Cell. Mol. Life Sci. 65 (2008) 1544 – 1565
1420-682X/08/101544-22
DOI 10.1007/s00018-008-7543-2

Cellular and Molecular Life Sciences

Review

Base excision DNA repair

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Received 27 November 2007; received after revision 9 January 2008; accepted 18 January 2008
Online First 9 February 2008

Abstract. DNA repair is a collection of several multienzyme, multistep processes keeping the cellular genome intact against genotoxic insults. One of these processes is base excision repair, which deals with the most ubiquitous lesions in DNA: oxidative base damage, alkylation, deamination, sites of base loss and single-strand breaks, *etc.* Individual enzymes acting in base excision repair have been identified. The recent years were marked with many advances in understanding of their structure and many interactions that make base excision repair a functional, versatile system. This review describes the current knowledge of structural biology and biochemistry of individual steps of base excision repair, several subpathways of the common base excision repair pathway, and interactions of the repair process with other cellular processes.

Keywords. DNA damage, DNA repair, DNA glycosylase, AP endonuclease, DNA polymerase, DNA ligase.

DNA damage and repair: An introduction

The integrity of the genome of any living organism on Earth is under continuous threat from exogenous and endogenous agents that attack and damage nucleic acids. The offending factors include ultraviolet light, ionizing radiation, xenobiotic chemicals, water environment, and the cell's own metabolites such as activated oxygen or methyl group carriers ([1, 2] and references therein). Multiple systems of damage repair and tolerance thus have evolved, whose proper functioning is critical for survival and prevention of mutagenesis.

Currently, there is no unified estimate of either absolute or relative amounts of different DNA lesions. Small deoxynucleotide (dN) lesions are likely the most widespread type of damage [3]. Such lesions result from several chemical processes. Base deamination produces uracil (Ura) from cytosine; purine dNs are prone to spontaneous hydrolysis of their *N*-glycosidic bond, resulting in abasic (apurinic/apyrimidinic, AP) sites; oxidation of DNA can lead to formation of many modified nucleobases; ring nitrogens and exocyclic groups of nucleobases are sites of electrophilic addition, *etc.* As an example of the incidence of small lesions in mammalian cells, 8-oxo-7,8-dihydroguanine (8-oxoGua), one of the most abundant oxidatively damaged bases, is found at the frequency of $1/10^6$ Gua bases [4]. Other types of damage, such as DNA adducts with large organic moieties, are less common but their level may be significantly elevated by environmental factors [5].

There are six broadly defined pathways of DNA repair (reviewed in [1]). First, several unrelated processes eliminate lesions in DNA but do not involve excision and re-synthesis of a part of DNA; for this reason these processes (visible light-dependent splitting of cyclobutane pyrimidine dimers by photolyases, base dealkylation by specific suicide alkyltransferases, oxidative dealkylation of ring *N*-alkylated nucleobases by DNA repair oxygenases, and direct ligation of DNA single-strand breaks with unmodified termini)

are usually referred to as 'direct reversal'. All other DNA repair processes involve degradation of at least the damaged nucleotide followed by DNA re-synthesis. The second mechanism of DNA repair is 'nucleotide excision repair', which removes bulky helix-distorting lesions (*e.g.*, adducts of many xenobiotics to DNA bases). 'Mismatch repair' corrects errors made by DNA polymerases during replication, excising canonical nucleotides incorporated into mismatches, as well as small insertion/deletion loops, from the daughter DNA strand. 'Non-homologous end-joining' seals double-strand breaks after partial degradation of frayed ends, whereas 'recombination repair' also participates in correction of double-strand breaks as well as of lesions that cannot be resolved by other ways. This review is devoted to the sixth type of DNA repair, 'base excision repair' (BER), which predominantly deals with non-bulky, mostly nucleobase lesions that are generated in abundance by tens of thousands every day in each cell.

Base excision repair: BER essentials

BER is initiated with excision of the damaged base by one of the dedicated enzymes, DNA glycosylases (detailed reviews are available in [6–8]), which catalyze hydrolysis of the *N*-glycosidic bond of the damaged deoxynucleoside (Fig. 1). The removal of lesions as free bases distinguishes BER from all other types of repair, involving other enzymes that remove lesions (if at all) as dNMPs or short oligonucleotides. Base-containing damaged dN is thus converted into an intermediate product of BER, an AP site, which is a substrate for AP endonucleases. These enzymes hydrolyze the phosphodiester bond immediately 5′ to the AP site (Fig. 1). Some DNA glycosylases ("AP lyases" or "bifunctional DNA glycosylases") are also capable of cleaving AP sites but do it by elimination of its 3′-phosphate (β-elimination). This difference defines the first branching point of BER: AP endonucleases produce 3′ termini that can serve as substrates for DNA polymerases but the 5′-ends harbor the fragment of the damaged dN and must be trimmed before the repair is complete, whereas AP lyases produce unmodified 5′-ends and blocked 3′-ends. Some DNA glycosylases catalyze two consecutive elimination steps (β,δ-elimination), producing a single-nucleotide gap flanked by phosphates, in which case the 3′-terminal phosphate must also be removed (Fig. 1).

Trimming of the modified ends is carried out by different enzymes depending on whether the abasic sugar fragment is removed from the 5′ or 3′ terminus. The hanging 5′-abasic dNMP (2'-deoxyribo-5′-phosphate, dRP) can be excised *via* β-elimination by a dRP lyase. The 3′-abasic unsaturated product of AP lyases is hydrolyzed by AP endonucleases. The 3'-phosphate produced by β,δ-elimination is removed by the bacterial AP endonucleases Xth or Nfo (reviewed in [9]) or polynucleotide kinase in mammals [10] (Fig. 1). The gap that appears in DNA after the three-step excision of the damaged dN is then filled by a DNA polymerase. The repair synthesis step is where BER again branches in two major sub-pathways, single-nucleotide-patch BER (SP-BER) and long-patch BER (LP-BER, Fig. 1). In the former case, a single dNMP is incorporated into DNA, and the nick in DNA is sealed by a DNA ligase. In the latter branch, the newly synthesized, more extensive patch (2–20 dNMPs [11, 12]) displaces a stretch of old DNA into a flap structure, which is then processed by a flap endonuclease. The result is also a nick in DNA, followed by ligation.

This outline of basic enzymatic processes occurring during BER is encumbered by a multitude of details, enabling exquisite tuning of the whole process to the cell's needs. The proteins involved in BER in bacteria, yeast and humans are listed in Table 1.

Major BER enzymes

Most of the BER enzymes had been characterized by the early 1990 s. In the past decade, three-dimensional structures became available for a number of them, providing an insight into mechanisms of lesion recognition and catalysis (Fig. 2). In this section, major BER enzymes are described in more detail, with an emphasis on the recently obtained structural information.

DNA glycosylases

DNA glycosylases initiate BER in most cases if the damaged dN still contains a base. Any biological species possesses several different DNA glycosylases, some of which have rather broad substrate specificities (*e.g.*, endonuclease III from *E. coli*, removing many oxidized pyrimidines), while others are much more narrow in this respect (*e.g.*, ultraviolet endonuclease from *Micrococcus luteus*, specific for *cis-syn* isomer of cyclobutane pyrimidine dimers only). A steady flow of structural data in the past decade (generally summarized in [13, 14]) led to an emergence of a view of DNA glycosylases as proteins that may have very similar folds yet entirely disparate substrate specificities due to intricate differences in the active site organization. Currently, most DNA glycosylases can be grouped into three main superfamilies, each superfamily organized around one or

