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Toxicology 193 (2003) 3–34
TOXICOLOGY
www.elsevier.com/locate/toxicol

Mechanisms of human DNA repair: an update

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Abstract

The human genome, comprising three billion base pairs coding for 30 000–40 000 genes, is constantly attacked by endogenous reactive metabolites, therapeutic drugs and a plethora of environmental mutagens that impact its integrity. Thus it is obvious that the stability of the genome must be under continuous surveillance. This is accomplished by DNA repair mechanisms, which have evolved to remove or to tolerate pre-cytotoxic, pre-mutagenic and pre-clastogenic DNA lesions in an error-free, or in some cases, error-prone way. Defects in DNA repair give rise to hypersensitivity to DNA-damaging agents, accumulation of mutations in the genome and finally to the development of cancer and various metabolic disorders. The importance of DNA repair is illustrated by DNA repair deficiency and genomic instability syndromes, which are characterised by increased cancer incidence and multiple metabolic alterations. Up to 130 genes have been identified in humans that are associated with DNA repair. This review is aimed at updating our current knowledge of the various repair pathways by providing an overview of DNA-repair genes and the corresponding proteins, participating either directly in DNA repair, or in checkpoint control and signaling of DNA damage.

Keywords: DNA-repair gene; DNA-repair protein; DNA-damage signaling

1. Introduction

Fifty years after discovery of the structure of DNA (Watson and Crick, 1953), DNA repair has become one of the most interesting topics in modern biology. The sequencing of the human genome (Lander et al., 2001; Venter et al., 2001) yielded a first overview of the huge number of proteins involved in the protection of the genome. Recently, two papers compiled data of ∼130 human DNA repair genes, which were cloned and sequenced. Not all of them, however, have been characterised yet as to their function (Ronen and Glickman, 2001; Wood et al., 2001). DNA-repair genes can be sub-grouped into genes associated with signaling and regulation of DNA repair on the one hand and on the other into genes associated with distinct repair mechanisms such as mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER), direct damage reversal and DNA double-strand break (DSB) repair. Mutations in genes involved in DNA repair are responsible for the development of tumors and various hereditary diseases characterised by complex metabolic alterations (see Table 1).

DNA repair genes and their corresponding proteins are also responsible for the development of cytostatic drug resistance in tumour cells. Historical aspects pertaining to the field of DNA repair have recently been highlighted (Friedberg, 2003) and several reviews on different areas of DNA repair appeared (Hoeijmakers, 2001; Lehmann, 2002; Lindahl, 2001; Svejstrup, 2002;

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doi:10.1016/S0300-483X(03)00287-7

Table 1
Hereditary human DNA-repair-deficient disorders

Disease	Deficiency in	Reference
Hereditary non-polyposis colon cancer (HNPCC)	MMR: MSH2 PMS1, PMS2 MLH1	Leach et al., 1993; Nicolaides et al., 1994; Papadopoulos et al., 1994
Xeroderma pigmentosum variant	Translesion synthesis: XPV	Masutani et al., 1999
Trichothiodystrophy, Xeroderma pigmentosum, Cockayne's syndrome	NER: XPA–XPG, CSA, CSB	Vermeulen et al., 1997; van Hoffen et al., 1993
Ataxia telangiectasia	DNA damage signaling: ATM	Savitsky et al., 1995
Nijmegen breakage syndrome, Werner syndrome, Bloom syndrome, Rothmund–Thomson syndrome	DSB repair: Nbs, Wrn, Blm, RecQL4	Thompson and Schild, 2002; Varon et al., 1998; Yu et al., 1996; Ellis et al., 1995; Kitao et al., 1999
Fanconi anemia	DNA cross-link repair: FANCA–FANCG	Joenje and Patel, 2001

Thompson and Schild, 2002). However, this field is expanding so rapidly that it justifies updating. In this review, we will focus on the function and cooperation of human DNA repair proteins, their regulation, the corresponding genes and the role they play in DNA-damage signaling.

2. Reversion repair

2.1. Single-step repair by MGMT

Treatment of cells with S_N1 and S_N2 alkylating agents gives rise, to an extent depending on the agent, to *N*-alkylated and *O*-alkylated purines and pyrimidines as well as phosphotriesters. One of the most critical *O*-alkylated lesions is O^6-alkylguanine, although only amounting to less than 8% of total alkylations (Beranek, 1990). O^6-Alkylguanine, notably O^6-methylguanine (O^6MeG) and O^6-ethylguanine, are mispairing lesions providing the main source of GC → AT transition mutations after alkylation. Another pre-mutagenic alkylation lesion is O^4-methylthymine, which is induced, however, in minor amounts (<0.4%). In *Escherichia coli*, resistance to alkylating agents is mediated by the induction of four genes, *ada*, *alkA*, *alkB* and *aidB* (for review see Sedgwick and Lindahl, 2002), with Ada being involved in the repair of O^6MeG. In human cells, O^6-alkylation lesions can be repaired in a single-step reaction by O^6-methylguanine–DNA methyltransferase (MGMT; also known as ATase, AGT, AGAT), which is the homologue of the Ada (or the constitutively expressed OGT) gene product of *E. coli*. The human MGMT gene is located in the chromosome band 10q26, and consists of one non-coding and four coding exons that encode a protein of 207 amino acids with a molecular weight of 24 kDa (Tano et al., 1990). The repair protein transfers the methyl or chloroethyl group from the alkylated guanosine in a one-step reaction onto an internal cystein residue in its active centre (for review see Pegg et al., 1995). This alkyl group transfer leads to irreversible inactivation of the MGMT protein, and targets it for ubiquitination and proteasome-mediated degradation. The activity of MGMT has been determined in various human tumour and normal tissue such as brain, colon, ovary, testis and breast, revealing a highly variable expression notably in tumour tissue (for review see Margison et al., 2003). MGMT-deficient cells are unable to repair O^6MeG and are therefore sensitive to alkylating agents (Day et al., 1980; Yarosh et al., 1983), while MGMT transfection provokes expression-dependent resistance to O^6-alkylating agents. It also protects against alkylation-induced gene mutations, SCEs and chromosomal aberrations (Kaina et al., 1991). MGMT knockout mice are viable, show a higher frequency of spontaneous tumours and are sensitive to treatment with alkylating agents (Tsuzuki et al., 1996). Conversely, MGMT-overexpressing mice show a reduced

frequency of tumours in liver, thymus or skin (Becker et al., 1996; Dumenco et al., 1993; Nakatsuru et al., 1993; Zhou et al., 2001b). MGMT overexpression specifically protects against tumour initiation without affecting tumour promotion in two-stage carcinogenesis experiments (Becker et al., 1996, 1997). It also protects against tumour progression (Becker et al., 2003) upon exposure to O^6-alkylating agents. MGMT was the first mammalian DNA repair gene shown to be inducible by genotoxic stress (Fritz et al., 1991) and glucocorticoids (Biswas et al., 1999; Grombacher et al., 1996), leading to an adaptive response of cells to the cytotoxic and mutagenic effects of simple alkylating agents (Boldogh et al., 1998; Fritz et al., 1991). MGMT expression is highly regulated by methylation of both the gene and promoter. Methylation of the promoter provokes inhibition (Qian et al., 1995), whereas methylation of the gene results in increased expression of MGMT (Wang et al., 1992). Methylation was also shown to be involved in the development of acquired resistance of melanoma cells towards chloroethylating anticancer drugs (Christmann et al., 2001).

2.2. DNA-damage reversal by AlkB homologues

As already mentioned, in *E. coli*, pre-mutagenic DNA alkylation damage is reverted by the adaptive response system comprising the proteins Ada and AlkB. The expression of not only Ada but also AlkB in human cells increases their resistance to alkylating agents (Chen et al., 1994). Whereas the function of Ada was clarified soon after its discovery, AlkB remained enigmatic for a long time. Only recently its function has been illuminated, revealing a new mode of DNA restoration. AlkB specifically repairs methylation damage in both single- and double-stranded DNA and binds preferentially to single-stranded DNA in vitro (Dinglay et al., 2000). AlkB displays neither nuclease nor DNA glycosylase or methyltransferase activity. Instead it shares similarity with a superfamily of 2-oxoglutarate- and iron-dependent dioxygenases (Falnes et al., 2002; Trewick et al., 2002). AlkB repairs DNA alkylation damage such as 1-methyladenine and 3-methylcytosine in an oxygen, ketoglutarate and Fe(II)-dependent reaction, by coupling oxidative decarboxylation of ketoglutarate to hydroxylation of methylated bases (for review see Falnes et al., 2002). Recently three homologues of AlkB were identified in human cells which were designated as ABH1, ABH2 and ABH3. The ABH1 gene is localised at chromosome position 14q24, contains an open reading frame of 924 bp and encodes a 34 kDa protein which displays 23% identity to AlkB (Wei et al., 1996). ABH2 is located in chromosome 12q24 and consists of four exons. ABH3 is located at position 11q11 and harbours 10 exons. Similar to the bacterial AlkB, ABH2 and ABH3 belong to the superfamily of ketoglutarate- and Fe(II)-dependent dioxygenases, harbour the Fe(II)-binding motif and share 30.8 and 23.1% identity, respectively, with the core region of AlkB (Aas et al., 2003; Duncan et al., 2002). While the human ABH2 and ABH3 have been shown to rescue MMS sensitivity of AlkB-deficient *E. coli* mutants, the role of ABH1 is not yet clear. Thus ABH1 was shown to partially protect against MMS-induced cell killing in *E. coli* (Wei et al., 1996) which was contradicted, however, by another report (Duncan et al., 2002), leaving the question open whether ABH1 is indeed a functional AlkB homologue. Both enzymes, ABH2 and ABH3, have been shown to repair 1-methyladenine, 3-methylcytosine and 1-ethyladenine, but they differ in template specificity. While ABH3 repairs RNA and single-stranded DNA, ABH2 repairs preferentially single- and double-stranded DNA. It is supposed that ABH2 and ABH3 remove the methylation in an alpha-ketoglutarate-dependent mechanism similar to the AlkB protein, involving oxidative demethylation leading to direct damage reversal and restoration of the undamaged base.

