guanine-cytosine intrastrand cross-link lesion in vivo, Nucleic Acids Res. 35 (2007) 7118–7127.
[429] G.S. Madugundu, J.R. Wagner, J. Cadet, K. Kropachev, B.H. Yun, N.E. Geacintov, V. Shafirovich, Generation of guanine-thymine cross-links in human cells by one-electron oxidation mechanisms, Chem. Res. Toxicol. 26 (2013) 1031–1033.

[430] D. Pittet, R.P. Wenzel, Nosocomial bloodstream infections. Secular trends in rates, mortality, and contribution to total hospital deaths, Arch. Intern. Med 155 (1995) 1177–1184.
[431] M. Glick, M.A. Siegel, Viral and fungal infections of the oral cavity in immunocompetent patients, Infect. Dis. Clin. North Am. 13 (1999) 817–831 (vi).
[432] M. Legrand, C.L. Chan, P.A. Jauert, D.T. Kirkpatrick, Analysis of base excision and nucleotide excision repair in Candida albicans, Microbiology 154 (2008) 2446–2456.
[433] Q. Huang, D. Liu, P. Majewski, L.C. Schulte, J.M. Korn, R.A. Young, E.S. Lander, N. Hacohen, The plasticity of dendritic cell responses to pathogens and their components, Science 294 (2001) 870–875.
[434] S.D. Kathe, R. Barrantes-Reynolds, P. Jaruga, M.R. Newton, C.J. Burrows, V. Bandaru, M. Dizdaroglu, J.P. Bond, S.S. Wallace, Plant and fungal Fpg homologs are formamidopyrimidine DNA glycosylases but not 8-oxoguanine DNA glycosylases, DNA Repair (Amst.) 8 (2009) 643–653.
[435] S. Duclos, P. Aller, P. Jaruga, M. Dizdaroglu, S.S. Wallace, S. Doublie, Structural and biochemical studies of a plant formamidopyrimidine-DNA glycosylase reveal why eukaryotic Fpg glycosylases do not excise 8-oxoguanine, DNA Repair (Amst.) 11 (2012) 714–725.
[436] E.H. Radany, E.C. Friedberg, A pyrimidine dimer-DNA glycosylase activity associated with the v gene product of bacteriophage T4, Nature 286 (1980) 182–185.
[437] E.H. Radany, L. Naumovski, J.D. Love, K.A. Gutekunst, D.H. Hall, E.C. Friedberg, Physical mapping and complete nucleotide sequence of the denV gene of bacteriophage T4, J. Virol. 52 (1984) 846–856.
[438] K.A. Latham, R.S. Lloyd, T4 endonuclease V. perspectives on catalysis, Ann. N. Y. Acad. Sci. 726 (1994) 181–196.
[439] R.C. Manuel, K.A. Latham, M.L. Dodson, R.S. Lloyd, Involvement of glutamic acid 23 in the catalytic mechanism of T4 endonuclease V, J. Biol. Chem. 270 (1995) 2652–2661.
[440] M. Dizdaroglu, T.H. Zastawny, J.R. Carmical, R.S. Lloyd, A novel DNA N-glycosylase activity of E. coli T4 endonuclease V that excises 4,6-diamino-5-formamidopyrimidine from DNA, a UV-radiation- and hydroxyl radical-induced product of adenine, Mutat. Res. 362 (1996) 1–8.
[441] P.W. Doetsch, T.H. Zastawny, A.M. Martin, M. Dizdaroglu, Monomeric base damage products from adenine, guanine, and thymine induced by exposure of DNA to ultraviolet radiation, Biochemistry 34 (1995) 737–742.
[442] M. Furuta, J.O. Schrader, H.S. Schrader, T.A. Kokjohn, S. Nyaga, A.K. McCullough, R.S. Lloyd, D.E. Burbank, D. Landstein, L. Lane, J.L. Van Etten, Chlorella virus PBCV-1 encodes a homolog of the bacteriophage T4 UV damage repair gene denV, Appl. Environ. Microbiol. 63 (1997) 1551–1556.
