Roldan-Arjona, T. and R. R. Ariza (2009). "Repair and tolerance of oxidative DNA damage in plants." Mutat. Res. 681(2-3): 169-179.

Repair and tolerance of oxidative DNA damage in plants

Teresa Roldán-Arjona and Rafael R. Ariza

Departamento de Genética, Universidad de Córdoba, 14071 Córdoba, Spain

Corresponding Author:
Rafael R. Ariza
Departamento de Genética
Edificio Gregor Mendel
Campus de Rabanales s/n
Universidad de Córdoba
14071-Córdoba
SPAIN
Tel: +34 957 218 979
Fax: +34 957 212 072
e-mail: ge1roarr@uco.es

Keywords: Arabidopsis; DNA glycosylase; base excision repair; translesion synthesis.

Abstract

DNA damage caused by exposure to reactive oxygen species is one of the primary causes of DNA decay in most organisms. In plants, endogenous reactive oxygen species are generated not only by respiration and photosynthesis, but also by active responses to certain environmental challenges, such as pathogen attack. Significant extracellular sources of activated oxygen include air pollutants such as ozone and oxidative effects of UV light and low-level ionizing radiation. Plants are well equipped to cope with oxidative damage to cellular macromolecules, including DNA. Oxidative attack on DNA generates both altered bases and damaged sugar residues that undergo fragmentation and lead to strand breaks. Recent advances in the study of DNA repair in higher plants show that they use mechanisms similar to those present in other eukaryotes to remove and/or tolerate oxidized bases and other oxidative DNA lesions. Therefore, plants represent a valuable model system for the study of DNA oxidative repair processes in eukaryotic cells.

1. Introduction

Reactive oxygen species (ROS) are generated by cellular aerobic metabolism and by exposure to ionizing radiation, near-ultraviolet light or redox-active compounds, and can readily oxidize most types of macromolecules, including lipids, proteins and nucleic acids. Major targets in living cells are the electron-rich bases of DNA, which undergo oxidation to produce a diverse range of genotoxic modifications [1]. Oxidative DNA lesions constitute a ubiquitous threat to the faithful maintenance of the genome, and their frequency and importance have provoked the development of specific cellular repair functions, some of which have been highly conserved during evolution.

Biochemical and genetic analysis of DNA repair pathways have generally focused on bacterial, yeast and mammalian systems [2], thus neglecting plants and their exceptional status among life forms. As sessile organisms, plants are continuously exposed to a range of environmental genotoxic agents, including the ultraviolet (UV) component of sunlight and air pollutants. In addition, they lack a reserved germline and produce meiotic cells late in development, so mutations arising in somatic cells may be represented in gametes [3]. In recent years, substantial knowledge has been accumulated about DNA repair processes in plants [4-7]. This review will concentrate on those studies, mostly performed in Arabidopsis, that have produced information about how plants repair and tolerate oxidative DNA damage.

2. Sources of oxidative DNA damage in plants

Plants continuously generate ROS as byproducts of metabolic reactions that take place in chloroplasts, mitochondria and peroxisomes [8]. ROS generated by chloroplasts as byproducts of photosynthesis include singlet oxygen ($^1O_2$) and the superoxide radical ($O_2^{\bullet-}$), whereas the main species generated by peroxisomes are $O_2^{\bullet-}$ and hydrogen peroxide (H_2O_2) [9,10]. In the

dark, most ROS production is generated by mitochondria, which mainly form $O_2^{\bullet-}$ by over-reduction of the electron transport chain [11]. ROS are also actively generated by oxidases and peroxidases in response to certain environmental challenges, such as pathogen recognition and other stimuli, and they perform important roles in regulating development [12,13]. The NADPH oxidase system in the plasma membrane, one of the active mechanisms of ROS generation, produces $O_2^{\bullet-}$ that participates in several physiological processes, such as the "oxidative burst" that occurs during pathogen attack [14]. In addition to endogenous processes, ROS may also be generated in plants by exposure to environmental pollutants, such as ozone [15], UV light [16] and low levels of ionizing radiation [17].