2.3. Evolutionary changes of photoreactivation

Other proteins involved in DNA-damage reversion belong to the photolyase/cryptochrome family (for review see Thompson and Sancar, 2002). These enzymes are monomeric proteins of about 55–70 kD containing two non-covalently bound chromophores: the first chromophore is flavin (FADH) and the second, folate (MTHF) or deazaflavin (8-HDH). The photolyase binds to DNA damage induced by UV light in a light-independent way. The repair reaction however is light-dependent. Photolyases are able to revert both cyclobutane pyrimidine dimers (CPDs) and (6-4) photoproducts [(6-4)-PPs]. Photolyases have been found in bacteria, *S. cerevisiae*, *D. melanogaster*, *X.*

laevis, marsupialia and several plants but not in higher mammals, including *H. sapiens*. In humans, protein homologues to photolyases have been identified which are no longer required for DNA repair but for the regulation of the circadian rhythm. The following genes were cloned: *hCry1*, *hCry2*; *mCry1*, *mCry2*; (Hsu et al., 1996; Todo et al., 1997). *Cry1* and *Cry2* are expressed in several tissues such as liver, testis, brain and retina acting as circadian photoreceptors. *Cry1* and *Cry2* are thought to play antagonistic roles because *cry1*-/- mice display shortened and *cry2*-/- mice lengthened circadian periods (Thresher et al., 1998; van der Horst et al., 1999; Vitaterna et al., 1999). Cry reveals an interesting evolutionary change of a DNA repair enzyme into a protein with entirely different functions.

3. Base excision repair (BER)

BER is responsible for removing DNA-damaged bases, which can be recognised by specific enzymes, the DNA glycosylases. The main lesions subjected to BER are oxidised DNA bases, arising spontaneously within the cell, during inflammatory responses, or from exposure to exogenous agents, including ionising radiation and long-wave UV light. Another main source of lesions repaired by BER is DNA alkylation induced by endogenous alkylating species and exogenous carcinogens such as nitrosamines. Also, various anticancer drugs such as DTIC and temozolomide induce alkylation lesions repaired by BER. Lesions removed from DNA by BER include incorporated uracil, fragmented pyrimidines, *N*-alkylated purines (7-methylguanine, 3-methyladenine, 3-methylguanine), 8-oxo-7,8-dihydroguanine (8-OxoG) and thymine glycol and many others (see Table 2). The major oxidised purine, 8-OxoG, is highly mutagenic because of mispairing with adenine. *N*-Alkylpurines are vulnerable to spontaneous hydrolysis of the *N*-glycosylic bond, giving rise to apurinic/apyrimidinic (AP) sites, which are one of the most frequent (>10^4 formed per day per cell; Lindahl, 1990) and potent lethal (Loeb, 1985) lesions. Both modified bases and AP sites are repaired by BER, the mechanism of which is shown in Fig. 1. It proceeds in the following steps:

1. *Recognition, base removal and incision*: The first step in BER is carried out by specific DNA glycosylases which recognize and remove damaged or incorrect (e.g. uracil) bases by hydrolyzing the *N*-glycosidic bond (for review see Scharer and Jiricny, 2001). In mammalian cells, 11 different glycosylases have been found characterised by different substrate specificities and modes of action (summarised in Table 2). These DNA glycosylases are subgrouped into type I and type II glycosylases. Type I glycosylases remove modified bases leaving an AP site in DNA (e.g. MPG), whereas type II enzymes remove the base and subsequently cleave the AP site by an endogenous 3′-endonuclease activity giving rise to a single-strand break (e.g. OGG1). For type I glycosylases, incision into the phosphodiester bond of the AP site occurs by AP endonuclease (APE1 alias APEX, Ref-1 or HAP1) resulting in 5′-deoxyribose-5-phosphate (5′dRP) and 3′-OH (Wilson and Barsky, 2001). APE1 has been shown to interact with and to be stimulated by XRCC1 (Vidal et al., 2001). The deoxyribose residue at a regular AP site can either be in the furanose or aldehyde form.
2. *Nucleotide insertion*: The insertion of the first nucleotide is not dependent on the chemical structure of the AP site. During short-patch BER, 5′dRP is displaced by DNA polymerase β (Polβ), which inserts a single nucleotide (Dianov et al., 1992; Sobol et al., 1996; Wiebauer and Jiricny, 1990). Polβ is also involved in long-patch BER (Dianov et al., 1999; Klungland and Lindahl, 1997), inserting the first nucleotide at reduced AP sites (Podlutsky et al., 2001).
3. *Decision between short- and long-patch repair*: The critical step in the decision between short- and long-patch BER is the removal of 5′dRP upon the insertion of the first nucleotide. Besides polymerisation activity, Polβ also exerts lyase activity and is thereby able to catalyze the release of the hemiacetal form of 5′-dRP residues from incised AP sites by β-elimination (Matsumoto and Kim, 1995; Prasad et al., 1998; Sobol et al., 2000). In contrast, oxidised or reduced AP sites, 3′-unsaturated aldehydes or 3′-phosphates are resistant to β-elimination by Polβ (Nakamura et al., 2000). Upon dissociation of Polβ from damaged DNA, further processing occurs by

Table 2
Human DNA glycosylases

Glycosylase	Specificity	Reference
MBD4	U and T opposite G	Hendrich and Bird, 1998; Hendrich et al., 1999
MPG	3-MeA, 7-MeG, 3-MeG ethenoA, hypoxanthine	O'Connor and Laval, 1991; Chakravarti et al., 1991; Samson et al., 1991
MYH	A opposite 8-OxoG	Slupska et al., 1996; Slupska et al., 1999
NEIL1	Formamidopyrimidines oxidised pyrimidines (e.g. thymine glycol)	Hazra et al., 2002a; Hazra et al., 2002b
NEIL2	5-Hydroxyuracil; 5-hydroxycytosine	Hazra et al., 2002a; Hazra et al., 2002b
NEIL3	Fragmented and oxidised pyrimidines	Takao et al., 2002
NTH1	Ring-saturated, oxidised and fragmented pyrimidines	Aspinwall et al., 1997; Hilbert et al., 1997
OGG1	8-OxoG paired with C, T and G	Rosenquist et al., 1997; Radicella et al., 1997; Bjoras et al., 1997
SMUG1	Uracil	Nilsen et al., 2001; Haushalter et al., 1999
TDG	U, T or ethenoC, opposite G T opposite G, C and T	Neddermann et al., 1996; Neddermann and Jiricny, 1993; Neddermann and Jiricny, 1994
UNG	Uracil	Olsen et al., 1989; Muller and Caradonna, 1991

PCNA-dependent long-patch repair (Frosina et al., 1996; Matsumoto et al., 1999). For example, the removal of 8-OxoG occurs mainly via short-patch BER; only 25% of lesions are repaired via the long-patch repair pathway (Dianov et al., 1998).

4. *Strand displacement and DNA-repair synthesis by long-patch BER*: In contrast to short-patch repair, in which upon single base insertion by Polβ the DNA backbone is directly sealed, several additional steps occur during long-patch repair. After dissociation of Polβ, strand displacement and further DNA synthesis is accomplished by Polε or Polδ together with PCNA and RF-C (Stucki et al., 1998), resulting in longer repair patches of up to 10 nucleotides. The removal of the deoxyribosephosphate flap structure (5′-dRPflap) is executed by flap endonuclease FEN1 stimulated by PCNA (Klungland and Lindahl, 1997).
5. *Ligation*: The ligation step is performed by DNA ligases I and III (for review see Tomkinson et al., 2001). Ligase I interacts with PCNA and Polβ and participates mainly in long-patch BER (Prasad et al., 1996; Srivastava et al., 1998). DNA ligase III interacts with XRCC1, Polβ and PARP-1 [poly(ADP-ribose) polymerase-1] and is involved only in short-patch BER (Kubota et al., 1996).

An important role in the regulation of BER is played by p53. p53 stimulates BER in vitro by direct interaction with APE and Polβ, stabilizing Polβ binding to AP sites (Zhou et al., 2001a). Whether or not transcriptional activation by p53 is involved in the regulation of BER is not yet clear. Thus it has been shown that mutated p53 lacking transcriptional activity is even more effective in stimulating BER than wt p53 (Offer et al., 2001). On the other hand, DNA alkylation damage induced by MMS is efficiently repaired in cells expressing wt p53, whereas p53-deficient cells display slower repair (Seo et al., 2002), which is accompanied by increased chromosomal and killing sensitivity (Lackinger and Kaina, 2000). This p53-related phenotype is presumably based on the expression of Polβ, which is significantly lower in p53-deficient cells (Seo et al., 2002). Also, treatment of mice with the oxidative agent 2-nitropropane induces the expression of p53 and Polβ, and enhances BER activity (Cabelof et al., 2002).

An enzyme not directly involved in BER but reducing the level of oxidised purines in DNA is MTH1. It hydrolyzes 8-oxo-dGTP ot 8-oxo-dGMP, thereby removing it from the nucleotide pool and preventing 8-OxoG from becoming incorporated into DNA (Furuichi et al., 1994; Sakumi et al., 1993).