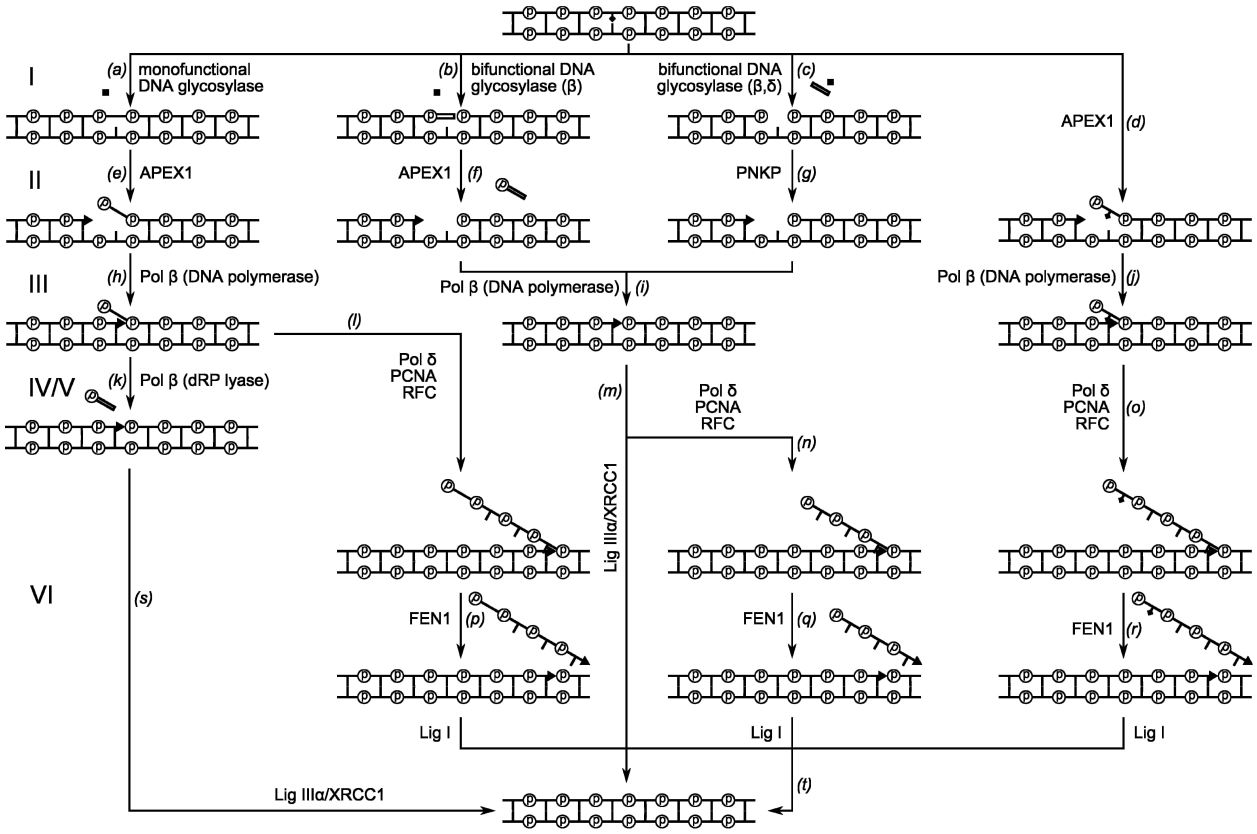

Figure 1. General scheme of base excision repair (BER) in mammalian cells. Damaged base can be excised (stage I) by a monofunctional DNA glycosylase (arrow *a*; UNG, TDG, SMUG1, MBD4, MPG, or MUTYH), a bifunctional DNA glycosylase catalyzing β-elimination (*b*; OGG1, NTHL1), or a bifunctional DNA glycosylase catalyzing β,δ-elimination (*c*; NEIL1, NEIL2, and possibly NEIL3). The extendable 3′ terminus is generated (stage II) by nicking of the AP site (*e*) or excision of the unsaturated 3′-terminal aldehyde (*f*) by APEX1, or by dephosphorylation by PNKP (*g*). Alternatively, repair can be initiated by strand incision 5′ to the damaged base (*d*), yielding an extendable 3′ terminus. The first replacing dNMP is inserted (stage III) by Pol β (*h*, *i*, *j*). The dRP is removed (stage IV) by Pol β lyase activity (*k*); alternatively, a flap is displaced (V) by Pol δ/PCNA loaded by RFC (*l*, *n*, *o*), and the flap is removed by FEN1 (*p*, *q*, *r*). The ligation step (VI) is carried out by Lig IIIα/XRCC1 (*m*, *s*) or Lig I (*t*). Classical single-nucleotide-patch BER (SP-BER) goes along the pathway denoted by arrows $a \rightarrow e \rightarrow h \rightarrow k \rightarrow s$ or $b \rightarrow f \rightarrow i \rightarrow m$; classical long-patch BER (LP-BER) is $a \rightarrow e \rightarrow h \rightarrow l \rightarrow p \rightarrow t$ or $b \rightarrow f \rightarrow i \rightarrow n \rightarrow q \rightarrow t$; AP endonuclease-less BER can follow pathways $c \rightarrow g \rightarrow i \rightarrow m$ (SP) or $c \rightarrow g \rightarrow i \rightarrow n \rightarrow q \rightarrow t$ (LP), and nucleotide incision repair (NIR) goes along $d \rightarrow j \rightarrow o \rightarrow r \rightarrow t$. In the DNA schemes, the small black square denotes the damaged base; circled P stands for an internucleoside phosphate; triangle is a free 3'-OH terminus, and a double line denotes an unsaturated sugar fragment.

more core families. The core families are characterized by the presence of conserved folds and motifs that are present in most members of the superfamily but some of which may be lost in the peripheral members.

Uracil-DNA glycosylase superfamily. Uracil-DNA glycosylase superfamily includes at least five groups of enzymes with similar substrate specificities and overall folds. However, their sequence similarity, aside from very short conserved active site motifs, is low. All uracil-DNA glycosylases are organized around a central parallel four-stranded β-sheet sandwiched between at least two α-helices from each side ([13–18] and references therein). Loops connecting these elements carry amino acids that form the active site and the lesion-recognition pocket and bind DNA phosphates.

The most widely distributed members of the superfamily are proper uracil DNA glycosylases (Ung in *E. coli*, Ung1p in yeast, UNG in humans). They excise Ura from both single- and double-stranded DNA and are completely inactive towards canonical pyrimidines in DNA as well as Ura in RNA ([6] and references therein). A characteristic feature of these enzymes is their inhibition by Ugi, a protein encoded by *Bacillus*-infecting bacteriophages containing uracil instead of thymine in DNA (reviewed in [19]). Ung and all other uracil-DNA glycosylases do not produce breaks in DNA after base excision (reviewed in [1, 6]). In contrast to Ung/UNG, which excise Ura paired to any canonical base, the second family includes glycosylases (Mug in bacteria, TDG in eukaryotes) exclusively specific for Ura or Thy mismatched with Gua ([6, 16, 20] and references therein). In addition, these

Table 1. Proteins involved in different steps of BER in *E. coli*, budding yeast and human cells.

	E. coli	*S. cerevisiae*	*H. sapiens*
DNA glycosylases			
Uracil-DNA glycosylase superfamily	Ung	Ung1p	UNG
	Mug		TDG
			SMUG1
Nth superfamily	Nth	Ntg1p, Ntg2p	NTHL1
	MutY		MUTYH
		Ogg1p	OGG1
	AlkA	Mag1p	
			MBD4
	Tag		
Fpg superfamily	Fpg, Nei		NEIL1, NEIL2, NEIL3
Others			MPG
AP endonucleases			
Xth family	Xth	Apn2p	APEX1, APEX2
Nfo family	Nfo	Apn1p	
PALF family			PALF
DNA polymerases[a]			
Family A	Pol I	Pol γ	Pol γ
Family B		Pol δ, Pol α (?), Pol ε (?)	Pol δ, Pol ε, Pol α(?), Pol ζ(?)
Family X			Pol β, Pol λ
DNA ligases			
NAD^+-dependent	LigA		
ATP-dependent		Cdc9p	Lig I, Lig IIIα
Other proteins			
Flap endonuclease		Rad27p	FEN1
3′-phosphodiesterase		Rad1p–Rad10p, Mus81p–Mms4p	
XRCC1			XRCC1
PARP			PARP1
PCNA[a]		Pol30p	PCNA
9–1–1 complex[a]		Ddc1p–Rad17p–Mec3p	RAD9B–RAD1–HUS1
RFC[a]		RFC	RFC

[a] RFC, 9–1–1 and many DNA polymerases are heterooligomeric proteins; individual subunits of DNA polymerases and RFC are not listed for brevity. PCNA is a homotrimer.

enzymes are primary glycosylases for removal of 3,N^4-ethenocytosine from DNA in both bacteria and humans [21].

The third family, SMUG1 proteins, has been so far characterized from eukaryotes only (reviewed in [16, 22]). These enzymes have been initially described as specific for Ura in single-stranded DNA, but later double-stranded substrates were found to be preferred if AP endonuclease is present to stimulate the turnover of the enzyme (see *Stimulation of DNA glycosylases by other proteins* below) [17, 22]. SMUG1 also excises 5-hydroxymethyluracil, 5-formyluracil and 5-hydroxyuracil from DNA [23].