The half-life, reactivity and diffusivity of the various ROS greatly influence their potential to inflict cellular damage. Whereas H_2O_2 is relatively stable, reaching concentrations in the micromolar range in plant cells [18], the remaining ROS have very short half-lives. $O_2^{\bullet-}$ can be converted into H_2O_2, in a reaction catalyzed by superoxide dismutases, and it is likely that H_2O_2 serves as an inert diffusible species that can give rise to reactive $^{\bullet}OH$ through the catalysis by free transition metal ions [19]. The hydroxyl radical is the most reactive of primary ROS, and oxidizes all known biomolecules at diffusion-limited rates of reaction. It has been estimated that the average diffusion distance before $^{\bullet}OH$ reacts with a cellular component is only 3 nm, approximately the average diameter of a typical protein [20]. Therefore, $^{\bullet}OH$ needs to be generated in close vicinity to DNA in order to oxidize it.

The extent of the cytotoxic damage induced by ROS ultimately depends on the balance between ROS detoxification and ROS production mechanisms in the cell. In addition to enzymatic defenses to scavenge ROS, plants synthesize abundant small molecule antioxidants including L-ascorbic acid (Vitamin C), glutathione, α-tocopherol (Vitamin E) and carotenoids [21]. These small antioxidants may be essential for a balanced response to ROS production.

Thus, an Arabidopsis mutant hypersensitive to ozone was found to be deficient in ascorbic acid, and it also showed sensitivity to other ROS-generating sources, such as sulphur dioxide and UV-B light [22].

3. Types of oxidative DNA damage and their genotoxic consequences

Oxidative attack to DNA generates both altered bases and damaged sugar residues that undergo fragmentation and lead to strand breaks. Oxidative attack to DNA bases generally involves •OH addition to double bonds, while sugar damage mainly results from hydrogen abstraction from deoxyribose [23].

Hydroxyl radical initiates pyrimidine damage by attacking the C5-C6 double bond at diffusion-controlled rates to produce 5-hydroxy-6-yl and 6-hydroxy-5-yl radicals that further react to form numerous stable DNA lesions [23]. Some of the major pyrimidine oxidation products are ring-saturated derivatives, particularly thymine glycol, 5,6-dihydro-thymine, and cytosine glycol [24-26]. Products of cytosine may be converted into uracil derivatives; thus, cytosine glycol yields uracil glycol by deamination and 5-hydroxyuracil by deamination and dehydration [26,27]. In addition to saturation or oxidation the pyrimidine ring can also undergo fragmentation to generate methyltartronylurea, 5-hydroxy-hydantoin, N-formamido-urea or urea [26,28]. Hydroxyl radical also reacts with purines by addition to C4-, C5- and C8- positions [28]. Probably the best-studied purine oxidation product is 7-hydro-8-oxoguanine (abbreviated as 8-oxoG), which results from the oxidation of the C8-OH adduct radical [29-31]. Another important guanine-derived lesion is the imidazole ring-opened derivative 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FaPyGua) [23]. Less studied are the oxidized derivatives of adenines, which include 8-oxoadenine and 4,6-diamino-5-formamidopyrimidine (FaPyAde) [32,33].

Besides direct oxidation, DNA bases may be also indirectly damaged through reaction with reactive products generated by ROS attack to other macromolecules. One of the major sources of such indirect oxidative damage is lipid peroxidation, caused by attack of oxygen radicals to the polyunsaturated fatty acid residues of membrane phospholipids [34]. Major reactive products of lipid peroxidation are malondialdehyde, acrolein and crotonaldehyde. Malondialdehyde reacts with G residues in DNA to form the pyrimidopurinone adduct called M_1G [35]. Acrolein and crotonaldehyde generate etheno modifications of DNA bases, such as etheno-A and etheno-C [36].