4. Mismatch repair (MMR)

The mismatch repair (MMR) system is responsible for removal of base mismatches caused by spontaneous and induced base deamination, oxidation,

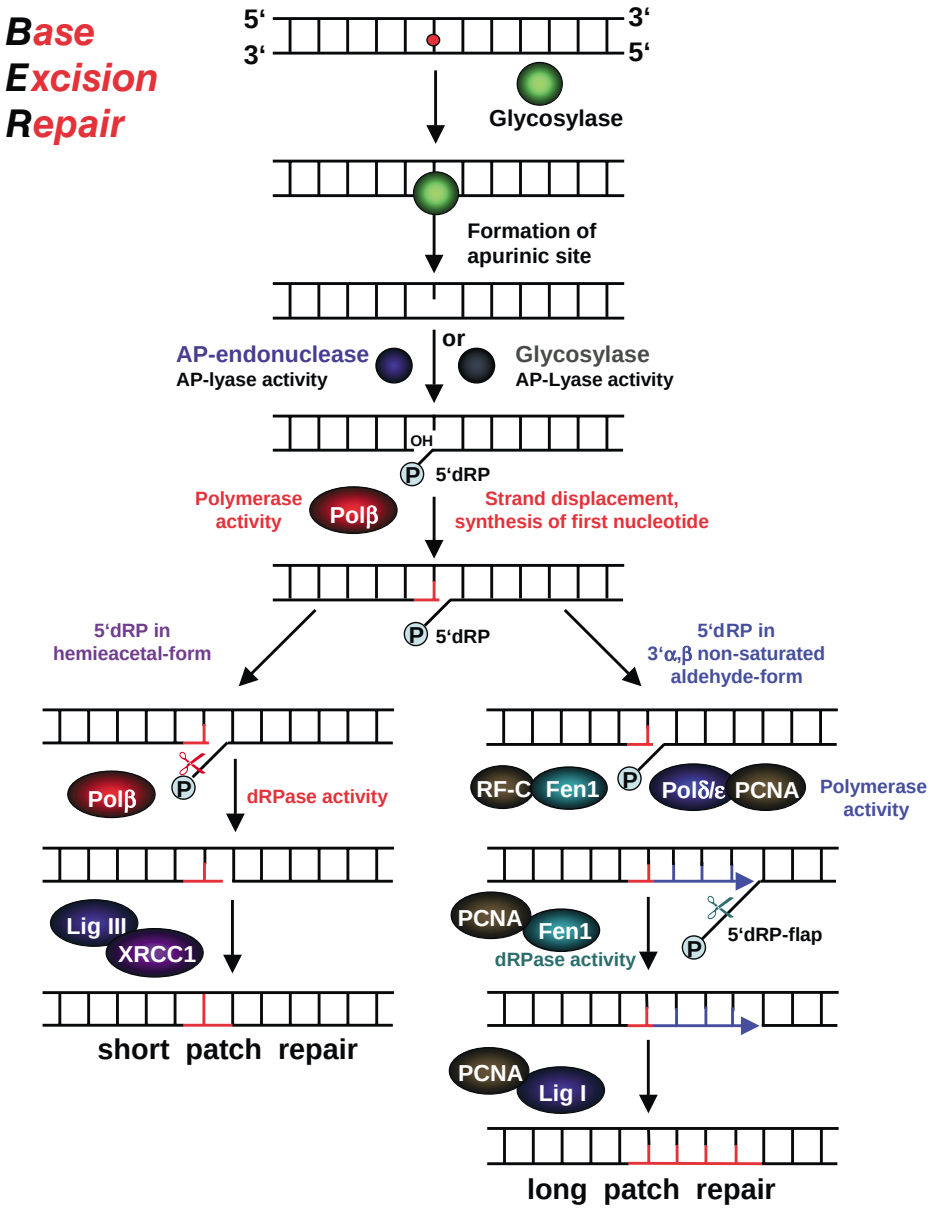

Fig. 1. Mechanism of base excision repair (BER). Recognition of the DNA lesion occurs by a specific DNA glycosylase which removes the damaged base by hydrolyzing the *N*-glycosidic bond. The remaining AP site is processed by APE. Depending on the cleavability of the resulting 5′dRP by Polβ, repair is performed via the short or long patch BER pathway. For further description see text.

methylation and replication errors (Modrich and Lahue, 1996; Umar and Kunkel, 1996). The main targets of MMR are base mismatches such as G/T (arising from deamination of 5-methylcytosine), G/G, A/C and C/C (Fang and Modrich, 1993). MMR not only binds to spontaneously occurring base mismatches but also to various chemically induced DNA lesions such as alkylation-induced O^6-methylguanine paired with cytosine or thymine (Duckett et al., 1996), 1,2-intrastrand (GpG) cross-links generated by

cisplatin (Mello et al., 1996; Yamada et al., 1997), UV-induced photoproducts (Wang et al., 1999), purine adducts of benzo[*a*]pyrene-7,8-dihydrodiol-9,10-epoxides (Wu et al., 1999a), 2-aminofluorene or *N*-acetyl-2-aminofluorene (Li et al., 1996), and 8-oxoguanine (Colussi et al., 2002). The importance of MMR in maintaining genomic stability and reducing mutation load is clearly illustrated by MMR deficiency syndromes such as HNPCC (Aaltonen et al., 1993; Lynch et al., 1993). The steps by which MMR proceeds are as follows (see Fig. 2):

1. *Recognition of DNA lesions*: The recognition of mismatches or chemically modified bases is performed by the so-called MutSα complex, which binds to the lesions. MutSα is composed of the MutS homologous proteins MSH2 (Fishel et al., 1993; Leach et al., 1993) and MSH6 (also known as GT-binding protein, GTBP; Palombo et al., 1995). For an efficient binding to mismatches, phosphorylation of the MutSα complex is required (Christmann et al., 2002). MSH2 can also form a complex with the mismatch repair protein MSH3. This complex is designated MutSβ (Acharya et al., 1996; Palombo et al., 1996). Depending on the binding partner, the heterodimers have different substrate specificities and, therefore, play a different role in mismatch repair. Thus, the MutSα complex is able to bind to base–base mismatches and to insertion/deletion mismatches (Umar et al., 1994), whereas MutSβ is only capable of binding to insertion/deletion mismatches (Genschel et al., 1998; Palombo et al., 1996).
2. *Strand discrimination*: Presently, it is not clear how MMR discriminates between the parental and the newly synthesised DNA strand. It is supposed that the daughter strand is identified by non-ligated single-strand breaks (SSB) arising during replication (Thomas et al., 1991). The problem with this model is that the SSB and the mismatch can be separated from each other by a great distance. How then can MutSα recognize both the SSB and the mismatch? An answer could be provided by the studies concerning the role of ATP during MMR. Both proteins (MSH2 and MSH6) contain ATP/ADP-binding sites (Gradia et al., 1999). Mutation of these sites leads to attenuation of MMR activity but not to abrogation of GT binding. Two models are under consideration concerning the role of ATP/ADP binding and ATP hydrolysis: In the molecular switch model (Fishel, 1998; Gradia et al., 1997), it is assumed that the MutSα–ADP complex is responsible for the recognition and binding of the mismatch (‘active state’). Binding to a mismatch triggers ADP → ATP transition and stimulates the intrinsic ATPase activity (Berardini et al., 2000; Gradia et al., 2000), leading to conformational changes and the formation of a hydrolysis-independent sliding clamp (Gradia et al., 1999). This sliding clamp passively diffuses from the mismatch and signals the dissociation of the MMR proteins from the DNA (‘inactive state’) (Gradia et al., 1997). In this model, hydrolysis of ATP by MutSα provokes conformational changes and thereby enables the binding of

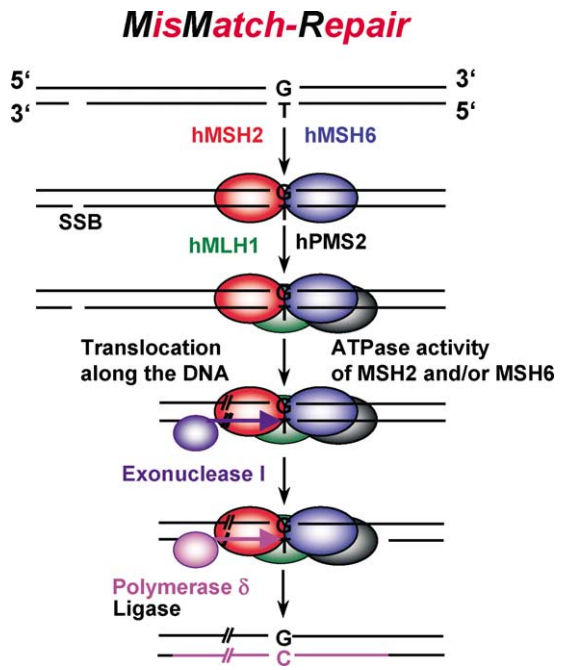

Fig. 2. Mechanism of mismatch repair (MMR). Recognition of DNA lesions occurs by MutSα (MSH2–MSH6). According to the molecular switch model, binding of MutSα–ADP triggers ADP → ATP transition, stimulates intrinsic ATPase activity, and provokes the formation of a hydrolysis-independent sliding clamp, followed by binding of the MutLα complex (MLH1–PMS2). According to the hydrolysis-driven translocation model, ATP hydrolysis induces translocation of MutSα along the DNA. After formation of a complex composed of MutSα and MutLα, excision is performed by ExoI and repair synthesis by Polδ.

MutLα. In addition, dissociation of MutSα from the DNA depends on ATP binding and not hydrolysis (Alani et al., 1997; Iaccarino et al., 1998). In the hydrolysis-driven translocation model, MutSα uses the energy gained by ATP hydrolysis to translocate actively along the DNA from the site of mismatch recognition to a site responsible for signaling the strand specificity (most likely SSB). The assembly of the MutLα complex occurs at this signaling site (Blackwell et al., 1998a,b, 2001).

3. *Excision and repair synthesis*: Upon binding to the mismatch, MutSα associates with another heterodimeric complex (MutLα), consisting of the MutL homologous mismatch repair proteins MLH1 and PMS2 (Li and Modrich, 1995; Nicolaides et al., 1994; Papadopoulos et al., 1994). The excision of the DNA strand containing the mispaired base is performed by exonuclease I (Genschel et al., 2002) and the new synthesis by Polδ (Longley et al., 1997). Whether or not MMR is inducible by genotoxic stress is still a matter of debate. The promoter of MSH2 harbours a p53-binding site and was found to be inducible upon co-transfection with p53 and Fos/Jun (Scherer et al., 2000; Warnick et al., 2001). Increase of MSH2 mRNA in genotoxin-exposed cells however still needs to be demonstrated. Treatment of cells with alkylating agents such as MNNG provoked nuclear translocation of MSH2/MSH6 and increase of MutSα-mismatch binding activity (Christmann and Kaina, 2000). Therefore, both transcriptional and post-translational mechanisms appear likely to be involved in the regulation of MMR.