Other families of uracil-DNA glycosylases are known only from a handful of bacterial and archaeal species. Family IV uracil-DNA glycosylases differ from all other members of the superfamily in that they possess an iron–sulfur (FeS) cluster. Both these and family V uracil-DNA glycosylases remove Ura from all DNA contexts, and family V enzymes are also capable of

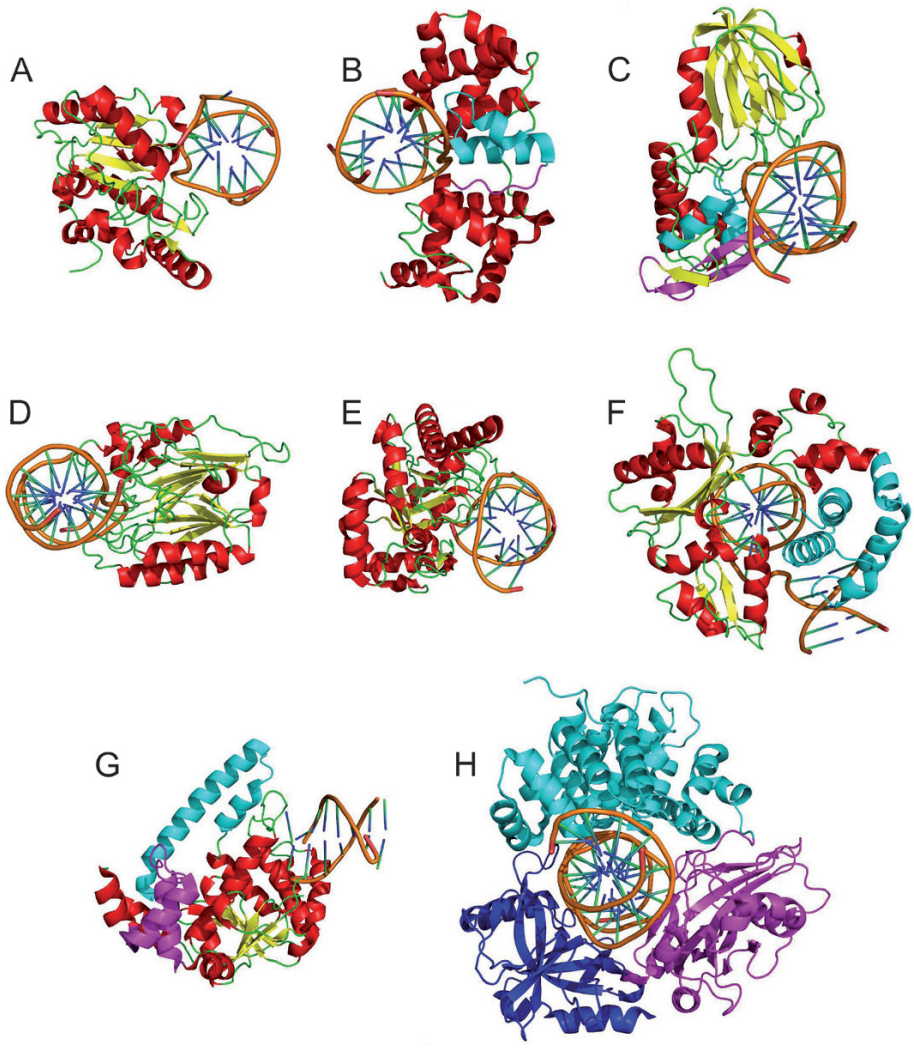

Figure 2. Three-dimensional structures of the core members of the different BER protein families. Unless otherwise noted, α-helices are colored red, β-sheets, yellow, and loops, green; DNA backbone is shown schematically as an orange tube, and bases, as green/blue spikes. DNA glycosylases: (*A*) human uracil-DNA glycosylase (Protein Data Bank code 1EMH [270]); (*B*) Nth from *Bacillus stearothermophilus* (1ORN, [271]), the HhH motif is shown in cyan, and the GPD motif, in magenta; (*C*) Fpg from *E. coli* (1K82, [272]), the helix-two-turn-helix motif is shown in cyan, and the zinc finger, in magenta. AP endonucleases: (*D*) human APEX1 (1DEW, [273]); (*E*) Nfo from *E. coli* (1QUM, [274]). DNA polymerases: (*F*) human Pol β (1BPY, [275]), the N-terminal dRP lyase domain is shown in cyan. Flap endonucleases: (*G*) FEN1 from *Archaeoglobus fulgidus* (1RXW, [70]), the arching loop is shown in cyan, and the helix–three turn-helix motif, in magenta. DNA ligases: (*H*) human Lig I (1X9N, [76]), the DNA-binding domain is shown in cyan, the adenylation domain, in magenta, and the oligonucleotide-binding fold domain, in blue.

excising hypoxanthine, 5-hydroxymethyluracil, and 1,N^4-ethenocytosine [1, 24].

The structures of human UNG bound to damaged DNA (reviewed in [13, 15]) reveal several features strikingly conserved among nearly all DNA glycosylases regardless of the superfamily to which they belong. DNA is bound in a positively charged groove on the surface of the protein; in uracil-DNA glycosylases, the groove is rather narrow and shallow, while in other DNA glycosylases it may divide the protein into two well-defined domains (see *Fpg/Nei superfamily* and *Nth superfamily* below). The enzyme binds DNA in the minor groove. The DNA molecule is sharply kinked at the site of the lesion, and the damaged dN is everted from the double helix and inserted in an active site pocket in the DNA-binding groove of the enzyme.

Fpg/Nei superfamily. The Fpg/Nei superfamily is defined by two homologous *E. coli* enzymes, formamidopyrimidine-DNA glycosylase (Fpg) and endonuclease VIII (Nei) ([25] and references therein). Both are bifunctional DNA glycosylases possessing β,δ-elimination activity. The crystal structures reveal that they consist of two domains connected by a flexible linker [25]; the N-terminal domain is organized around a two-sheet β-sandwich, and the C-terminal domain includes two DNA-binding motifs: a helix–two-turn–helix motif and a zinc finger motif. Several eukaryotic proteins show homology to Fpg and Nei, but may lack some of these conserved motifs or have additional domains. Vertebrate genomes encode three such homologues, NEIL1–NEIL3 [26, 27]. Whereas NEIL2 has all conserved motifs, NEIL1 lacks the Cys residues coordinating Zn^{2+} in the zinc finger. However, the structure of NEIL1 shows a "zinc-less finger", a β-hairpin virtually indistinguishable from a zinc finger [28]. NEIL3, in addition to all conserved elements, has a C-terminal extension

that carries a RanBP-type zinc finger and a topoisomerase IIIα homology domain.

The function of Fpg/Nei enzymes is repair of oxidative DNA lesions. Fpg is the main enzyme in *E. coli* that excises 8-oxoGua and formamidopyrimidine derivatives of Gua and Ade, whereas Nei is specific mainly for oxidized pyrimidines. Overall, Fpg and Nei have been reported to excise ~20 lesions each; however, many of these are likely irrelevant to their biological activity as they are only removed from oligonucleotide substrates but not from damaged genomic DNA ([25, 29] and references therein). NEIL1 efficiently removes oxidized pyrimidines and formamidopyrimidines from DNA [26, 27, 30]. NEIL2 also removes oxidized pyrimidines but has a unique preference for these lesions in bubble structures [31], possibly contributing to transcription-associated repair.

Nth superfamily. The most diverse group of DNA glycosylases is related to endonuclease III (Nth). This enzyme is a bifunctional DNA glycosylase specific for oxidized pyrimidine bases (reviewed in [6, 29]). Like Fpg/Nei enzymes, Nth also consists of two well-defined domains but its organization is entirely different ([13, 14] and references therein). One domain is a six-helix barrel containing a helix–hairpin–helix (HhH) motif, found in many DNA-dependent enzymes, followed by a loop rich in Gly and Pro residues with an absolutely conserved Asp residue (GPD motif). The other domain contains a FeS cluster, whose function attracted special attention in the past few years. In early reports, this cluster has been described as redox-inert and playing mostly a structural role. Recently, however, several studies have shown that binding of non-damaged DNA by Nth family enzymes activates the FeS clusters towards oxidation, possibly providing a mechanism for signaling oxidative damage to the repair enzyme at a distance through charge transport along DNA [32, 33]. An important cellular messenger, nitric oxide, also easily reacts with the FeS clusters of Nth and inactivates the enzyme [34].