[443] A.K. McCullough, M.T. Romberg, S. Nyaga, Y. Wei, T.G. Wood, J.S. Taylor, J.L. Van Etten, M.L. Dodson, R.S. Lloyd, Characterization of a novel *cis-syn* and *trans-syn*-II pyrimidine dimer glycosylase/AP lyase from a eukaryotic algal virus, Paramecium bursaria chlorella virus-1, J. Biol. Chem. 273 (1998) 13136–13142.
[444] J.F. Garvish, R.S. Lloyd, The catalytic mechanism of a pyrimidine dimer-specific glycosylase (pdg)/abasic lyase, Chlorella virus-pdg, J. Biol. Chem. 274 (1999) 9786–9794.
[445] J.F. Garvish, R.S. Lloyd, Active-site determination of a pyrimidine dimer glycosylase, J. Mol. Biol. 295 (2000) 479–488.
[446] P. Jaruga, R. Jabil, A.K. McCullough, H. Rodriguez, M. Dizdaroglu, R.S. Lloyd, Chlorella virus pyrimidine dimer glycosylase excises ultraviolet radiation- and hydroxyl radical-induced products 4,6-diamino-5-formamidopyrimidine and 2,6-diamino-4-hydroxy-5-formamidopyrimidine from DNA, Photochem. Photobiol. 75 (2002) 85–91.
[447] M. Suzan-Monti, S.B. La, D. Raoult, Genomic and evolutionary aspects of Mimivirus, Virus Res. 117 (2006) 145–155.
[448] V. Bandaru, X. Zhao, M.R. Newton, C.J. Burrows, S.S. Wallace, Human endonuclease VIII-like (NEIL) proteins in the giant DNA mimivirus, DNA Repair (Amst.) 6 (2007) 1629–1641.
[449] K. Imamura, S.S. Wallace, S. Doublie, Structural characterization of a viral NEIL1 ortholog unliganded and bound to abasic site-containing DNA, J. Biol. Chem. 284 (2009) 26174–26183.
[450] K. Imamura, A. Averill, S.S. Wallace, S. Doublie, Structural characterization of viral ortholog of human DNA glycosylase NEIL1 bound to thymine glycol or 5-hydroxyuracil-containing DNA, J. Biol. Chem. 287 (2012) 4288–4298.
[451] A. Prakash, B.E. Eckenroth, A.M. Averill, K. Imamura, S.S. Wallace, S. Doublie, Structural investigation of a viral ortholog of human NEIL2/3 DNA glycosylases, DNA Repair (Amst.) 12 (2013) 1062–1071.
[452] V.V. Koval, N.A. Kuznetsov, D.O. Zharkov, A.A. Ishchenko, K.T. Douglas, G.A. Nevinsky, O.S. Fedorova, Pre-steady-state kinetics shows differences in processing of various DNA lesions by Escherichia coli formamidopyrimidine-DNA glycosylase, Nucleic Acids Res. 32 (2004) 926–935.
[453] O.G. Berg, R.B. Winter, P.H. von Hippel, Diffusion-driven mechanisms of protein translocation on nucleic acids. 1. Models and theory, Biochemistry 20 (1981) 6929–6948.
[454] R.B. Winter, O.G. Berg, P.H. von Hippel, Diffusion-driven mechanisms of protein translocation on nucleic acids. 3. The Escherichia coli lac repressor? operator interaction: kinetic measurements and conclusions, Biochemistry 20 (1981) 6961–6977.
[455] R.B. Winter, P.H. von Hippel, Diffusion-driven mechanisms of protein translocation on nucleic acids. 2. The Escherichia coli repressor–operator interaction: equilibrium measurements, Biochemistry 20 (1981) 6948–6960.