5. Nucleotide excision repair (NER)

Bulky DNA adducts, such as UV-light-induced photolesions [(6-4) photoproducts (6-4PPs) and cyclobutane pyrimidine dimers (CPDs)], intrastrand cross-links, large chemical adducts generated from exposure to aflatoxine, benzo[*a*]pyrene and other genotoxic agents are repaired by nucleotide excision repair (NER) (for review see Friedberg, 2001; Hanawalt, 2001; Mullenders and Berneburg, 2001). In NER about 30 proteins are involved. Cells defective in NER belong to different complementation groups and UV-hypersensitive disorders such as xeroderma pigmentosum (XP), Cockayne's syndrome (CS), trichothiodystrophy (TTD), UV-sensitive syndrome (UVSS) and a variety of UV-hypersensitive rodent lines, in which the defect can be completed by human genes belonging to the excision repair cross-complementing group (ERCC) (for review see Vermeulen et al., 1997). NER consists of two distinct pathways termed global genomic repair (GGR) and transcription-coupled repair (TCR) (Fig. 3). GGR is thought to be largely transcription-independent and removes lesions from the non-transcribed domains of the genome and the non-transcribed strand of transcribed regions. 6-4PPs, which distort the DNA more than CPDs, are removed rapidly and predominantly by GGR, such that it may be difficult to detect TCR experimentally. In contrast, CPDs are removed very slowly by GGR. Their removal occurs more efficiently by TCR from the transcribed strand of expressed genes (for review see Balajee and Bohr, 2000; Hanawalt, 2002; Mullenders and Berneburg, 2001).

TCR removes different RNA-polymerase-blocking lesions from the transcribed strand of active genes (Bohr et al., 1985; Mellon et al., 1987). Defects in TCR are directly linked to the Cockayne's syndrome (Cockayne, 1936; van Hoffen et al., 1993), which involves two complementation groups: CSA (Henning et al., 1995) and CSB (Troelstra et al., 1992). CS cells display increased sensitivity to UV light, normal GGR and deficient TCR (Evans and Bohr, 1994; Venema et al., 1990). Since CS cells show a severe defect in the resumption of RNA synthesis, CS is also referred to as a 'transcription syndrome' besides being a 'repair syndrome' (Bootsma and Hoeijmakers, 1993). As opposed to most other UV-sensitive syndromes (with the exception of UVSS), CS patients do not suffer from elevated tumour incidences, which is most likely explained by efficient elimination of damaged cells by apoptosis (Ljungman and Zhang, 1996). CSA and CSB as well as XPB, XPD (as part of TFIIH) and XPG protein are essential for TCR (Le Page et al., 2000; Schaeffer et al., 1993). The reduced transcription in CSB cells upon UV irradiation is caused by blockage of RNA polymerase II (RNAPII) at the photoproduct sites (Selby et al., 1997). RNAPII activity is reduced in CSA-, CSB- and XPB-deficient cells (Balajee et al., 1997; Dianov et al., 1997), and CSB but not CSA interacts directly with RNAPII (Tantin

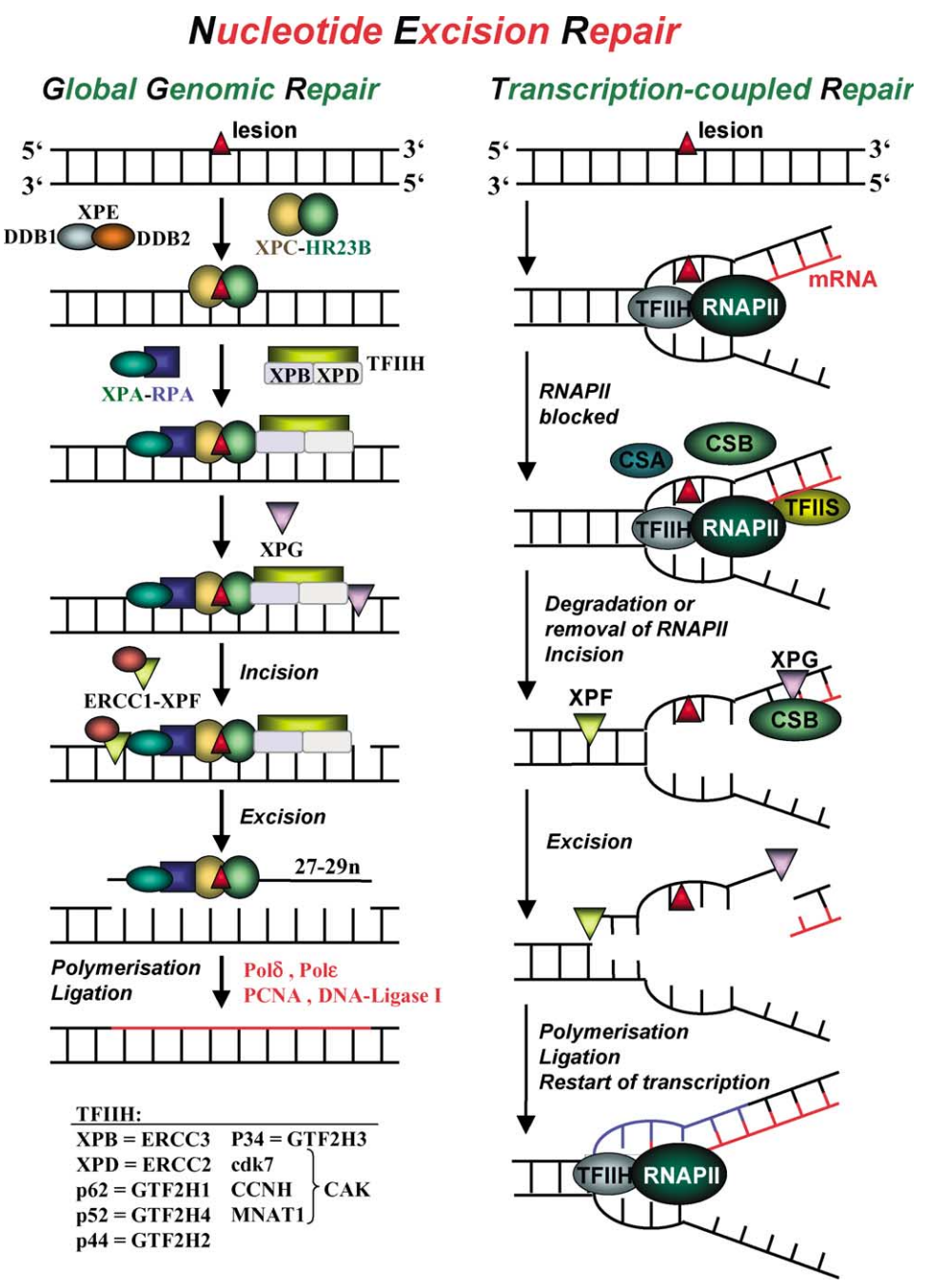

Fig. 3. Mechanism of nucleotide excision repair (NER). During global genomic repair (GGR), recognition of the DNA lesion occurs by XPC–HR23B, RPA–XPA or DDB1–DDB2. DNA unwinding is performed by the transcription factor TFIIH, and excision of the lesion by XPG and XPF–ERCC1. Finally, resynthesis occurs by Polδ or Polϵ and ligation by DNA ligase I. During transcription-coupled repair (TCR) the induction of the lesion results in blockage of RNAPII. This leads to assembly of CSA, CSB and/or TFIIS at the site of the lesion, by which RNAPII is removed from the DNA or displaced from the lesion, making it accessible to the exonucleases XPF–Ercc1 and XPG cleaving the lesion-containing DNA strand. Resynthesis again occurs by Polδ or Polϵ and ligation by DNA ligase I.

et al., 1997; van Gool et al., 1997). When RNAPII is blocked at the site of DNA lesions, CSA and CSB mediate the activation of the common NER pathway by release of the stalled RNAPII elongation complex from the damaged DNA (see Fig. 3). TCR and GGR could be linked through a direct interaction of CSB and XPG (Iyer et al., 1996). The way CSB interferes with the RNAPII transcription activity is not yet clear, although CSB likely acts as a 'repair-transcription uncoupling factor' (van Oosterwijk et al., 1996). Recent work suggests that CSB uses its DNA translocase activity to remove the RNAPII complex from the lesion (Svejstrup, 2003). Exposure to DNA-damaging agents such as cisplatin and UV light induces CSA- and CSB-dependent ubiquitination of the RNAPII at stalled transcription forks, facilitating its displacement and degradation by proteolysis (Bregman et al., 1996; Yang et al., 2003). In *S. cerevisiae*, an additional factor (Def1) has been identified, which interacts with Rad26 (the CSB homologue; van Gool et al., 1994) and which is supposed to be responsible for ubiquitination and proteolysis of RNAPII when the lesion cannot be repaired (Woudstra et al., 2002). Whether or not this factor is also present in human cells remains to be established. Interestingly, UV irradiation reduces the amount of the hypophosphorylated (DNA-binding) form of RNAPII and thereby suppresses the initiation of transcription upon UV. Reactivation of transcription initation could thus be mediated by restoration of the hypophosphorylated form of RNAPII (Rockx et al., 2000). In vitro studies have shown that the factor TFIIS may play a role in some situations, in which it unleashes a cryptic nucleolytic activity of the RNAPII to cleave up to 35 nucleotides from the 3′ end of the nascent RNA product as it regresses on the template, so that the arresting lesion becomes accessible for repair, before the re-elongation reaction resumes (Tornaletti et al., 1999). In this context, it was shown that RNAPII can be displaced from CPDs and cisplatin intrastrand cross-link in a TFIIS-dependent manner without being released from template DNA. Displacement of RNAPII for approximately 20 nucleotides from the lesion produces enough space for effective repair (Tornaletti et al., in press). An additional factor reported to be associated with TCR is the human homologue of factor 2 (HuF2, TTF2) and ATP-dependent RNA polymerase II termination factor (Liu et al., 1998), which was shown to release RNA polymerases I and II stalled at CPDs (Hara et al., 1999). We should note that MMR involving MSH2 was reported to stimulate TCR. This work however could not be confirmed by others and was finally retracted.