Nth and its close homologues from other species (*e.g.*, Ntg1p and Ntg2p in yeast and NTHL1 in humans) form one of the central families of the Nth superfamily. There are four other central families, three of which contain rarely encountered enzymes with the same structural organization as Nth but quite different substrate specificities [13, 35]. One of them comprises DNA glycosylases specific for cyclobutane pyrimidine dimers (Pdg), so far characterized only from *M. luteus*. The third family is that of MIG, archaeal glycosylases specific for Thy and Ura mismatched with Gua similar to Mug/TDG (see *Uracil-DNA glycosylase superfamily* above), illustrating clearly that the same substrate can be processed by DNA glycosylases with entirely unrelated structures. The same can be said of the members of the MpgII family, found in several bacterial species and specific for ring-alkylated purines, which in other species are excised by enzymes unrelated or only distantly related to MpgII (see below in this section and *Other DNA glycosylases*). The fifth central family of the Nth superfamily is formed by the MutY enzymes, DNA glycosylases that remove Ade from Ade:8-oxoGua or Ade:Gua mispairs. Like Nth, MutY is also present in many species (MutY in *E. coli*, MUTYH in human) but missing, for example, from *S. cerevisiae* or protostomes [35]. Structurally, MutY keeps all motifs characteristic of Nth but possesses an additional C-terminal domain (reviewed in [13, 14]). This domain is organized similarly to NUDIX deoxynucleoside triphosphate hydrolases and confers specificity for mismatches containing 8-oxoGua; however, the structure of MutY bound to 8-oxoGua-containing DNA [36] reveals that the interactions of this lesion with the NUDIX domain are completely different from those in NUDIX hydrolases [37].

Peripheral members of the Nth superfamily lose the FeS cluster but usually keep the HhH and GPD motifs and, in some cases, preserve the overall organization of the central families [13, 14]. Two small families of archaeal 8-oxoguanine-DNA glycosylases, OGGII [35] and AGOG [38, 39], and another small family of bacterial 3-methyladenine-DNA glycosylases III (MagIII) [40] provide examples of the enzymes that have lost the Fe_4S_4 cluster but still have the same overall structure of typical Nth-like proteins. In eukaryotic 8-oxoguanine-DNA glycosylases (OGG1) and bacterial 3-methyladenine-DNA glycosylases II (AlkA), the domain topology starts to diverge from the Nth model, and both OGG1 and AlkA possess a third domain, sharing its fold with the TATA-box binding protein TBP. Eukaryotic MBD4 protein, a glycosylase specific for Thy and Ura mismatched with Gua in the CpG sequence context, also possesses an Nth-like, Fe_4S_4-less domain [41] plus an N-terminal methyl-CpG-binding domain. Even further from the central families, bacterial 3-methyladenine-DNA glycosylases I (Tag) retain only the HhH motif [42].

The core HhH/GPD structure is versatile enough to allow glycosylases of the Nth superfamily to cover nearly the full spectrum of lesions that are repaired by BER. Oxidized pyrimidines are excised from DNA by Nth; oxidized purines, by OGG1, OGGII, and AGOG; mismatched bases, by MutY, MIG, and MDB4; ring-alkylated purines, by AlkA, Tag, MpgII, and MagIII; and pyrimidine dimers, by Pdg. In addition, AlkA is the major bacterial activity

towards 1,N^6-ethenoadenine and hypoxanthine lesions and is even capable of limited removal of normal bases from DNA ([6, 7, 43] and references therein).

Other DNA glycosylases. Several DNA glycosylases do not belong to the three major superfamilies. Methylpurine-DNA glycosylase of higher eukaryotes (MPG) is characterized by an α/β fold similar to the C-terminal domain of methionyl-$tRNA_f^{Met}$ formyltransferase (reviewed in [13]). Despite its distinctive structure, this enzyme is remarkably similar to AlkA in its mechanism and substrate specificity, removing 3- and 7-alkylpurines, 1,N^6-ethenoadenine and hypoxanthine (reviewed in [6, 7, 43]). Another structurally unique enzyme is endonuclease V of bacteriophage T4 (DenV); this smallest known DNA glycosylase is a single-domain, completely α-helical protein (reviewed in [44]). The final known group includes the AlkD protein of *Bacillus cereus*, a 3-methyladenine-DNA glycosylase organized in an α-α superhelix fold and containing several HEAT repeats [45].

AP endonucleases

AP endonucleases are much less numerous than DNA glycosylases. Generally, each organism possesses one or two known AP endonucleases, which belong to two groups (Table 1). The prototypic members of these groups are exonuclease III (Xth) and endonuclease IV (Nfo), two *E. coli* enzymes with similar functions but unrelated at the structure level. Xth is a member of the DNase I structural family, an α+β protein with a β-sandwich core, while Nfo is a TIM β/α barrel protein related to xylose isomerase (reviewed in [46]). In view of their structural difference, Xth- and Nfo-like AP endonucleases have somewhat dissimilar reaction requirements and specificities ([9] and references therein). Xth was first described as a Mg^{2+}-dependent 3'→5'-exonclease, and, besides the AP endonuclease activity, also possesses the activities of 3'-phosphatase, 3'-phosphodiesterase, and RNase H. In addition to natural AP sites, Xth can process a number of their structural analogs, such as reduced or oxidized AP sites or urea deoxyribonucleotides (reviewed in [9]). Nfo is also a metalloenzyme, but, unlike Xth, relies on Zn^{2+} ions, three of which are tightly bound in the enzyme molecule ([46] and references therein). Its activities partially coincide with those of Xth (reviewed in [9]); however, Nfo lacks exonuclease activity and is capable of nicking DNA next to some base-containing lesions (see *Nucleotide incision repair: Glycosylase-less BER* below). In yeast, Apn1p, an Nfo homologue, is the main AP endonuclease, while an Xth homologue Apn2p is a complementary protein, and 3'-phosphodiesterase complexes Rad1-p–Rad10p and Mus81p–Mms4p can perform some of AP endonuclease functions, such as 3'-end processing ([47] and references therein).

The major mammalian AP endonuclease, APEX1, and its lately discovered paralog APEX2, are both Xth homologues (reviewed in [9, 46, 48]), and APEX1 is structurally similar to Xth [46]. However, while APEX1 provides a robust AP endonuclease activity in general BER, its 3'-processing activities are much lower than those of its bacterial counterpart (reviewed in [9]). In contrast, the 3'→5' exonclease activity of APEX2 is higher than its AP endonuclease activity and may represent a major biological function of this enzyme [49]. Recently, a third mammalian AP endonuclease (PALF) with endo- as well as exonuclease activities was reported (although this finding has not yet been independently confirmed). It is unrelated to known AP endonucleases but has homology to polynucleotide kinase, a forkhead-associated domain, and a CYR domain found in several DNA-dependent enzymes [50]. Eukaryotic AP endonucleases often possess additional domains that may be involved in functions outside of BER. For example, Rrp1, the *Drosophila* homologue of Xth, has an N-terminal addition harboring strand transferase activity involved in recombination ([9, 48] and references therein). Perhaps the most thoroughly studied case is the N-terminal REF-domain of APEX1 [51] that is dispensable for DNA repair activity but regulates DNA binding of several important mammalian transcription factors (*e.g.*, Jun–Fos) by reducing a conserved Cys residue in these proteins.

dRP processing enzymes

Removal of dRP after base excision and AP strand nicking can in principle proceed hydrolytically or by β-elimination, with the same DNA product but a different excised pentose product generated. In bacterial cells, Pol I, the major DNA repair polymerase, possesses a strong 5′→3′ exonuclease activity and can degrade the blocked dRP terminus. Several dRP-processing enzymes from *E. coli* have also been reported, including hydrolytic activities of exonuclease I and RecJ, and dRP lyase activities of Fpg and Nei (reviewed in [52–54]).

The major dRP-removing activity in mammals belongs to Pol β where it resides in a separate N-terminal 8-kDa domain (reviewed in [55, 56]), which contains an Nth-like HhH motif. The extreme sensitivity of Pol β-null cells to methyl methane sulfonate can be rescued by overexpression of the separate dRPase domain but not the catalytic polymerase domain, suggesting that dRPase activity is critical for efficient removal of at least some types of lesions.

Although Pol β seems to be the primary dRP lyase in mammalian BER, this enzymatic activity has been

observed in several other DNA polymerases: translesion polymerases Pol ι and Pol λ and mitochondrial DNA polymerase γ (reviewed in [57, 58]). In Pol ι, which belongs to a structural family different from Pol β, the dRP lyase activity has been mapped to a separate C-terminal domain [59]. Additionally, strong dRP lyase activity has been found in NEIL1 and NEIL2 glycosylases [60]. In principle, these proteins could supplement Pol β dRP lyase function in some special cases of BER.