An additional major source of oxidative damage is ROS attack to DNA sugars, which leads to single-strand breaks (SSB). This frequently occurs through abstraction of the hydrogen atom from the C4′ position of deoxyribose, which gives rise to a deoxyribose radical that further reacts to produce DNA strand breakage [37]. When DNA damage is induced by endogenous ROS, the main type of DNA fragmentation produced is of the single-strand type. However, oxidative DNA damage generated by ionizing radiation can also cause double-strand breaks (DSB) through the generation of clusters of radicals that affect nearby sites on both strands [17].

The generation of oxidized bases in DNA may have serious consequences for the cell affected. The failure to repair a damaged base before it is encountered by the replication fork may cause blocking of the DNA polymerase. Alternatively, the lesion can be bypassed by the replication machinery or by specialized DNA polymerases and be potentially mutagenic, according to its mispairing ability [2]. Oxidative lesions have different genotoxic effects that depend on the extent of structural alteration undergone by the original base. Extreme forms of pyrimidine oxidation, such as urea, constitute strong blocks for DNA replication [38], whereas oxidized pyrimidines that retain an intact ring, such as dihydrothymine, usually do not block DNA synthesis and are readily bypassed by DNA polymerases [39]. Other lesions with saturated pyrimidine rings behave differently. Thus, thymine glycol strongly blocks replicative DNA

polymerases *in vitro* [39] but is bypassed by specialized DNA polymerases [40,41]. For purines, the major oxidation product 8-oxoG is a highly mutagenic lesion that can pair *in vitro* with cytosine or with adenine [42]. In agreement with the *in vitro* observations, the predominant mutations induced *in vivo* in plasmids modified with 8-oxoG are targeted GC→TA transversions in both prokaryotic [43-45] and eukaryotic systems [46]. FaPyGua, on the other hand, blocks DNA replication and is lethal but not mutagenic [47,48]. Unlike oxidative base damage, strand breaks arising from oxidative attack to deoxyribose are always a blocking obstacle for the replication fork and for the transcription machinery [2].

4. Excision of oxidized bases by plant DNA glycosylases

Oxidized bases in DNA are usually removed by the base excision repair pathway (BER) [2,49,50]. This process is initiated by repair enzymes termed DNA N-glycosylases that hydrolytically cleave the glycosylic bond between the target base and deoxyribose, thus releasing the free damaged base and leaving an apurinic/apyrimidinic (AP) site that must be further processed. DNA glycosylases are classified into two broad groups: (i) monofunctional DNA glycosylases, which catalyze only hydrolysis of the glycosylic bond, and (ii) DNA glycosylases/lyases, bifunctional enzymes that catalyses both the release of the damaged base and the cleavage of DNA backbone at the resulting abasic site [2]. Several DNA glycosylases acting upon oxidized bases have been identified in both prokaryotes and eukaryotes [2,49,50] and most of them are bifunctional DNA glycosylases/lyases that remove several structurally related lesions. Although their substrate specificities may be relaxed and often overlap, in general oxidative DNA base lesions are recognized by either a pyrimidine-specific or by a purine-specific enzyme.

The prototype of enzyme for repair of oxidized pyrimidines is *E. coli* Nth (also known as Endonuclease III). Nth removes a wide variety of damaged pyrimidine derivatives that result

form ring saturation, fragmentation or contraction [51-53]. A structural and functional homolog of Nth has been identified in Arabidopsis and termed AtNTH1 [54] (Table 1). AtNTH1 exhibits DNA-glycosylase activity on different types of DNA substrates with pyrimidine damage, being able to release both urea and thymine glycol from double-stranded polydeoxyribonucleotides. The enzyme also possesses an apurinic/apyrimidinic lyase activity on UV- and γ-irradiated DNA substrates. AtNTH1 sequence shows all the characteristics of an Nth homolog, including a helix-hairpin-helix (HhH) motif, and an iron-sulphur cluster [4Fe-4S] held in place by four conserved Cys residues. The presence of a conserved Lys at position 240 in AtNTH1 correctly predicted the AP/lyase activity of the enzyme [54]. This critical Lys residue is conserved in all functionally characterized Nth homologs, and it is absent from other DNA-glycosylases with very similar sequences but which lack AP lyase activity [55].