Another syndrome involved in TCR of CPDs is the so-called UV-sensitive syndrome (UVSS) (Itoh et al., 1995; Spivak et al., 2002) which does not belong to either of the CS complementation groups, indicating TCR to be more complex than initially thought. In contrast to TCR, the mechanism of GGR has been elucidated in great detail. It proceeds as follows (see Fig. 3):

1. *DNA-damage recognition*: The XPC–HR23B and RPA–XPA complexes identify DNA lesions. The XPC–HR23B complex recognizes UV-induced 6-4PPs with high specificity (Hey et al., 2002); it does not recognize CPDs, 8-oxoguanine or O^6-methylguanine (Kusumoto et al., 2001). In contrast, the RPA–XPA complex recognizes 6-4PPs and DNA treated with cisplatin (Burns et al., 1996; He et al., 1995; Jones and Wood, 1993; Vasquez et al., 2002). Not solved yet is the question of which complex is first during the sequential assembly of the NER proteins. Some authors claim that XPC–HR23B binds first to a helix distortion, which is verified by RPA–XPA and TFIIH (Sugasawa et al., 2001). Others suggest that RPA–XPA is the first DNA-damage recognition factor (Wakasugi and Sancar, 1999). Another important factor involved in the UV damage recognition process is the 'damaged DNA binding protein' (DDB), a heterodimer of two polypeptides DDB1 (p127) and DDB2 (p48) that belong to the XPE-complementation group (for review see Tang and Chu, 2002). DDB has been shown to be involved in recognition and to stimulate the excision of CPDs in vitro with high efficiency, whereas 6-4PPs are only marginally recognised. Cells lacking DDB display defective GGR but normal TCR (Hwang et al., 1999). DDB has a very high affinity to UV-damaged DNA (500 000-fold preference over undamaged DNA) and thus has been proposed to bind first to the lesion, thereby recruiting XPC/HR23B to the lesion in non-transcribed strand (Hwang et al., 1999). DDB was however also suggested to recruit XPA–RPA to the site

of DNA damage (Wakasugi et al., 2001, 2002), indicating presumably several ways of recruitment. An important observation was made by the demonstration that human p53-deficient primary fibroblasts display a defect in the repair of CPDs and reduced GGR efficiency (Ford and Hanawalt, 1995, 1997). This seems to be based on attenuated, DNA-damage-induced expression of the NER-associated genes XPC and DDB2 (alias p48). Both genes are inducible in human fibroblasts upon exposure to UV-C light, which occurs through p53 (Adimoolam and Ford, 2002; Hwang et al., 1999). p53-deficient Li–Fraumeni syndrome cells do not show DDB2 upregulation and they are correspondingly defective in repair of CPDs (Ford and Hanawalt, 1995). This defect however can be restored by transfection with p53, whose overexpression on its own is able to stimulate DDB2 transcription (Hwang et al., 1999). XPC is also inducible by ionizing radiation and alkylating agents (Amundson et al., 2002), and by treatment with benzo[*a*]pyrene diol epoxide (Wang et al., 2003). Whereas p53-dependent induction of DDB2 was shown in human cells, in mice DDB2 does not seem to be inducible upon UV-C exposure (Tan and Chu, 2002). Therefore most rodent cell lines are considered to be impaired in GGR. In the absence of p53, XPC and DDB2 can also be induced via overexpression of BRCA1 (Hartman and Ford, 2002; Takimoto et al., 2002).

2. *DNA unwinding*: After recognition of the lesion, the transcription factor TFIIH consisting of seven different proteins (XPB, XPD, GTF2H1, GTF2H2, GTF2H3, GTF2H4, CDK7, CCNH and MNAT1) is recruited to the site of DNA damage. This recruitment is most likely mediated by the XPC–HR23B complex (Yokoi et al., 2000). TFIIH harbours DNA helicase activity, which is exerted by its helicase subunits XPB (Schaeffer et al., 1993) and XPD (Schaeffer et al., 1994). It is responsible for unwinding the DNA around the lesion (Evans et al., 1997a).
3. *Excision of the DNA lesion*: After damage recognition and the formatin of an open complex, excision of the lesion is carried out by dual incisions at defined positions flanking the DNA damage (Evans et al., 1997b). 3′-incision is performed by XPG (Habraken et al., 1994; O'Donovan et al., 1994), and 5′-incision by the XPF–ERCC1 complex (Sijbers et al., 1996).
4. *Repair synthesis*: The arising DNA gap is filled in by Polδ and Polε and sealed by DNA ligase I and accessory factors (Aboussekhra et al., 1995; Araujo et al., 2000; Mu et al., 1995).

6. DNA double-strand break repair

DNA double-strand breaks (DSBs) are highly potent inducers of genotoxic effects (chromosomal breaks and exchanges) and cell death (Dikomey et al., 1998; Lips and Kaina, 2001; Pfeiffer et al., 2000). In higher eukaryotes a single non-repaired DSB inactivating an essential gene can be sufficient for inducing cell death via apoptosis (Rich et al., 2000). There are two main pathways for DSB repair, homologous recombination (HR) and non-homologous end-joining (NHEJ), which are error-free and error-prone, respectively (see Figs. 4 and 5). In simple eukaryotes like yeast, HR is the main pathway, whereas in mammals the NHEJ pathway predominates (Cromie et al., 2001; Haber, 2000). The usage of NHEJ and HR also depends on the phase of the cell cycle. NHEJ occurs mainly in G0/G1, whereas HR occurs during the late S and G2 phases (Johnson and Jasin, 2000; Takata et al., 1998).

The NHEJ system ligates the two ends of a DSB without the requirement of sequence homology between the DNA ends (for review see Critchlow and Jackson, 1998). The first step in NHEJ is the binding of a heterodimeric complex consisting of the proteins Ku70 (Reeves and Sthoeger, 1989) and Ku80 (alias XRCC5; Jeggo et al., 1992) to the damaged DNA, thus protecting the DNA from exonuclease digestion. Following DNA binding, the Ku heterodimer associates with the catalytic subunit of DNA–PK (XRCC7, DNA–PKcs; Sipley et al., 1995; Hartley et al., 1995) thereby forming the active DNA–PK holoenzyme (Gottlieb and Jackson, 1993; Smith and Jackson, 1999). DNA–PKcs is activated by interaction with a single-strand DNA at the site of DSB (Hammarsten et al., 2000; Martensson and Hammarsten, 2002) and displays Ser/Thr kinase activity (Kim et al., 1999). One of the targets of DNA–PKcs is XRCC4 (Leber et al., 1998), which

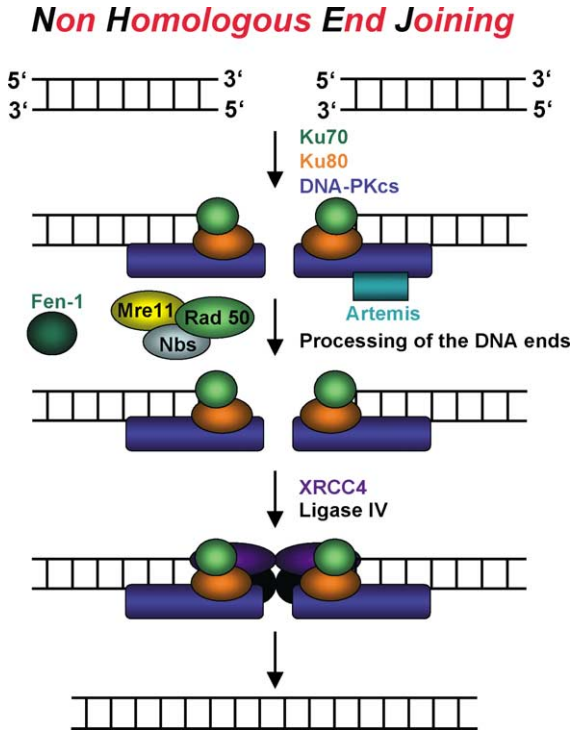

Fig. 4. Mechanism of non-homologous end joining (NHEJ). Recognition of and binding to damaged DNA occurs by the Ku70–Ku80 complex. Thereafter, the Ku heterodimer binds to DNA–PKcs, forming the DNA–PK holoenzyme. DNA–PK activates XRCC4–ligase IV, which links the broken DNA ends together. Before re-ligation by XRCC4–ligase IV, the DNA ends are processed by the MRE11–Rad50–NBS1 complex, presumably involving FEN1 and Artemis.

forms a stable complex with DNA ligase IV. The XRCC4–ligase IV complex binds to the ends of DNA molecules and links together duplex DNA molecules with complementary but non-ligatable ends (Lee et al., 2003). The XRCC4–ligase IV complex cannot directly re-ligate most DSBs generated by mutagenic agents—they have to be processed first. Processing of DSBs is mainly performed by the MRE11–Rad50–NBS1 complex (Maser et al., 1997; Nelms et al., 1998), which displays exonuclease, endonuclease and helicase activity (Paull and Gellert, 1999; Trujillo et al., 1998) and removes excess DNA at 3′ flaps. One candidate responsible for removal of 5′ flaps is the flap endonuclease 1 (FEN1). Deficiency for this protein leads to a strong reduction in the usage of the NHEJ pathway (Wu et al., 1999b). Another protein involved in processing overhangs during NHEJ is the protein Artemis, which acts in a complex with DNA–PK (Moshous et al., 2001). Artemis displays single-strand-specific exonuclease activity. Upon forming a complex with and being phosphorylated by DNA–PKcs, Artemis acquires endonuclease activity, degrading single-strand overhangs and hairpins, which seems to be necessary for processing 5′ and 3′ overhangs during NHEJ (Ma, 2002).