DNA polymerases

Seven structural families of DNA polymerases are known to date (A–D, X, Y, and RT) [61]. Of these, participation in the DNA re-synthesis step of BER has been described for families A (bacterial Pol I and eukaryotic mitochondrial Pol γ), B (eukaryotic DNA polymerases δ and ε and possibly α and ζ), and X (eukaryotic DNA polymerases β and λ) ([1, 57, 58, 62, 63] and references therein). Pol I and Pol β are the main gap-filling DNA polymerases in bacteria and eukaryotes, respectively. In higher eukaryotes, Pol δ/ε play an important role in DNA re-synthesis (see *Single-nucleotide-patch and long-patch BER* below). Structures of many DNA polymerases have been solved but are not discussed here, as they do not reflect specific BER functions; numerous in-depth reviews on this topic can be found elsewhere (*e.g.*, [56, 64–66]). Recent years have seen an explosion in the number of known prokaryotic and eukaryotic DNA polymerases, many of them belonging to the Y family (reviewed in [64, 67]). These enzymes mostly catalyze translesion synthesis or have other specialized functions and are generally not involved in BER *per se.* Nevertheless, some of the translesion polymerases could be recruited to provide an accessory polymerase or dRP lyase function for BER.

Flap endonucleases

Processing of flap structures during LP-BER has been investigated in most detail in eukaryotic systems, where it depends on the structure-specific endonuclease FEN1 (reviewed in [1, 68]). FEN1 is a Mg^{2+}-dependent endonuclease, with a 5'-flap (either RNA or DNA) as a preferred substrate. The enzyme is probably loaded on the free 5'-end of the flap and tracks along until it encounters the junction with double-stranded DNA. Structures of archaeal FEN1 [69, 70] reveal a two-domain structure containing a wide loop arching over the active site. This loop most likely clamps on the single-stranded flap during tracking, while double-stranded DNA is bound in the groove containing a helix–three turn–helix motif, resembling the two-helical motifs in DNA glycosylases and Pol β. The active site of FEN1 contains two Mg^{2+} ions and a number of acidic residues, consistent with the two-metal nuclease mechanism proposed for this enzyme [71]. In addition, the RAD2 domain of human exonuclease 1, a protein related to FEN1, also exhibits flap endonuclease activity [72].

In eubacteria, FEN1 does not exist as a separate entity. Pol I contains a separate 5'→3' exonuclease domain with a limited homology to FEN1 but similar structural organization. During Pol I-catalyzed synthesis with strand displacement in *E. coli*, the flap can be excised by the intrinsic flap endonuclease activity of this domain (reviewed in [68]).

DNA ligases

BER is completed by ligation of the single-stranded nick in DNA. This reaction is catalyzed by DNA ligases, the enzymes that are involved in most aspects of DNA metabolism and utilize the energy of phosphoanhydride hydrolysis to make a phosphodiester bond (reviewed in [1, 73, 74]). All cells possess at least one type of DNA ligase that is absolutely required for joining of Okazaki fragments during replication; the majority of DNA ligases are ATP dependent, while some (including that from *E. coli*) are NAD^+ dependent.

In *E. coli*, LigA participates both in replication and in BER. Genomes of eukaryotes generally contain three genes for DNA ligases (*lig1*, *lig3* and *lig4* in mammals). Their products are ATP-dependent DNA ligases with some functional specialization. Lig I is the main DNA ligase, which participates in replication and in LP-BER. Lig IV is a dedicated ligase for non-homologous end joining. In mammals, the *lig3* gene produces two isoforms of the mature enzyme by alternative splicing. DNA ligase IIIα (Lig IIIα) is ubiquitously expressed, whereas DNA ligase IIIβ (Lig IIIβ) is found only in testes and is therefore believed to be involved in homologous recombination during meiosis. The main role for Lig IIIα seems to be in SP-BER, which requires formation of a complex with the XRCC1 accessory protein (see *Scaffold proteins in BER* and *Single-nucleotide-patch and long-patch BER* below). Structures of several DNA ligases from different sources were determined in the past decade, revealing similar modular organization in both ATP-dependent and NAD^+-dependent enzymes (reviewed in [14, 74]). A minimal DNA ligase contains an oligonucleotide-binding fold domain, typical of many nucleic acid-binding proteins, and a catalytic adenylation domain. The enzymes from higher organisms may display additional domains, such as a BRCT domain found in many DNA repair proteins and involved in protein–-protein interactions [75], or a $RuvA_2$-like domain consisting of four HhH motifs and a zinc finger, constituting a second DNA-binding element in

NAD^+-dependent ligases. ATP-dependent Lig I, in addition to its oligonucleotide-binding domain, possesses a large DNA-binding domain, functionally equivalent to the $RuvA_2$-like domain. In the absence of DNA, this domain is well separated from the rest of the protein, while in the DNA-bound form it folds back, completely encircling DNA [76–78].

Scaffold proteins in BER

The enzymes discussed above constitute a core BER pathway and are sufficient to reconstitute BER *in vitro*. Nevertheless, a number of accessory proteins may be additionally involved in BER *in vivo* and stimulate the pathway *in vitro*. Three accessory proteins very often appear in BER reactions to provide a scaffold for the core BER enzymes; they are described below in more detail.

X-ray cross-complementation group 1 protein. XRCC1 protein preferentially binds DNA containing nicks or short gaps [79, 80], and physically interacts with and activates Lig IIIα [81, 82] but not Lig IIIβ [83]. XRCC1 contains two BRCT domains, which likely mediate its interactions with LigIIIα and PARP1 [84], while a number of its reported interactions with other main and accessory BER proteins (Pol β, PCNA, polynucleotide kinase, APEX1, OGG1, NEIL1, NEIL2, NTHL1, and MPG) may be effected through other parts of XRCC1 as well [14, 85–91]. The effect of these interactions may be either activation or inhibition of the partners. At least for the XRCC1–Pol β and XRCC1–Lig III interaction, binding of XRCC1 to the enzyme is functionally important [92, 93]. Interaction of XRCC1 with a truncated form of Pol β found in many tumors is followed by unproductive binding of this heterodimer to the sites of BER thereby preventing normal repair. The absence of XRCC1 significantly reduces the ligation efficiency in SP-BER, a sub-pathway where Lig III is involved; in living cells, the functional interactions may also involve stabilization of the ligase by XRCC1, since XRCC1-deficient hamster cells show a reduced level of Lig III protein, apparently due to proteasomal degradation [82, 94, 95].

Poly(ADP-ribose) polymerase 1. Poly(ADP-ribose) polymerases (PARP) are enzymes that use NAD^+ to modify themselves and other polypeptides with branched polymeric chains consisting of adenosine 5′-(5′-ribose)diphosphate units (reviewed in [96]). Of the PARP paralogs known in humans, the most studied is PARP1. PARP1 is activated by binding to nicks in DNA and then modifies a number of DNA repair and damage response proteins. PARP1 consists of several functional domains, including a DNA-binding domain, an automodification domain, and a catalytic domain.

As BER in the extracts of PARP1-deficient mice is only marginally compromised [97] and since the pathway can be reconstituted from purified enzymes without PARP1, this protein seems to be dispensable for BER. However, PARP1 is ubiquitously found at sites of BER [98, 99] and is involved in a number of regulatory processes (reviewed in [100]). For instance, it is required for efficient repair of 8-oxoGua in Pol β^- cells by LP-BER [101]. The main role of PARP1 may be related to histone poly(ADP)-ribosylation, which facilitates the access of BER enzymes to the site of the DNA break (reviewed in [102]), or to recruitment of XRCC1 and Pol β through their interaction with automodified PARP1 (reviewed in [100, 103]). For BER to proceed, PARP1 must be displaced from the nick, which is possible only after its automodification; the requirement for PARP1 displacement could protect cells from chromosome degradation by unrestrained BER if excessive DNA damage occurs [99].

Proliferating cell nuclear antigen and 9–1–1 complex. Proliferating cell nuclear antigen (PCNA) is an accessory factor required in eukaryotes for efficient replication by DNA polymerase δ (reviewed in [104, 105]), and, as such, is required for LP-BER supported by Pol δ. In addition to its role as a polymerase processivity clamp, PCNA functions as a scaffold molecule to facilitate exchange and recruitment of proteins to replication forks, in particular, when resolving obstacles during replication (reviewed in [64]). The role of PCNA in targeting translesion DNA polymerases to the site of stalled replication is well established ([64] and references therein); PCNA may also attract BER enzymes to repair lesions encountered during replication.