[456] E.I. Zaika, R.A. Perlow, E. Matz, S. Broyde, R. Gilboa, A.P. Grollman, D.O. Zharkov, Substrate discrimination by formamidopyrimidine-DNA glycosylase: a mutational analysis, J. Biol. Chem. 279 (2004) 4849–4861.
[457] G.L. Verdine, S.D. Bruner, How do DNA repair proteins locate damaged bases in the genome? Chem. Biol. 4 (1997) 329–334.
[458] L. Chen, K.A. Haushalter, C.M. Lieber, G.L. Verdine, Direct visualization of a DNA glycosylase searching for damage, Chem. Biol. 9 (2002) 345–350.
[459] D.C. Malins, G.K. Ostrander, R. Haimanot, P. Williams, A novel DNA lesion in neoplastic livers of feral fish: 2,6-diamino-4-hydroxy-5-formamidopyrimidine, Carcinogenesis 11 (1990) 1045–1047.
[460] D.C. Malins, R. Haimanot, 4,6-Diamino-5-formamidopyrimidine, 8-hydroxyguanine and 8-hydroxyadenine in DNA from neoplastic liver of English sole exposed to carcinogens, Biochem. Biophys. Res. Commun. 173 (1990) 614–619.
[461] D.C. Malins, R. Haimanot, Major alterations in the nucleotide structure of DNA in cancer of the female breast, Cancer Res. 51 (1991) 5430–5432.
[462] R. Olinski, T. Zastawny, J. Budzbon, J. Skokowski, W. Zegarski, M. Dizdaroglu, DNA base modifications in chromatin of human cancerous tissues, FEBS Lett. 193 (1992) 198–198.
[463] D.C. Malins, E.H. Holmes, N.L. Polissar, S.J. Gunselman, The etiology of breast cancer: characteristic alterations in hydroxyl radical-induced DNA base lesions during oncogenesis with potential for evaluating incidence risk, Cancer 71 (1993) 3036–3043.
[464] D.C. Malins, Identification of hydroxyl radical-induced lesions in DNA base structure: biomarkers with a putative link to cancer development, J. Toxicol. Environ. Health 40 (1993) 247–261.
[465] P. Jaruga, T.H. Zastawny, J. Skokowski, M. Dizdaroglu, R. Olinski, Oxidative DNA base damage and antioxidant enzyme activities in human lung cancer, FEBS Lett. 341 (1994) 59–64.
[466] S. Sentürker, B. Karahalil, M. Inal, H. Yilmaz, H. Muslumanoglu, G. Gedikoglu, M. Dizdaroglu, Oxidative DNA base damage and antioxidant enzyme levels in childhood acute lymphoblastic leukemia, FEBS Lett. 416 (1997) 286–290.
[467] E. Mambo, S.G. Nyaga, V.A. Bohr, M.K. Evans, Defective repair of 8-hydroxyguanine in mitochondria of MCF-7 and MDA-MB-468 human breast cancer cell lines, Cancer Res. 62 (2002) 1349–1355.
[468] D.C. Malins, P.M. Johnson, E.A. Barker, N.L. Polissar, T.M. Wheeler, K.M. Anderson, Cancer-related changes in prostate DNA as men age and early identification of metastasis in primary prostate tumors, Proc. Natl. Acad. Sci. U. S. A. 100 (2003) 5401–5406.
[469] A.R. Trzeciak, S.G. Nyaga, P. Jaruga, A. Lohani, M. Dizdaroglu, M.K. Evans, Cellular repair of oxidatively induced DNA base lesions is defective in prostate cancer cell lines, PC-3 and DU-145, Carcinogenesis 25 (2004) 1–12.
[470] E. Mambo, A. Chatterjee, N.C. de Souza-Pinto, S. Mayard, B.A. Hogue, M.O. Hoque, M. Dizdaroglu, V.A. Bohr, D. Sidransky, Oxidized guanine lesions and hOgg1 activity in lung cancer, Oncogene 24 (2005) 4496–4508.