During HR, the damaged chromosome enters into physical contact with an undamaged DNA molecule with which it shares sequence homology and which is used as template for repair (for review see Sonoda et al., 2001). HR is initiated by a nucleolytic resection of the DSB in the 5′–3′ direction by the MRE11–Rad50–NBS1 complex. The resulting 3′ single-stranded DNA is thereafter bound by a heptameric ring complex formed by Rad52 proteins (Stasiak et al., 2000), which protects against exonucleolytic digestion. Rad52 competes with the Ku complex for the binding to DNA ends. This may determine whether the DSB is repaired via the HR or the NHEJ pathway (Van Dyck et al., 1999). Rad52 interacts with Rad51 (Kagawa et al., 2001; Reddy et al., 1997; Shen et al., 1996) and RPA (Park et al., 1996), stimulating DNA strand exchange activity of Rad51 (New et al., 1998). The human Rad51 protein is the homologue of the *E. coli* recombinase RecA. It forms nucleofilaments, binds single- and double-stranded DNA and promotes ATP-dependent (Benson et al., 1994) and RPA-stimulated (Sigurdsson et al., 2001) interaction with a homologous region on an undamaged DNA molecule. Thereafter Rad51 catalyzes strand-exchange events with the complementary strand in which the damaged DNA molecule invades the undamaged DNA duplex, displacing one strand as D-loop (Baumann and West, 1997; Gupta et al., 1998). In yeast, Rad54 (ATRX) displays dsDNA-dependent ATPase activity (Petukhova et al., 1998) and uses the energy for unwinding of the dsDNA (Petukhova et al., 1999), thus stimulating DNA strand exchange. The assembly of the Rad51 nucleoprotein filament is facilitated by five different paralogues of Rad51 (Rad51B, C and D; and XRCC2 and XRCC3) that could play a role during pre-synapsis (Liu et al., 2002; Masson et al., 2001; Schild et al., 2000; Takata et al., 2000; Wiese et al., 2002). Another

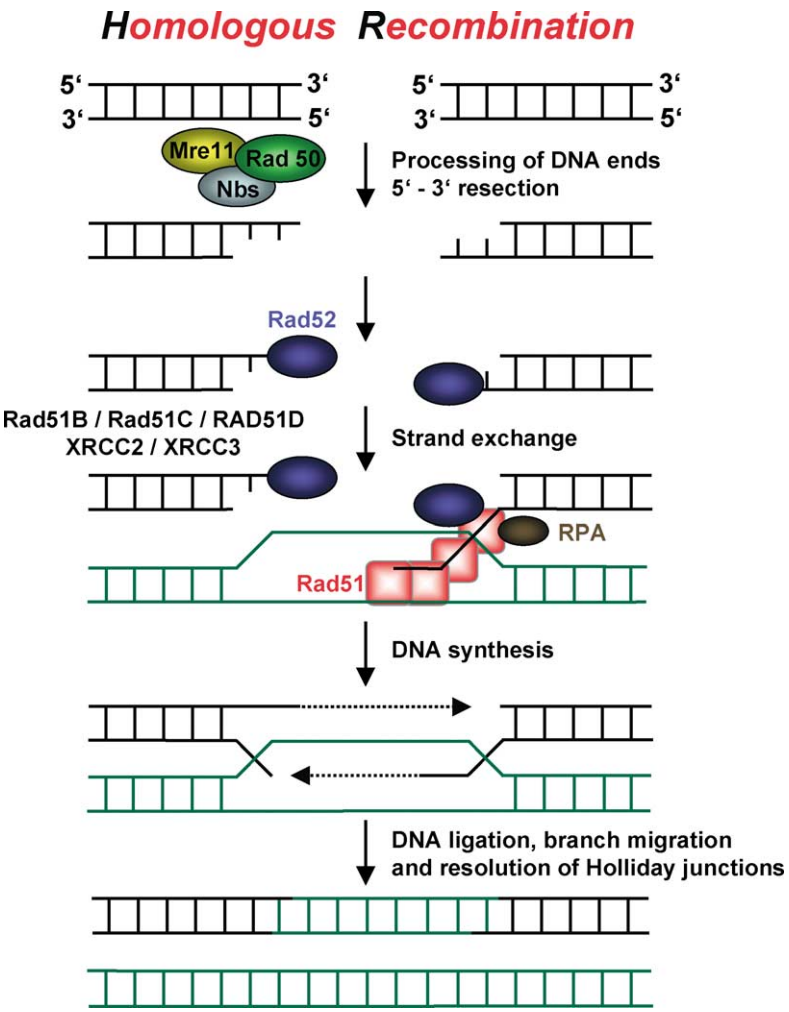

Fig. 5. Mechanism of homologous recombination (HR). Homologous recombination starts with nucleolytic resection of the DSB in the 5′ → 3′ direction by the MRE11–Rad50–NBS1 complex, forming a 3′ single-stranded DNA fragment to which Rad52 binds. Rad52 interacts with Rad51, provoking a DNA strand exchange with the undamaged, homologous DNA molecule. Assembly of the Rad51 nucleoprotein filament is facilitated by different Rad51 paralogues (such as Rad51B, Rad51C and Rad51D, XRCC2 and XRCC3). After DNA synthesis, ligation and branch migration, the resulting structure is resolved.

important protein that interacts with Rad 51 is RPA (Golub et al., 1998; Park et al., 1996). It is supposed that RPA stabilizes Rad51-mediated DNA pairing by binding to the displaced DNA strand (Eggler et al., 2002). After DSB recognition and strand exchange performed by Rad proteins, the resulting structures are resolved according to the classical model of Holliday (Holliday, 1964; see also Constantinou et al., 2001).

7. DNA-damage signaling and checkpoint control: ATM and ATR

Recognition and signaling of DNA damage is a prerequisite for the induction of subsequent cellular responses such as increased repair, cell cycle arrest and apoptosis. Recognition of DNA breaks is accomplished by a group of phosphatidylinositol-3-kinases. These kinases are ATM (ataxia telangiectasia mutated;

Savitsky et al., 1995; Smith et al., 1999), ATR (ataxia telangiectasia related) and the catalytic subunit of DNA–PK (Hartley et al., 1995). Their targets share the consensus sequence Ser–Thr–Gln–Glu (Kim et al., 1999). ATR and ATM can bind to DNA ends of damaged DNA, which results in activation of the kinase activity (Smith and Jackson, 1999; Suzuki et al., 1999; Unsal-Kacmaz et al., 2002). Activation of ATM in response to ionizing radiation is most likely not dependent on direct binding of ATM to DNA strand breaks but rather on changes in chromatin structure. These changes are thought to induce, by a yet unknown mechanism, autophosphorylation of ATM at Ser1981, leading to dissociation of ATM dimers into active monomers (Bakkenist and Kastan, 2003). Several DNA-damage repair proteins such as BRCA1, MSH2, MSH6, MLH1, ATM, BLM, and the RAD50–MRE11–NBS1 complex, can be co-immunoprecipitated in the so called BRCA1-associated surveillance complex, named BASC (Wang et al., 2000a). Latest results indicate that MLH1 and MSH2 are directly involved in the activation of ATM. Thus it was shown that, upon exposure to IR, MLH1 binds to ATM and MSH2 binds to CHK2 (Brown et al., 2003). Therefore, it is tempting to speculate that the MMR system recognises IR-induced lesions forming a molecular scaffold that allows ATM to phosphorylate CHK2, thereby activating the S-phase checkpoint.

ATM phosphorylates Chk2 (Matsuoka et al., 2000; Zhou et al., 2000) at Thr 68, whereas ATR targets Chk1 by phosphorylation at Ser345 (Guo et al., 2000; Liu et al., 2000). Both Chk2 and Chk1 are able to phosphorylate p53 at Ser20 (Shieh et al., 2000), giving rise to blockage of the MDM2-binding site-thus leading to release of p53 from MDM2-a protein that normally targets p53 for ubiquitin-dependent degradation (Chehab et al., 1999, 2000; Hirao et al., 2000; Unger et al., 1999). ATM and ATR can also directly phosphorylate p53 at Ser15, thereby increasing its transactivation activity (Banin et al., 1998; Canman et al., 1998). Stabilisation and increased transactivation activity of p53 leads to the induction of p21, which inhibits the Cdk2–cyclin E–PCNA complex, resulting in G1/S blockage. ATR-activated Chk1 can also phosphorylate Cdc25a at Ser123. This leads to ubiquitination and degradation of Cdc25a (Mailand et al., 2000), which is thereafter not able anymore to activate the Cdk2–cyclin E complex by dephosphorylation of CDK2 at Thr14 and Tyr15, resulting in p53-independent G1/S arrest. ATR-activated Chk1 was also shown to phosphorylate Cdc25c at Ser216, which induces binding of Cdc25c to 14-3-3σ protein (Peng et al., 1997; Sanchez et al., 1997). Within this complex, Cdc25c is transported out of the nucleus and therefore unable to dephosphorylate/activate Cdk1–CyclinB, which finally leads to G2/M arrest (Dalal et al., 1999).

Besides regulation of cell cycle checkpoints, ATM and ATR have been shown to regulate DNA repair. Thus ATM phosphorylates several DNA-repair associated proteins such as Nbs1 (Gatei et al., 2000; Lim et al., 2000), Brca1 (Xu et al., 2002), Rad9 (Chen et al., 2001) and c-Abl, resulting in phosphorylation of Rad51 (Chen et al., 1999; Shangary et al., 2000). It also phosphorylates 2AX (Burma et al., 2001). ATM-mediated phosphorylation of Nbs1 in response to ionizing radiation at Ser343 and Ser278 is necessary for the formation of nuclear Nbs1/Rad50/Mre11 foci at the site of DNA damage (Zhao et al., 2000). NF-κB activation in response to DSBs is mediated via ATM-dependent phosphorylation of IκB kinase (Li et al., 2001). Similar to ATM, ATR has also been shown to phosphorylate several DNA repair proteins or repair-associated factors such as Rad17 (Post et al., 2001) and Brca1 (Tibbetts et al., 2000). In addition, upon DNA damage ATM and DNA–PKcs mediate the phosphorylation of c-Abl; this targets p53 and p73, which exert pro-apoptotic activity (Kharbanda et al., 1998; Wang, 2000). Overall, ATM/ATR-mediated phosphorylation of proteins, notably Chk1, Chk2 and p53, is crucial in provoking the signal leading to the G1/S and G2/M cell cycle arrest, apoptosis and enhanced DNA repair (see Fig. 6).