The genome of Arabidopsis encodes a putative second Nth homolog (AtNTH2) (Table 1), thus resembling other eukaryotes such as *S. cerevisiae* [56]. In a detailed phylogenetic analysis of the HhH superfamily the two homologs from each species were grouped together, suggesting that they are paralogs generated by lineage-specific gene duplication events that occurred after plant and yeast divergence [57]. Differential sorting to the nucleus and mitochondria has been reported for the two Nth homologs from *S. cerevisiae* [58], but no information about subcellular targeting is available for the two Arabidopsis proteins. In *E. coli* there is a second DNA glycosylase that repairs oxidized pyrimidines, designated Nei (Endonuclease VIII) [59]. Although the human genome encodes three Nei-like enzymes [50], plant genomes sequenced so far seem to be devoid of Nei homologs.

The archetypal DNA glycosylase for repair of oxidized purines is *E. coli* MutM. This enzyme, also known as Fpg, is a DNA glycosylase/lyase that excises 8-oxoG from DNA and processes the resulting abasic site cleaving both 3′ and 5′ phosphodiester bonds by successive β- and δ-elimination [60-62]. MutM shows a clear preference for C as the base opposite 8-oxoG,

thus avoiding mutagenic repair of 8-oxoG:A mispairs to T:A. The repair of 8-oxoG:A mispairs is initiated instead by MutY, a DNA glycosylase that catalyzes excision of the misincorporated A [63].

Genes similar to bacterial *mutY* have been identified and their products characterized in several eukaryotic and archaeal species [64]. Most eukaryotes, including yeast and mammalian cells, possess 8-oxoG-DNA glycosylases that do not share sequence identity with bacterial MutM proteins. The first of these MutM analogs, designated Ogg1, was first identified in *S. cerevisiae* [65,66] and later in mammals [67-69]. The Ogg1 protein is a bifunctional DNA glycosylase/lyase that catalyzes both the release of 8-oxoG and the cleavage of DNA at the resulting abasic site via a β-elimination reaction, rather than β□ δ-elimination [70].

Interestingly, plant nuclear genomes encode functional orthologs of both MutM and Ogg1 [71-73] (Table 1). The Arabidopsis *mutM* homolog (*AtMMH*) generates two alternatively spliced transcripts, and the longer protein variant (AtMMH-1) exhibits nicking activity for 8-oxoG paired with cytosine, guanine and thymine, but not for 8-oxoG paired with adenine [71]. Additional forms of AtMMH produced by alternative splicing have been reported, but their enzymatic roles and substrate specificities remain unknown [74]. Two genes encoding MutM orthologs have been recently identified in the mononocot plant sugarcane [75].

The Arabidopsis Ogg1 ortholog (AtOGG1) is a bifunctional DNA glycosylase/lyase able to cleave a duplex DNA at an 8-oxoG:C mispair, in a reaction proceeding through an imine intermediate that leads to a β-elimination [73]. Expression of the plant protein in *E. coli* almost completely suppresses the spontaneous mutator phenotype of a *mutM mutY* mutant, which is deficient in repair of endogenously produced 8-oxoG [72,73]. The substrate specificity and excision kinetics of AtOGG1 has been analyzed in detail [76]. AtOGG1 efficiently excises 8-oxoG and FapyGua from DNA containing multiple lesions generated from pyrimidines and

purines by ionizing radiation [76]. The enzyme preferentially excises 8-oxoG paired to guanine, with 8-oxoG:A pairs being particularly poor substrates [76].