The possible role of PCNA in replication-coupled BER is supported by known physical association of PCNA with multiple BER proteins. Besides Pol δ, association with PCNA has been reported for UNG, MPG, MUTYH, NTHL1, APEX1, APEX2, Pol β, FEN1, and Lig I [85, 89, 106–111]. Some evidence points to the existence of pre-formed Ura repair-competent complexes containing UNG, APEX1, Pol β, Pol δ, PCNA, XRCC1 and one of the DNA ligases [112]. Also, Ade:8-oxoGua mismatches, as they appear during replication, may possibly be corrected by PCNA-bound MUTYH, perhaps even without pausing of the polymerase (reviewed in [113]). In LP-BER not associated with replication, clamp assembly factor RFC is likely required for PCNA loading. Consistent with this requirement, PCNA is recruited to the sites of DNA damage slower than XRCC1 [114].

In addition to PCNA, which is a trimer of identical subunits, eukaryotic cells possess another polymerase clamp, a heterotrimer termed 9–1–1 complex for its constituents, Rad9, Rad1 and Hus1 proteins (reviewed in [115]). Its main function probably consists in recruitment of damage-processing proteins to the sites of stalled replication, where it eventually replaces PCNA. The 9–1–1 complex interacts with and stimulates many BER proteins, such as MUTYH [116, 117], NEIL1 [118], TDG [119], APEX1 [120], Pol β [120, 121], FEN1 [110, 122] and Lig I [123, 124], raising the possibility of its involvement in replication-associated BER in a mode similar to that of PCNA.

BER step by step: Recent advances

Lesion search

A long-standing puzzle of DNA repair is the mechanism of lesion search. Thermodynamic and kinetic considerations all but prohibit the search for sparse lesions by three-dimensional diffusion of repair enzyme molecules; consequently, the favored model of search is that of one-dimensional random walk ([8] and references therein). Recent data suggest some intriguing possibilities of how such a search may operate at the atomic level.

A series of structures of 8-oxoGua DNA glycosylases Fpg and OGG1 complexed with undamaged DNA, or with damaged DNA in a non-catalytic conformation of the enzyme, has been published in the past few years [125–128]. Both enzymes impose significant structural distortion on undamaged DNA, which assumes a kinked conformation closely resembling damaged DNA in the complex with the enzyme. In the case of Fpg, the enzyme wedges a Phe side chain into DNA and uses it to probe for stability of adjacent base pairs, which remain fully intrahelical [126]. OGG1 also intercalates wedging residues into DNA, but fully disrupts normal base pairs and everts undamaged dGuo, although this does not go all the way into the enzyme's active site, residing instead in an "exo-site" [125]. When OGG1 approaches the lesion and samples a base 3'-adjacent to 8-oxoGua, a steric clash precludes full eversion of the latter, placing it into a unique conformation and enabling the enzyme to "sense" the lesion [127]. The diffusion constant for one-dimensional sliding along DNA measured for Fpg by single-molecule microscopy is higher than for OGG1 [129], suggesting that OGG1 may be slowed down by the need for base eversion.

UNG searching for its Ura substrate in DNA also samples normal Thy base in a half-everted state [130]. NMR data suggest that UNG does not actively promote eversion of the sampled dN but instead stabilizes the open conformation arising spontaneously during DNA breathing [130–132]. Whether this mechanism is operative for other DNA glycosylases has not yet been addressed.

Stimulation of DNA glycosylases by other proteins

With a great multitude of protein–protein interactions between different BER components (reviewed in [85, 89, 111]) it is not surprising that some of them activate the participating enzymes. DNA glycosylases present an especially interesting case of such activation. Many DNA glycosylases, assayed as purified enzymes, are inhibited by the AP site reaction product. In recent years, a number of mammalian DNA glycosylases have been reported to be stimulated by AP endonucleases or other proteins, involved in BER (other glycosylases [133], XRCC1 [86, 90], PCNA [107, 109] or 9–1–1 [118, 119]), DNA repair beyond BER {XPC-HR23B damage sensor protein [134, 135], p53 [106], XPG and MSH2/MSH6 heterodimer (reviewed in [85]), and Werner syndrome helicase [136]}, and proteins with no other known connections to BER {YB-1 transcription factor (reviewed in [85]), estrogen receptor α [137], SUMO ubiquitin-like modifiers [138]}. Many of these interactions are idiosyncratic for a particular DNA glycosylase. However, the stimulation by APEX1 seems nearly universal, being reported for UNG, TDG, SMUG1, MPG, OGG1, NTHL1, and MUTYH [85, 89, 109, 111, 139–142]. In many of these cases, AP endonucleases do not form stable complexes with the glycosylases they stimulate. Two competing (but not mutually exclusive) models account for this stimulation: the product scavenging model, in which AP endonucleases cleave or sequester the AP site product released by DNA glycosylases and thus prevent re-association of the glycosylase with it, and the direct displacement model, in which AP endonucleases recognize glycosylase–DNA complexes, form an unstable ternary intermediate, and promote dissociation of the glycosylase from the complex [142]. It is possible that the stimulation *in vitro* reflects enhanced efficiency of DNA glycosylases acting as part of intracellular repair complexes.

Single-nucleotide-patch and long-patch BER

Detailed dissection of the two BER sub-pathways in the past 15 years probably represents the greatest advance in the field since the discovery of BER as a distinct process. The mechanisms and regulation of the two main BER branches is known in most detail from eukaryotic cells. There, both SP-BER and LP-BER start in the same way, with DNA polymerase β incorporating one dNMP into DNA after the 3'-end has been properly processed [143]. Pol λ, Pol δ or Pol ε can possibly substitute for Pol β in this reaction [144].

If the dRP fragment is present, it is eliminated by the dRP lyase activity of Pol β after the dNMP insertion. In this case, the repair is completed immediately by ligation carried out by Lig III/XRCC1, or, in some cases, by Lig I ([145] and reviewed in [146]). If the 5' terminus cannot be processed, a polymerase switch may occur, with Pol δ/ε continuing the strand synthesis with displacement of the DNA strand ahead of the polymerase. LP-BER is stimulated by protein factors supporting general or repair-specific DNA synthesis, such as RPA, PCNA, RFC, or the 9–1–1 complex [110, 120, 123, 146] through their interactions with nearly all major enzyme components of LP-BER. In addition, Pol β itself is also capable of strand displacement synthesis, especially if stimulated by FEN1 [147], PCNA or 9–1–1 [112, 123, 144], and cross-linking of DNA polymerases to BER intermediates predominantly reveals Pol β [148]. Pol λ is less prone to strand-displacement synthesis and is not efficiently stimulated by accessory factors [144]. The flap structure is nicked by FEN1 a few nucleotides 3′ to the initial lesion (reviewed in [146]). Alternatively, in Pol β-mediated LP-BER, the enzymes may act in a "hit-and-run" mode, with FEN1 degrading a patch of DNA to form a small gap that is later filled by Pol β [147].

What factors guide the choice between SP- and LP-BER? The nature of the lesion can prevent SP-BER if the 5′-end formed after incision by AP endonuclease is refractory to dRP lyase activity. For example, 2'-deoxyribonolactone, an oxidized form of AP site, is repaired by LP-BER because it is resistant to elimination [149], and, moreover, covalently traps dRP lyases attempting to remove it [150, 151]. There are multiple examples of the nature of the damaged base directing the patch length. These differences are likely accounted for by the type of DNA glycosylase removing the damaged base. *In vitro*, AP sites, 8-oxoGua, thymine glycol, and ring-alkylated purines are processed mainly *via* SP-BER, and Ura, hypoxanthine and 1,N^6-ethenoadenine, by both SP- and LP-BER [12, 112, 146, 152]. However, *in vivo* efficiency of conversion of genetic markers engineered downstream of the lesion suggest that LP-BER may in fact be a dominant sub-pathway, at least for 8-oxoGua [153].

Obviously, the choice between SP- and LP-BER ultimately depends on kinetic competition between enzymes engaged in these pathways. For example, the choice between Pol β-dependent SP- and LP-BER apparently depends on ATP concentration after the dRP excision step: if it is high, ligation by Lig III prevails to complete SP-BER, otherwise, extension by Pol β establishes LP-BER. This regulation may also operate in *E. coli*, where the rate-limiting step of BER is ligation [11]. The ratio of different BER proteins is also important: excess of PARP1 blocks LP-BER, while excess of APEX1 over Pol β promotes it, possibly owing to stimulation of Pol β, FEN1 and Lig I by APEX1 [154, 155].