8. Role of PARP in DNA repair

An important role in the regulation of DNA repair is played by the members of the so-called poly(ADP-ribose) polymerase (PARP) family. These chromatin-associated enzymes modify several proteins by poly(ADP-ribosyl)ation. During this process PARP consumes NAD^+ to catalyze the formation of highly negatively charged poly(ADP-ribose) polymers of linear or branched structure with a length

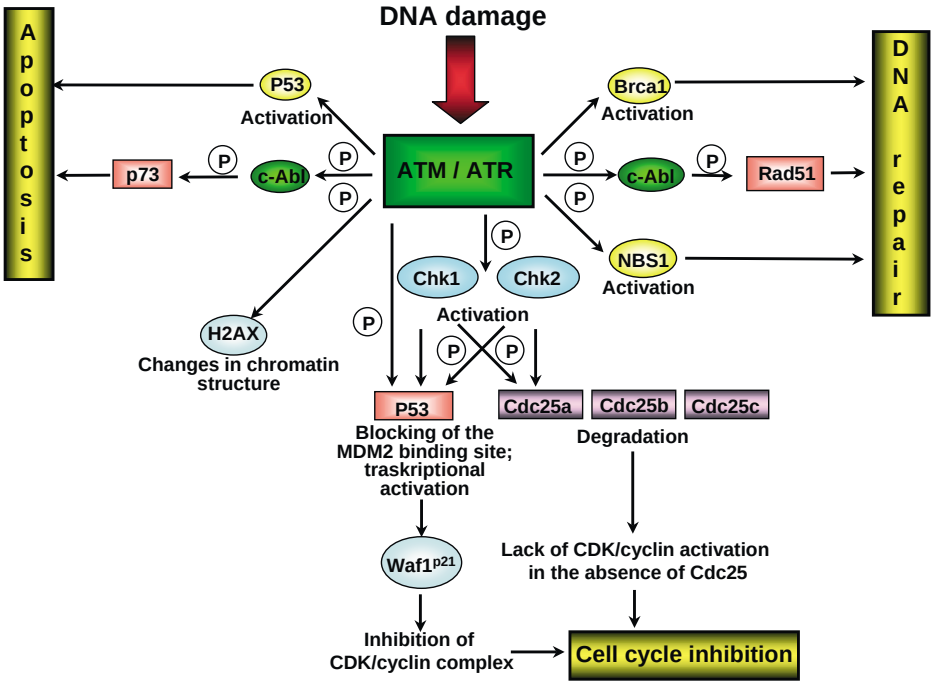

Fig. 6. ATM/ATR in DNA repair, cell cycle control and apoptosis. Recognition and signaling of DNA damage is mediated by ATM and ATR, which bind to broken DNA ends and possibly some DNA adducts. Upon activation of their intrinsic kinase activity, ATM and/or ATR phosphorylate Chk1 and Chk2, which in turn phosphorylate p53 and CDc25, thus provoking cell cycle arrest. In addition, ATM and/or ATR phosphorylate several other proteins (NBS1, Brca1) and thereby stimulate DNA repair or, at high damage level, the induction of apoptosis (via c-Abl, p53).

of 200–400 monomers, releasing nicotinamide as a by-product (for review see Lindahl et al., 1995). The degradation of polymers is performed by poly(ADP-ribose) glycohydrolase (PARG). PARG exhibits endoglycosidic and exoglycosidic activity and produces a mono(ADP-ribosyl)ated protein plus mono(ADP-ribose) (Brochu et al., 1994; Thomassin et al., 1992).

Up to now, six different PARPs have been described, sharing a conserved catalytic domain responsible for poly(ADP-ribose) synthesis. While PARP-1 (Alkhatib et al., 1987; Cherney et al., 1987) plays an important role in DNA repair, the role of PARP-2 (Ame et al., 1999; Berghammer et al., 1999; Still et al., 1999), PARP-3 (Johansson, 1999), vPARP (Kickhoefer et al., 1999), Tankyrase 1 and 2 (Chi and Lodish, 2000; Kaminker et al., 2001; Lyons et al., 2001; Smith et al., 1998), and TiPARP (Ma et al., 2001) is not yet completely determined. Besides its role in the regulation of DNA repair, PARP-1 has also been implicated in mammalian longevity (for review see Bürkle, 2001). It is considered to be a master switch between apoptosis and necrosis (for review see Soldani and Scovassi, 2002). PARP-1 has a molecular weight of 113 kDa and comprises three different domains: the N-terminal DNA-binding domain consisting of two zinc-fingers and the nuclear location signal, the C-terminal catalytic subunit which binds NAD^+, and an internal domain which functions as acceptor site for poly(ADP-ribose) (Kameshita et al., 1984). In response to DNA damage induced by ionizing radiation or alkylating agents, PARP-1 can specifically bind to SSBs (Gradwohl et al., 1989; Menissier-de Murcia et al., 1989). Upon binding to DNA, PARP-1 becomes auto-poly-(ADP-ribosyl)ated, which allows it to non-covalently interact with other proteins (for review see Lindahl et al., 1995). It has been argued that PARP-1 (and presumably PARP-2) is involved in DNA repair by three different mechanisms (summarised in Fig. 7): (i) By direct interaction

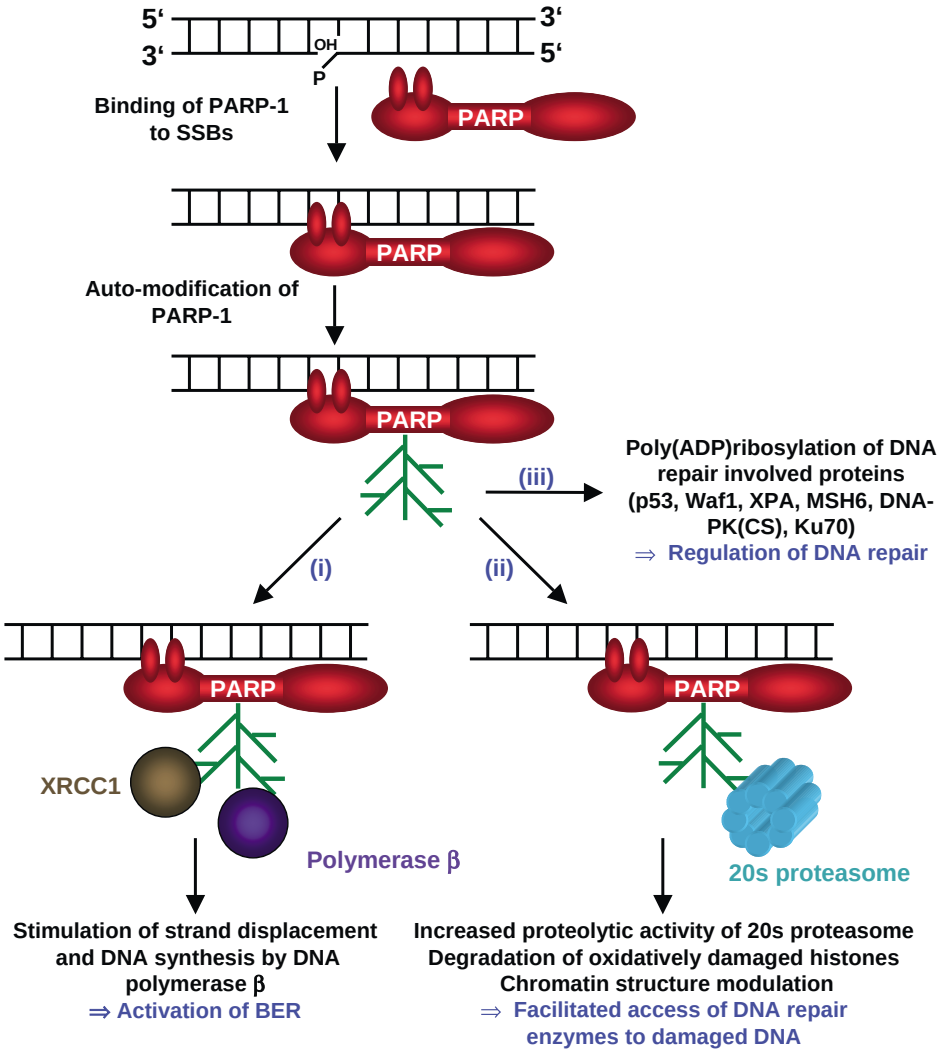

Fig. 7. Role of PARP in the regulation of DNA repair. Binding of PARP-1 to SSBs results in auto-poly(ADP)-ribosylation and increased activity. Activated PARP-1 is involved in DNA repair via: (i) direct interaction and poly(ADP) ribosylation of XRCC1 and Polβ, leading to stimulation of BER; (ii) poly(ADP) ribosylation and activation of the 20S proteasome, leading to relaxation of the chromatin structure; and (iii) potential poly(ADP) ribosylation of DNA-repair proteins, thus modulating DNA repair.

of automodified PARP-1 with XRCC1 (Caldecott et al., 1996; Masson et al., 1998) and Polβ (Dantzer et al., 2000), which are both key proteins in BER. PARP-2 interacts with XRCC1, Polβ, and DNA ligase III (Schreiber et al., 2002). PARP-1 stimulates in vitro, together with FEN-1, strand displacement and DNA-repair synthesis by Polβ, thus stimulating long-patch BER (Lavrik et al., 2001; Prasad et al., 2001; Sanderson and Lindahl, 2002). It should be noted that PARP-1-deficient mice are hypersensitive to methylnitrosurea (MNU) and cell lines generated from these animals are hypersensitive to MMS, showing reduced DNA strand-break resealing and increased apoptosis (Beneke et al., 2000; Trucco et al., 1998). (ii) By remodelling of chromatin structure upon the induction of DNA damage. Thus it has been shown that automodified PARP-1 interacts with the 20s proteasome via ADP-ribose polymers. The

interaction and poly(ADP)-ribosylation of the 20s proteasome results in increased proteolytic activity of the proteasome (Mayer-Kuckuk et al., 1999). The activated 20s proteasome has been shown to be responsible for degradation of oxidatively damaged histones. Among different histones, histone H1 displays the highest degradation rate; after 30 min of oxidative stress, it is already fully degraded (Ullrich and Grune, 2001; Ullrich et al., 1999). Histone degradation leads to chromatin structure remodelling, giving DNA repair enzymes access to the site of DNA damage. (iii) A specific poly(ADP-ribose)-binding sequence motif was found in a number of DNA-repair and DNA-damage checkpoint proteins such as p53, p21, XPA, MSH6, DNA ligase III, XRCC1, DNA–PKcs, Ku70, NF-κB, Pole, inducible nitric oxide synthase, caspase-activated DNase and telomerase. By poly(ADP)-ribosylation of this motif, PARP-1 could potentially interfere with several functions these proteins are involved in, such as regulation of transcription, DNA repair, cell cycle regulation and apoptosis (Pleschke et al., 2000).