It has been reported that T-DNA insertion double mutants lacking functional *AtMMH* and *AtOGG1* genes do not show any obvious phenotype, although the accumulation of 8-oxoG in their DNA has not been measured [77]. Both *AtMMH* and *AtOGG1* genes are expressed in a wide range of different plant tissues [73], raising the question of their relative roles in plant cells. Since eukaryotic *MutM* orthologs seem to be restricted to plants, it has been proposed that this may be the result of a gene transfer from an ancestral chloroplast genome to the nucleus [71]. If this is the case, perhaps the relative roles of AtOGG1 and AtMMH may be related to their different phylogenetic origin, with a nuclear function for AtOGG1 and a repair role in the chloroplast for AtMMH. However, the precise subcellular location of both enzymes remains to be determined. The Arabidopsis genome encodes a putative MutY ortholog that is possibly involved in removing adenine from 8-oxoG:A pairs, but it has not been functionally characterized.

It has been reported that in bacteria and mammals the BER pathway not only removes oxidized bases, but also the exocyclic base adducts etheno-A and etheno-C generated by the lipid-peroxidation products acrolein and crotonaldehyde [36]. The DNA glycosylases responsible for this activity were identified as the *E. coli* mismatch-especific uracil DNA glycosylase (MUG) and its human homolog thymine DNA glycosylase (TDG) [36]. Since plants lack an identifiable homolog of MUG and TDG (Table 1), it remains an open question how they remove DNA adducts generated by endogenous products of lipid peroxidation. It should be noted that lipid peroxidation has been proposed as a major factor of seed deterioration [78] and that the loss of seed viability has been correlated to the accumulation of lipid-peroxidation products such as malondialdehyde [79]. However, the possible role of DNA damage during this process remains unknown.

5. Post-excision events during base excision repair of oxidative DNA damage in plants

Excision of the damaged base is only the first step in the BER pathway, and generates intermediates that have to be processed further to restore the structural and functional integrity of DNA [2]. AtNTH1 and AtOGG1 are bifunctional DNA glycosylases/lyases that cleave the abasic (AP) site by β-elimination generating a 3′ phospho α,β-unsaturated aldehyde (3′ dRP) at the strand break [54,73] (Figure 1). After base excision it is necessary to remove the products of the β-elimination to generate 3′ OH termini necessary for gap-filling repair synthesis by a DNA polymerase [80]. This process is catalyzed by enzymes called AP endonucleases, which also process AP sites generated through spontaneous degradation of DNA or through the actions of monofunctional glycosylases. In mammalian cells, the 3′ dRP generated after β elimination by NTH1 and OGG1 is efficiently removed by APEX1 [81,82]. The Arabidopsis genome encodes two APEX1 homologs, and one of them, termed Arp, has been shown to perform incisions in DNA containing abasic sites [83]. Mammalian genomes also encode a protein called APEX2 with unknown function *in vivo* [84], and one APEX2 ortholog is also present in plant genomes (Table 1).

In contrast to AtNTH1 and AtOGG1, AtMMH catalyzes β,δ-elimination at the AP site and removes the deoxyribose residue to produce a 3′ phosphate terminus at the DNA strand break [71] (Figure 1). In mammalian cells, the 3′ phosphate generated by β,δ-elimination is converted to a 3′ OH group by polynucleotide kinase 3′phosphatase (PNKP) [85], which also functions in the repair of DNA SSB generated by ionizing radiation [86]. A DNA 3′-phosphatase acting on the 3-phosphorylated termini of DNA SSB has been purified from maize [87]. Its Arabidopsis ortholog (AtZDP) is a 3′-phosphatase that binds SSB through an amino-terminal domain that contains three Cys_3-His zinc fingers [88] (Table 1). It is tempting to speculate that AtZDP could mediate processing of the 3′ phosphate group generated by β,δ-elimination catalysts such as

AtMMH in plants. In addition to participating in downstream BER steps during repair of oxidized bases, AtZDP may also play an important role in the repair of SSB directly arising from oxidative attack to sugar residues (see below).