The protein product of *adenomatous polyposis coli* gene, a well-known tumor suppressor, interacts with Pol β and FEN1 and blocks strand displacement synthesis and flap cleavage, thus shifting the balance in favor of SP-BER [156, 157]. A p24 apoptotic fragment of PARP1 also strongly inhibits LP-BER, apparently by the same mechanism [158], while full-length PARP1 may stimulate LP-BER, sometimes at the expense of SP-BER [159]. The cyclin-dependent kinase inhibitor p21 blocks LP-BER by sequestering PCNA and inhibiting DNA ligases and FEN1 (reviewed in [146]). On the other hand, binding of Pol β to XRCC1 enhances strand displacement synthesis by Pol β [160]. The same process is stimulated by WRN helicase [161, 162], and by telomere repeat binding factor TRF2 [163]. The high-mobility group box protein 1 binds AP sites and stimulates APEX1 and FEN1 while inhibiting the dRP lyase activity of Pol β, an effect also favoring LP-BER [164].

MUTYH-initiated repair of Ade:8-oxoGua mispairs presents an interesting case of switch between SP- and LP-BER. Apparently, this mispair can be repaired by both SP- and LP-BER in eukaryotes; however, a product of SP-BER is ligated much more efficiently when dAMP is inserted compared with dCMP [165]. Thus, SP-BER of Ade:8-oxoGua is futile, and the proficient repair must proceed through LP-BER.

BER fidelity

While DNA repair is meant to protect the genome from mutagenic load, it can itself be a source of mutations because DNA polymerases involved in BER are not perfect copiers. For example, when Pol β fills single-nucleotide gaps, mutations arise with the frequency ~3×10^{-4}, a common value for proofreading-deficient DNA polymerases (reviewed in [166]) but well above the overall mutation rate of ~10^{-10} mutations per base pair per replication round in eukaryotic cells [167]. Accordingly, UNG-initiated repair of Ura is shown to proceed with the mutation frequency rate of ~10^{-4} [166, 168]. For both SP- and LP-BER, most of the mutations produced are deletions of a single nucleotide, initially located opposite the lesion, indicating that DNA misalignment in the active site of a DNA polymerase is a major factor in BER errors [169, 170]. Overexpression of Pol β is mutagenic and confers a radiation-sensitive phenotype, and many tumor cells overexpress Pol β and have decreased BER fidelity; in addition, some human tumors express dominant negative mutant forms of Pol β (I260M or

the polymerase truncated at the C terminus) that interfere with normal BER [170–172]. Counteracting the low fidelity of Pol β is low efficiency of mismatch ligation (reviewed in [66]).

Participation of error-prone translesion DNA polymerases can be even more detrimental for BER fidelity because of their extremely high misincorporation rates on undamaged DNA. For instance, Pol η misincorporates dNMP with a frequency of ~10^{-2}–10^{-3}, while for Pol ι misincorporation rates can be as high as 10^{-1} depending on the nature of the template base and the incoming dNTP; Pol κ, on the other hand, efficiently (10^{-1}–10^{-2}) extends mismatched primer ends (reviewed in [64]). These enzymes (Pol η, Pol ι, and Pol κ) can in fact be recruited to the site of BER but quickly form a dead-end Schiff base complex with the dRP moiety, preventing the polymerases from dNMP insertion and directing the repair to the LP-BER pathway [173].

Another problem may arise at the ligation step of BER. Catalysis by DNA ligase involves covalent addition of an adenylate to the 5'-phosphate at the nick, at which step the reaction may abort. Such prematurely terminated intermediates are resolved by aprataxin, the product of *aptx* gene mutated in the neurological disorder ataxia oculomotor apraxia. This enzyme releases the adenylate moiety and clears the way for a second ligation attempt [174].

Special cases of BER

Nucleotide incision repair: Glycosylase-less BER

It has been known for some time that some AP endonucleases can recognize and incise certain substrates with DNA lesions still containing the base (reviewed in [175]). However, only recently has it been realized that such reactions are not *in vitro* oddities but represent a novel branch of repair operating in both bacterial and eukaryotic cells. This pathway, conventionally termed "nucleotide incision repair" (NIR, Fig. 1), operates mostly on oxidatively damaged pyrimidines and α-deoxynucleosides. NIR is initiated by AP endonucleases (Nfo, Apn1p, APEX1, or PALF), bypassing the glycosylase step [50, 176–181]. The AP endonuclease nicks DNA 5' to the lesion in the same manner as during regular BER. The 3'-OH end can be extended by DNA polymerases, but dRP lyase cannot operate and the repair inevitably proceeds by LP-BER.

The biological importance of NIR remains unclear. It has been argued that NIR allows the cell to avoid formation of potentially toxic AP site intermediates [176]; however, single-strand breaks formed during NIR are potentially as toxic as AP sites. Yet, Nfo mutants proficient in BER but defective in NIR cannot rescue *E. coli nfo* strains hypersensitive to oxidative stress, indicating that NIR pathway plays a role *in vivo* [180].

AP endonuclease-less BER

A special sub-pathway of BER operates in mammalian cells when BER is initiated by a DNA glycosylase capable of performing β,δ-elimination (NEIL1 or NEIL2). The product of these enzymes, a one-base gap in DNA flanked by phosphates, is not a substrate for DNA polymerases, and APEX1 of higher eukaryotes is not an efficient 3'-phosphatase (reviewed in [9]). In mammalian BER, this problem is circumvented by using polynucleotide kinase/3'-phosphatase (PNKP) for 3'-phosphate removal [10, 182]. After that, the reaction proceeds by regular SP-BER, with Pol β and Lig IIIα/XRCC1 as downstream effectors (Fig. 1). This mechanism likely operates for oxidized pyrimidines, the primary substrates of NEIL proteins. However, as OGG1 may be stimulated by NEIL1 with the AP site excised by the latter enzyme [133], the repair of 8-oxoGua in mammalian cells may also be channeled towards this sub-pathway.

Repair of clustered lesions

The general discussion of BER has so far been limited to repair of isolated lesions. However, under certain conditions lesions tend to appear close to each other. A classical example is provided by ionizing radiation where a single particle produces a track of water ionization products in its wake [2]. Lesions located approximately within one helical turn (clustered lesions) present a special problem: If located in the opposite DNA strands, they tend to produce double-strand breaks. BER of lesions in a cluster must be tightly coordinated to avoid double-strand break formation, as overactive BER produces double-strand breaks after ionizing irradiation *in vivo* [183–185].

Many DNA glycosylases and AP endonucleases have been studied in respect to their action with clustered lesions of various structures ([186] and references therein, [187–191]). Closely spaced lesions tend to inhibit the action of each enzyme on each lesion, inhibit the enzyme after processing only one of the lesions, or have no effect at all. Given the multitude of possible lesions and their positional relationships, it is not surprising that the results may vary dramatically between particular enzymes and clusters. As a general rule, base excision and/or DNA strand nicking proceed independently if the lesions do not fall under the enzyme footprint simultaneously. Excision of damaged bases is usually affected more than AP site nicking, and AP sites or single-strand breaks affect the enzyme activities to a greater extent than base lesions

do, likely due to loss of critical contacts at the enzyme–DNA interface [190].

When the full BER system is presented with a clustered lesion, usually nicking of one strand proceeds quickly and then the repair pauses, with the reaction at the second lesion in a cluster essentially not occurring [192–194]. The repair is mostly channeled to the SP-BER sub-pathway to avoid replacement of a patch that would be at risk of encountering another lesion in the cluster [193, 194]. Inhibition of repair glycosylases by the second DNA lesion *in vitro* generally correlates with *in vivo* observations. Ura, dihydrothymine, AP site or 8-oxoGua in a cluster with 8-oxoGua increases the mutagenicity of the latter in *E. coli* [195–199].

BER: New connections

The mainstream line of thinking about BER is concerned with its role in maintaining genomic integrity of the cell against spontaneous or environmental damage. However, BER is also associated with other cellular processes, some of which are now the subject of active research. The last section of the review briefly covers the current status of these different connections.