[471] D.C. Malins, K.M. Anderson, J.J. Stegeman, P. Jaruga, V.M. Green, N.K. Gilman, M. Dizdaroglu, Biomarkers signal contaminant effects on the organs of English sole (Parophrys vetulus) from Puget Sound, Environ. Health Perspect. 114 (2006) 823–829.
[472] D.C. Malins, K.M. Anderson, P. Jaruga, C.R. Ramsey, N.K. Gilman, V.M. Green, S. W. Rostad, J.T. Emerman, M. Dizdaroglu, Oxidative changes in the DNA of stroma and epithelium from the female breast: potential implications for breast cancer, ABBV Cell Cycle 5 (2006) 1629–1632.
[473] S.G. Nyaga, A. Lohani, P. Jaruga, A.R. Trzeciak, M. Dizdaroglu, M.K. Evans, Reduced repair of 8-hydroxyguanine in the human breast cancer cell line, HCC1937, BMC Cancer 6 (297) (2006).
[474] K.M. Anderson, P. Jaruga, C.R. Ramsey, N.K. Gilman, V.M. Green, S.W. Rostad, J. T. Emerman, M. Dizdaroglu, D.C. Malins, Structural alterations in breast stromal and epithelial DNA: The influence of 8,5'-cyclo-2'-deoxyadenosine, ABBV Cell Cycle 5 (2006) 1240–1244.
[475] H. Rodriguez, P. Jaruga, D. Leber, S.G. Nyaga, M.K. Evans, M. Dizdaroglu, Lymphoblasts of women with BRCA1 mutations are deficient in cellular repair of 8,5'-cyclopurine-2'-deoxynucleosides and 8-hydroxy-2'-deoxyguanosine, Biochemistry 46 (2007) 2488–2496.
[476] S.G. Nyaga, P. Jaruga, A. Lohani, M. Dizdaroglu, M.K. Evans, Accumulation of oxidatively induced DNA damage in human breast cancer cell lines following treatment with hydrogen peroxide, ABBV Cell Cycle 6 (2007) 1472–1478.
[477] S. Madhusudan, M.R. Middleton, The emerging role of DNA repair proteins as predictive, prognostic and therapeutic targets in cancer, Cancer Treat. Rev. 31 (2005) 603–617.
[478] M.R. Kelley, M.L. Fishel, DNA Repair in Cancer Therapy. Molecular Targets and Clinical Applications, Academic Press, Amsterdam, 2016.
[479] M.R. Kelley, Future directions with DNA repair inhibitors: a roadmap for disruptive approaches to cancer therapy, in: M.R. Kelley (Ed.), DNA Repair in Cancer Therapy, Molecular Targets and Clinical Applications, Elsevier, Amsterdam, 2012, pp. 301–310.
[480] C. Perry, R. Sultana, S. Madhusudan, Personalized cancer medicine: DNA repair alterations are promising predictive biomarkers in cancer, in: M.R. Kelley (Ed.), DNA Repair in Cancer Therapy: Molecular Targets and Clinical Applications, Elsevier, Amsterdam, 2012, pp. 257–282.
[481] T. Helleday, E. Petermann, C. Lundin, B. Hodgson, R.A. Sharma, DNA repair pathways as targets for cancer therapy, Nature Rev. Cancer 8 (2008) 193–204.
[482] T. Helleday, Amplifying tumour-specific replication lesions by DNA repair inhibitors – a new era in targeted cancer therapy, Eur. J. Cancer 44 (2008) 921–927.

[483] B.J. Moeller, W. Arap, R. Pasqualini, Targeting synthetic lethality in DNA damage repair pathways as an anti-cancer strategy, Curr. Drug Targets 11 (2010) 1336–1340.