Further steps for completion of BER require additional enzymes and accessory proteins (Figure 1). The processing of BER intermediates carried out by AP endonucleases or 3′ phosphatases leaves a 3′ OH and a 5′ phosphate at the strand termini. In mammalian cells, DNA polymerase β (pol β) fills the single nucleotide gap, preparing the strand for ligation by DNA ligase I or a complex of DNA Ligase III and XRCC1. Arabidopsis lacks any clear pol β homolog, but it has been proposed [4] that its role could be fulfilled by a homolog of another polymerase X family member termed pol λ [89]. Arabidopsis pol λ (AtPOLL) contains critical residues conserved in pol β and other DNA polymerases belonging to the X family [89]. Pol λ from rice has DNA polymerase activity and its expression is associated with cell proliferation in meristematic and meiotic tissue [90]. On the other hand, BER of oxidative damage outside the nucleus may require other DNA polymerases. Thus, two DNA polymerases similar to DNA polymerase I from cyanobacteria have been identified in Arabidopsis [91]. Both are localized in plastids and the expression of one of them (AtPolI-like B) is induced by H_2O_2, indicating a possible role in the repair of oxidative DNA damage [91]. A detailed biochemical characterization of its rice ortholog, OsPOLP1, suggests that this polymerase might be involved in plastidial DNA replication and BER [92].

XRCC1 interacts with Ligase III and other BER proteins in mammalian cells, and may function as a scaffold protein for the coordination of initial and late steps of repair [93]. The Arabidopsis genome encodes an XRCC1 ortholog [94], but its role during BER remains unknown. Arabidopsis has up to four genes encoding DNA ligases, although none of them is a Ligase III ortholog. AtLIG4 is an ortholog of mammalian DNA ligase IV and functions in double-strand break repair [95,96] (see below). AtLIG1 is an ortholog of mammalian DNA

ligase I and may function in DNA replication and repair [97,98]. Interestingly, isoforms of AtLIG1 are targeted to the nucleus or the mitochondria through the choice of alternative initiation sites [99]. In addition to the well-characterized AtLIG4 and AtLIG1 proteins the Arabidopsis genome encodes a second DNA ligase I ortholog and a predicted DNA ligase named AtLIG6 that could be unique to plants [100]. However, the functional roles of these two proteins remain to be determined.

A survey of the sequenced genomes of several plant species (Table 2) reveals orthologs of most of the Arabidopsis proteins involved in the repair of oxidative DNA damage, both in the excision and post-excision events. All Arabidopsis proteins discussed above have orthologs in dicots (grapevine), monocots (rice) and even in the moss *Physcomitrella patens*, suggesting a strong conservation of the oxidative DNA repair repertoire throughout the evolution of land plants. The unicellular green alga Chlamydomonas reinhardtii possesses orthologs of most Arabidopsis repair proteins, but lacks PARP and XRCC1 orthologs, which seem to be specific of multicellular eukaryotes. This conservation pattern confirms that the inventory of DNA repair proteins in Arabidopsis is highly representative of most plants, and validates its use as a key model system in DNA repair studies.

6. Role of nucleotide excision repair in removal of oxidative DNA lesions in plants

Although oxidatively damaged bases are mainly repaired by BER, some removal appears to occur though nucleotide excision repair (NER). This is a versatile repair pathway that can act on a wide range of substrates, including pyrimidine dimers induced by UV radiation or bulky DNA adducts generated by chemicals [2]. However, it is also considered an important backup pathway for repair of oxidative DNA lesions [101]. In addition, it has been reported that in

bacteria exocyclic DNA base adducts generated by endogenous products of lipid peroxidation are repaired through the NER pathway [35].