9. Replication arrest and translesion synthesis

Bulky DNA lesions block DNA replication directly. DNA-damage-induced replication arrest leads to the recruitment of several DNA repair proteins to the position of the DNA lesion, e.g. the arrested replication fork. The question of how this recruitment is mediated is not fully solved. During normal DNA replication PCNA (proliferating cell nuclear antigen) forms a sliding clamp (Thelen et al., 1999) and stimulates replication by DNA polymerases (Tsurimoto, 1998). Loading of PCNA onto the DNA is performed by a so-called clamp loader, which is identical to the replication factor C (RFC) (Ellison and Stillman, 2001; Waga and Stillman, 1998). It is assumed that upon replication arrest, various factors can take over the function of PCNA and RFC. The function of PCNA in DNA repair is most likely accomplished by a DNA-damage-specific clamp (Rad9-1-1 complex), formed by the proteins Rad9, Hus1 and Rad1 (Burtelow et al., 2001; Lieberman et al., 1996; Parker et al., 1998a; St. Onge et al., 1999; Volkmer and Karnitz, 1999). It could serve as a docking platform for various DNA repair proteins. In this context it should be noted that Hus1 translocates upon ionizing radiation from the cytosol into the nucleus, where it associates with PCNA and hRad9 (Komatsu et al., 2000). Another human protein, Rad17 (Parker et al., 1998b), binds to chromatin prior to DNA damage. It gets phosphorylated after the induction of DNA damage by ATR and thus recruits the Rad9-1-1 complex onto chromatin (Bao et al., 2001). Rad17 has been shown to interact directly with the Rad9-1-1 complex in yeast (Venclovas and Thelen, 2000) and in humans (Rauen et al., 2000). Rad17 is supposed to replace the major subunit of the RFC complex (RFC1), forming a new complex with the smaller RFC subunits designated as Rad17–RFC, as has already been shown in yeast (Kai et al., 2001). Rad17–RFC functions as a clamp loader for Rad9-1-1 (Shiomi et al., 2002; Zou et al., 2002), which is supposed to target DNA repair genes to the site of damage. In yeast it has been shown that the error-prone polymerase DinB interacts with Hus1/Rad1, and its association with chromatin is Rad17-dependent (Kai and Wang, 2003).

DNA repair proteins associated with recovery from and bypassing of the replication block (translesion synthesis) are named ‘error-prone’ DNA polymerases (for a recent review see Lehmann, 2002). Because of different naming of polymerases by different groups, the nomenclature of the polymerases is slightly confusing. A recent consensus was published by Burgers (Burgers et al., 2001). An overview on error-prone DNA polymerases and their specificities is given in Table 3.

Translesion DNA synthesis is mainly mediated by polymerase eta, kappa, iota, mu and zeta (for review see Kunkel et al., 2003). Pol eta (Polη alias PolH; hRad30; XPV; Johnson et al., 1999; Masutani et al., 1999; McDonald et al., 1999) is a low-fidelity enzyme, which lacks intrinsic proof-reading exonuclease activity and therefore shows high error rates (10^{-2} to 10^{-3}) (Matsuda et al., 2001; Washington et al., 2001). Polη is implicated in the development of the variant form of xeroderma pigmentosum (XP) and has been shown to reduce the UV sensitivity in XP cells (Yamada et al., 2000). The human polymerase kappa (Polκ; DINB; Gerlach et al., 1999, 2001; Johnson et al., 2000a; Ogi et al., 1999) is the homologue of the *E. coli dinB*-encoded DNA polymerase IV. Polκ also exhibits a high error rate; but in contrast to other error-prone DNA polymerases,

Table 3
Human error-prone DNA polymerases involved in bypass of DNA replication-blocking lesions

Polymerase	Specificity	Reference
Pol eta (Polη)	A-A opposite (T-T) dimer	Johnson et al., 2000b
	G opposite 3′ T of (6-4) T-T photoproduct	Johnson et al., 2001
	C opposite AAF-G	Masutani et al., 2000
	C opposite intrastrand cross-links	Masutani et al., 2000
	A or C opposite 8-OxoG	Haracska et al., 2000
	A or G opposite AP-sites	Zhang et al., 2000a
	A opposite thymine glycol	Zhang et al., 2000b
Pol kappa (Polκ)	AP-sites and (AAF)-adducts	Ohashi et al., 2000b
	A opposite thymine-glycol	Fischhaber et al., 2002
	A opposite 8-OxoG	Haracska et al., 2002
	A opposite AP-sites and 8-OxoG	Kusumoto et al., 2002
Pol iota (Polι)	T or G opposite the 3′ T of the CPD	Tissier et al., 2000a
	G>T>A opposite AP-sites	Zhang et al., 2001
	C>A opposite 8-oxoguanine	Zhang et al., 2001
	C opposite AAF-G	Zhang et al., 2001
	A opposite 3′ T of TT (6-4) photoproduct	Frank et al., 2001
	Base excision repair	Bebenek et al., 2001
Pol zeta (Polζ)	G opposite 3′ T of (6-4) T-T photoproduct	Johnson et al., 2001
	A opposite 5′ T of (6-4) T-T photoproduct	
Pol mu (Polμ)	8-Oxoguanine, AP-sites, AAF-G anti-benzo[*a*]pyrene-N(2)-dG	Zhang et al., 2002
	A-A opposite (T-T) dimer	Zhang et al., 2002
	V(D) J-recombination	Ruiz et al., 2001
	Non-homologous end-joining	Ruiz et al., 2001
Pol lambda (Polλ)	*Base excision repair*	Garcia-Diaz et al., 2000
Pol sigma (Polσ)	*Sister chromatid cohesion*	Wang et al., 2000b
Pol theta (Polθ)	*Interstrand cross-link repair*	Sharief et al., 1999

it has a moderate processivity and can synthesize more than 25 nucleotides during translesion synthesis (Ohashi et al., 2000a). Polymerase iota (Polι; RAD30B; McDonald et al., 2001) is the homologue of *S. cerevisiae* RAD30. It displays a high error frequency (1×10^{-2}), with adenine replicated with the highest and thymine with the lowest accuracy (Tissier et al., 2000b). The human polymerase mu (Polμ; Dominguez et al., 2000) has a strong homology to the terminal deoxynucleotidyl transferase. Polymerase zeta (Polζ; REV3L; Gibbs et al., 1998; Lin et al., 1999; Xiao et al., 1998) consists of two subunits (REV3 and REV7), which cooperate with REV1 (Murakumo, 2002; Murakumo et al., 2000, 2001).

Besides translesion synthesis, some error-prone DNA polymerases also appear to be involved in direct removal of lesions. Thus, human polymerase lambda (Polλ) exhibits 32% homology to Polβ, displays deoxyribose phosphate lyase (dRPase) activity, inserts nucleotides in small gaps containing a 5′-phosphate group (Garcia-Diaz et al., 2002) and is therefore associated with BER (Garcia-Diaz et al., 2000). Polι was shown to play a role in BER of G/U and A/U pairs by its intrinsic 5′-deoxyribose phosphate (dRP) lyase activity (Bebenek et al., 2001). Little is known about the human DNA polymerase sigma (Polσ, TRF4 [DNA topoisomerase I related function]; Walowsky et al., 1999), which is required for sister chromatid cohesion (Wang et al., 2000b). The same is true for polymerase theta (Polθ), which is homologous to the *mus308* gene of *Drosophila melanogaster*, coding for a putative DNA polymerase-helicase involved in interstrand cross-link repair (Sharief et al., 1999). Interestingly, human Polμ plays a role in somatic hypermutation of immunoglobulin genes (Reynaud et al., 2001) and participates in DNA end-filling

during V(D)J recombination and non-homologous end-joining (Ruiz et al., 2001), which indicates the pleiotropic functions of this group of enzymes.

Error-prone DNA polymerases are majorly responsible for mutations induced by DNA-damaging agents giving rise to bulky replication-blocking lesions. They are the missing link many laboratories have searched for between the error-generating SOS functions of *E. coli* (controlled by RecA and UmuCD) and the mammalian 'SOS response'. Their discovery opens up a broad field of future research, addressing highly important questions as to their role in genomic instability in tumours, in damage defense against environmental carcinogens and therapeutic drugs and in the cellular response and individual susceptibility to DNA-damaging toxic compounds.

Acknowledgements

We gratefully acknowledge support of our work by Deutsche Forschungsgemeinschaft (DFG Ka724/8-3, Ka724/10-1,2, SFB519/B4 and SFB432/B7) and Stiftung Rheinland Pfalz. (Az. 408/II). We are thankful to Drs. Philip Hanawalt, Leon Mullenders, Gregory Dianov, Sankar Mitra, Harry van Steeg, Alexander Bürkle and Klaus Becker for critical reading of the manuscript.

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