[484] N. Chan, R.G. Bristow, Contextual synthetic lethality and/or loss of heterozygosity: tumor hypoxia and modification of DNA repair, Clin. Cancer Res. 16 (2010) 4553–4560.
[485] J.L. Illuzzi, D.M. Wilson III, Base excision repair: contribution to tumorigenesis and target in anticancer treatment paradigms, Curr. Med. Chem. 19 (2012) 3922–3936.
[486] M.L. Fishel, C. Vascotto, M.R. Kelley, DNA base excision therapeutics: summary of targets with focus on APE1, in: S. Madhusudan, D.M. Wilson III (Eds.), DNA Repair and Cancer From Bench to Clinic, CRC Press, Baco Raton, 2013, pp. 233–287.
[487] N.J. Curtin, PARP and PARP inhibitor therapeutics, in: S. Madhusudan, D.M. Wilson III (Eds.), DNA Repair and Cancer From Bench to Clinic, CRC Press, Baco Raton, 2013, pp. 513–563.
[488] P.T. Reddy, P. Jaruga, B.C. Nelson, M. Lowenthal, M. Dizdaroglu, Stable isotope-labeling of DNA repair proteins, and their purification and characterization, Protein Expr. Purif. 78 (2011) 94–101.
[489] M. Dizdaroglu, P.T. Reddy, P. Jaruga, Identification and quantification of DNA repair proteins by liquid chromatography/isotope-dilution tandem mass spectrometry using their fully ^{15}N-labeled analogues as internal standards, J. Proteome. Res. 10 (2011) 3802–3813.
[490] G. Kirkali, P. Jaruga, P.T. Reddy, A. Tona, B.C. Nelson, M. Li, D.M. Wilson III, M. Dizdaroglu, Identification and quantification of DNA repair protein apurinic/apyrimidinic endonuclease 1 (APE1) in human cells by liquid chromatography/isotope-dilution tandem mass spectrometry, PLoS One 8 (2013) e69894.
[491] E. Coskun, P. Jaruga, P.T. Reddy, M. Dizdaroglu, Extreme expression of DNA repair protein apurinic/apyrimidinic endonuclease 1 (APE1) in human breast cancer as measured by liquid chromatography and isotope dilution tandem mass spectrometry, Biochemistry 54 (2015) 5787–5790.
[492] P.T. Reddy, P. Jaruga, B.C. Nelson, M.S. Lowenthal, A.S. Jemth, O. Loseva, E. Coskun, T. Helleday, M. Dizdaroglu, Production, purification, and characterization of ^{15}N-Labeled DNA repair proteins as internal standards for mass spectrometric measurements, Methods Enzymol. 566 (2016) 305–332.
[493] E. Coskun, P. Jaruga, A.S. Jemth, O. Loseva, L.D. Scanlan, A. Tona, M.S. Lowenthal, T. Helleday, M. Dizdaroglu, Addiction to MTH1 protein results in intense expression in human breast cancer tissue as measured by liquid chromatography-isotope-dilution tandem mass spectrometry, DNA Repair (Amst.) 33 (2015) 101–110.
[494] S. Madhusudan, D.M. Wilson III, DNA Repair and Cancer. From Bench to Clinic, CRC Press, Baco Raton, 2013.
[495] R.D. Kennedy, C.C. Chen, P. Stuckert, E.M. Archila, M.A. De la Vega, L.A. Moreau, A. Shimamura, A.D. D'Andrea, Fanconi anemia pathway-deficient tumor cells are hypersensitive to inhibition of ataxia telangiectasia mutated, J. Clin. Invest. 117 (2007) 1440–1449.
[496] L. Taricani, F. Shanahan, R.H. Pierce, T.J. Guzi, D. Parry, Phenotypic enhancement of thymidylate synthetase pathway inhibitors following ablation of Neil1 DNA glycosylase/lyase, ABBV Cell Cycle 9 (2010) 4876–4883.