NER is initiated by cleavage of the damaged DNA strand on both sides of the lesion and results in removal of the damage as part of an oligonucleotide, leaving a gap that is then filled and sealed [2]. Extensive studies in yeast and mammalian cells have identified the major players in eukaryotic NER, defining a complex DNA repair mechanism that requires the products of more than 30 genes, many of which are evolutionarily conserved [102].

Genetic analysis of Arabidopsis mutants hypersensitive to UV light or ionizing radiation has led to the identification of plant genes encoding some key components of the NER pathway, such as AtRAD1 [103-106] and AtERCC1 [105,107], which are members of the endonuclease that performs the 5′ incision. A plant mutant with a hyperrecombinogenic phenotype allowed identification of AtCEN2, a caltractin-like protein that modulates NER and participates in the DNA lesion recognition complex [108,109]. Sequence conservation has allowed the identification of other NER factors, such as AtXPB1 and AtXPB2, which, similarly to their yeast and mammalian orthologs, presumably function as helicases unwinding the damage-containing oligonucleotide [110-112]. Other conserved NER components have been identified through sequence searches in the Arabidopsis genome database [7,113]. There is some evidence that NER participates in the repair of oxidative DNA lesions in plants. Thus, plants depleted in AtRAD1 activity show reduced repair of methylene blue-induced oxidative lesions in *in vitro* NER assays, and they also exhibit greater sensitivity to H_2O_2 than do wild-type plants [114]. On the other hand, T-DNA insertion mutants defective in the *Arabidopsis thaliana* UV-damaged DNA binding protein 2 (AtUV-DDB2) also show greater sensitivity to H_2O_2 [115]. At least part of the sensitivity of NER-deficient plants to oxidants may be due to a possible role for this pathway in the repair of DNA adducts generated by lipid peroxidation products, as previously reported in bacteria [35].

7. Repair of strand breaks caused by oxidative attack

Single-strand breaks (SSB) are the most abundant DNA lesion in eukaryotic cells and may arise either directly by oxidative attack to the sugar-phosphate backbone, or indirectly as an enzymatic consequence of excision repair of oxidative base damage (see above) and spontaneous base loss [2]. In fact, the number of SSB arising from BER processing of oxidative base damage *in vivo* has been estimated to be approximately 1.5 x 10^5 per cell per day for human cells [116] and a similar or greater number of SSB may arise from direct oxidative attack on DNA. Therefore, the significance of SSB should not be underestimated, and cells certainly possess efficient enzymatic mechanisms for their recognition and elimination.

Most SSB arising from the direct attack of ROS on sugar residues have damaged termini, such as 3′ phosphate or phosphoglycolate end groups, that prevent DNA repair by a simple DNA ligation step [17]. Therefore, efficient SSB repair must perform the consecutive steps of break recognition, end processing, gap filling and ligation [2]. With the exception of the first step, the process of SSB repair broadly overlaps with the post-excision events that take place during BER (see above).

Members of the poly (ADP-ribose) polymerase (PARP) superfamily are widely considered as putative nick sensors in SSB repair in eukaryotes [2]. In mammals, PARP1 and PARP2 bind with high affinity to SSB or DSB and become activated to synthesize polymers of ADP ribose in a range of nuclear enzymes, including PARPs themselves, using NAD^+ as substrate [117]. The exact role of PARP proteins during SSB repair is unknown. In mammalian cells, autoribosylated PARP1 interacts with XRCC1, which is considered to be an essential scaffold protein for initial and late events during BER [118] (see above). Therefore, PARP1 may function as a nick sensor that attracts proteins needed for end processing, gap filling and sealing of SSB. Plants possess homologs of animal PARP1 and PARP2 [119,120]. Both plant proteins are localized in the nucleus and have poly (ADP-ribose) polymerase activity that is activated by DNA strand breaks

[119,120]. Strand breaks produced by ionizing radiation or oxidative stress induce rapid and massive accumulation of Arabidopsis AtPARP1 and AtPARP2 transcripts in all plant tissues [120-122]. There is also evidence that PARP may regulate programmed cell death (PCD) and DNA repair in response to oxidative stress in plants. Thus, inhibition of PARP activity in cultured soy bean cells reduces PCD triggered by H_2O_2, while transient overexpression of Arabidopsis *AtPARP2* cDNA promotes DNA repair [123]. In addition, it has been shown that plants with reduced PARP activity are tolerant of a broad range of stresses [124].