BER and immunoglobulin gene diversification

Recent years were marked with the discovery of an unexpected role of UNG in the immune system of vertebrates. During maturation, immunoglobulin (Ig) genes undergo gene conversion, class switch recombination (CSR) and somatic hypermutation (SHM), both processes aimed to increase the antibody diversity. Both processes are initiated by cytosine deaminase AID (reviewed in [200]), which converts Cyt in the target genes to Ura. UNG has been suggested to excise these Ura bases to produce non-instructional AP sites thereby initiating SHM, and further BER steps convert the AP sites to DNA breaks that initiate gene conversion and CSR. This scheme is based on the multiple observations that *ung*-deficient chicken cells, mice, and human hyperimmunoglobulinemia M patients have drastically decreased CSR and a SHM spectrum changed in a predictable manner [201–206] and that a combination of AID and UNG is mutagenic *in vivo* [207–211]. The function downstream of AID appears specific for UNG, since *mbd4*$^{-/-}$ mice have normal CSR and SHM [212], and SMUG1 is expressed at very low levels in B cells [213, 214]. However, RNA editing by AID had been proposed as an alternative explanation for Ig gene maturation, a mechanism supported by additional lines of evidence [204, 215–218]. It is noteworthy that the pattern of SHM and CSR in *ogg1*$^{-/-}$ and *mpg*$^{-/-}$ mice appears unaffected [219, 220], yet further studies are ongoing to delineate the possible involvement of other DNA glycosylases in these events.

BER in viral life cycle

Viral DNA glycosylases and proteins interacting with cellular BER have a venerable history dating back to the discovery of T4 DenV protein and PBS2 Ugi protein several decades ago [1]. Although phage glycosylases and glycosylase inhibitors were usually regarded as biochemical oddities because of their irregular occurrence, the past few years witnessed a resurging interest in viral processes entwined with BER in eukaryotic cells.

Of all BER constituents, UNG is found in genomes of herpesviruses and poxviruses (reviewed in [221, 222]). Mimivirus, the protozoan virus with the largest genome known, also contains homologues of NEIL proteins [223] and a far-diverged alkyladenine-DNA glycosylase [224]. Generally, the biochemical properties of viral UNGs are very similar to those of their cellular counterparts [225, 226]. Structures of the viral enzymes reveal the conserved UNG superfamily fold [16, 227, 228].

Unlike in the case of cellular organisms, where UNG plays an important but non-vital role, deletions of poxviral UNG severely suppress viral replication [221]. Site-directed mutants abolishing the glycosylase activity still support replication, indicating that it is not dependent on the excision of Ura from DNA [229]. In herpesviruses, UNG is not critical for viability in dividing culture but is required for efficient establishment in resting cells, where the level of endogenous UNG is low [221, 230]. UNG proteins from poxviruses and herpesviruses are also physically associated with processivity factors of the respective viral DNA polymerases [231, 232] and may be an important structural part of functional replication complex.

The RNA genome of human immunodeficiency virus 1 (HIV-1) is converted to a double-stranded DNA genome by a low-fidelity reverse transcriptase, which efficiently incorporates dUMP from the dUTP pool, leading to aberrant synthesis of the (+)-strand [233]. Also, cellular cytosine deaminases APOBEC3G and APOBEC3F target the DNA HIV-1 genome, introducing multiple Ura residues [234], possibly teaming up with UNG in prevention of viral propagation [235]. Thus, UNG could have a dual role in the life cycle of HIV-1: a certain amount of UNG may be required to cope with dUMP incorporation by the reverse transcriptase, while high APOBEC/UNG activity may effectively destroy the viral genome. HIV-1 does not possess its own UNG and subverts the cellular enzyme

for its own needs. Viral Vpr protein binds human UNG thus limiting HIV-1 mutation rate [221, 236, 237]. Fully functional UNG and SMUG1 are packaged into mature HIV-1 particles through interaction with Vpr or integrase [221, 237–240] and can be functionally replaced by incorporation of a dUTPase into the virion [241]. Whether APOBEC-mediated virus restriction involves cellular or virion-packed UNG, or requires other BER proteins, is presently controversial [235, 242]. To defuse this cellular defense mechanism, HIV-1 Vpr and Vif proteins target APOBEC3G, UNG and SMUG1 for proteasomal degradation [240, 243].

DNA glycosylases in plant development

Plants generally possess the set of DNA repair glycosylases similar to those found in other taxa [244]. In addition some plants have DNA glycosylases, DEMETER (DME) and REPRESSOR OF SILENCING 1 (ROS1), which are unique for this kingdom and are involved in the regulation of DNA methylation status. The *DME* gene, isolated during screening for *Arabidopsis* mutations that influence seed viability when inherited maternally but not paternally, regulates the expression of several genes in endosperm [245, 246]. DME possesses a domain with sequences typical of the Nth family, including HhH and GPD motifs with the intact Lys–Asp catalytic dyad, and a FeS cluster, and is capable of excising 5-methylcytosine bases from DNA by a bifunctional glycosylase mechanism [247, 248]. This reaction is required for activation of the target genes [245, 249]. The *ROS1* gene was first identified as the repressor of methylation-dependent transgene silencing [250, 251]. Like DME, ROS1 has a domain homologous to DNA glycosylases of the Nth family, and cleaves DNA at 5-methylcytosines [248, 250, 252]. As *ros1* plants are sensitive to methyl methane sulfonate and H_2O_2 [250], and ROS1 interacts with replication factor A [253], this glycosylase may also participate in canonical DNA repair pathways.

Conclusion: The future of BER

The past few decades improved our understanding of BER at the fundamental level, involving characterization of BER enzymes and their interactions. However, the processes occurring both at the level of protein structural dynamics and at the cellular level are much less clear and are subject to actively developing research.

The wealth of structural information for BER enzymes has been surprisingly hard to translate into mechanistic models of action of DNA repair enzymes. Despite the fact that the structure of almost all major DNA glycosylases is known, perhaps the only group where the base excision mechanism is essentially understood is Ung/UNG, for which an elegant series of studies by Stivers and colleagues provided a fully supported model for a dissociative reaction mechanism with electrostatic stabilization of the glycosyl carbocation transition state (reviewed in [7, 254]). As a result, it was possible to develop UNG inhibitors, both through screening and rational design, with a potential use in antiviral and anticancer therapy. Other DNA glycosylases have not been subject to mechanistic studies of similar breadth, and, although their general chemistry is understood, much more is to be done.

Structures of complexes of BER enzymes with their DNA substrates also reveal that enzyme binding to DNA is accompanied by multiple conformational changes. Therefore, several recent studies have used a stop-flow technique with fluorescent detection to address conformational dynamics of pre-chemical steps in reactions catalyzed by DNA glycosylases [255–258] and Pol β [259, 260]. The emerging view is that BER enzymes are highly dynamic, with the potential for selection or rejection of DNA substrates at each conformational change step. As the reaction coordinate of BER enzymes is usually scarcely sampled by experimentally determined structures, the stopped-flow studies will benefit from being supplemented with computer simulation to reveal the trajectories of the conformational movements [261, 262].

At the other end of the spectrum of BER-related phenomena is the integrated role of BER at the level of cells and the whole organism. In humans, BER is clearly involved in protection from carcinogenesis, aging and several diseases (recently reviewed in [263, 264]). Nevertheless, how exactly the physical and functional interactions involving BER proteins are translated into phenotypes is mostly unknown at present. As a striking example, many genes coding for BER enzymes have been knocked out in mouse models, with surprisingly unremarkable consequences upon glycosylase inactivation but embryonic lethality of knockouts of APEX1, Pol β, FEN1 or Lig I [265]. Another actively developing field is concerned with BER features in terminally differentiated cells, such as neurons or myocytes. In particular, the role of BER in pathogenesis of neurodegenerative diseases is an area of growing interest (amply reviewed in [266] and several other papers in the same issue). Considering only one BER protein, OGG1 DNA glycosylase, the enzyme is often mutated in Alzheimer's disease patients leading to reduced repair and increased oxidative damage load in brain tissue [267, 268],

while its normal action in triplet-repeating sequences was recently implicated in repeat expansion in Huntington disease [269].

The directions mentioned above by no means exhaust the promising leads that keep appearing in studies of BER. We can reasonably assume that this area of research will be rich in spectacular advances in the following years, bringing us closer to comprehension of the complex machinery acting to safeguard our genomes — and genomes of all things living.

Acknowledgments. I apologize for omitting a great many of original citations due to the publication size limit; the research done before 2003 has been referred through reviews wherever possible. This work was supported by Russian Academy of Sciences (RAS, Program 10.5), an Integrative Grant from the Siberian Division of RAS (Program 6), Russian Foundation for Basic Research (07–04–00395, 08–04–00596), and Russian Ministry of Science and Education (02.512.11.2194).

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