PARP1 and PARP2 homologs may not be the only sensors of SSB in plants. AtZDP, an Arabidopsis protein that recognizes DNA strand breaks and catalyzes the removal of 3′-end-blocking lesions (see above), is comprised of a catalytic domain preceded by three PARP-like Zinc finger modules [87,88,125]. Together with its maize ortholog, ZmDP2, AtZDP may be the prototype of a new family of DNA repair proteins, so far unique to plants, that can act as sensors and repair catalysts during DNA damage [88].

In addition to SSB, oxidative attack of DNA may also cause double-strand breaks (DSB), particularly as a consequence of the cluster of hydroxyl radicals generated by ionizing radiation [17]. DSB breaks also arise from exposure to other DNA damaging agents and from endogenous cellular processes, and all cells are endowed with elaborate mechanisms for their repair [2]. The field of DSB repair in plants has advanced considerably in recent years and excellent reviews have been published elsewhere [126,127].

8. Tolerance of oxidative lesions through translesion DNA synthesis

Although oxidative DNA damage is constantly monitored and removed by a variety of repair pathways, lesions that escape repair can severely impair DNA synthesis and obstruct the progress of the replication machinery. To overcome replication blockage, cells have evolved tolerance mechanisms to enable duplication of their genomes despite the presence of unrepaired

lesions [128]. An important damage tolerance mechanism is the direct synthesis of nascent DNA chains past the altered bases. Such translesion synthesis (TLS) may often involve incorporation of “wrong” nucleotides, i.e., nucleotides that are not the Watson-Crick complements of the altered bases [129]. A crucial result from recent mutagenesis research is the finding that TLS is not efficiently performed by high-fidelity replicative DNA polymerases, which are generally unable to copy defective templates, but rather by specialized DNA polymerases widely represented in bacteria, archaea and eukarya [130-132].

Most TLS DNA polymerases are structurally related and define a family of DNA polymerases, designated the Y-family, that are distinct from the A, B, C and X families [133]. The Y-family of DNA polymerases includes four subfamilies whose founding members are *E. coli* pol IV and pol V (previously known as DinB and UmuC, respectively), and *S. cerevisiae* pol η (Rad30) and Rev1. Unlike replicative DNA polymerases, Y-family enzymes have an open solvent-accessible active site but lack proofreading exonuclease activity [130]. Consequently, they have some remarkable biochemical properties, such as a low fidelity on undamaged DNA [134] and the ability to synthesize DNA opposite-damaged templates by translesion synthesis [135]. The current hypothesis is that these enzymes act transiently at arrested replication forks to copy any faulty nucleotides and extend the resultant non-canonical primer-template pairs with varying degrees of accuracy, but give way to high-fidelity replication downstream of the arrest point [2].

Although many TLS polymerases belong to the Y family, the "conventional" A, B, and X families of DNA polymerases also include members able to perform TLS and other specialized tasks in DNA repair and genome stability [132]. A prominent example is Pol ξ, whose catalytic subunit (REV3) belongs to the B family, which also includes the replicative polymerases α, δ and ε. Pol ξ lacks a proofreading exonuclease activity, synthesizes DNA over damaged templates and extend mispaired primers, and is required for the majority of both spontaneous

and damage-induced mutagenesis in yeast [136]. The X family include members mainly devoted to DNA repair and is comprised of up to five polymerases in mammals: Pol β, Pol λ, Pol μ, TdT (terminal deoxynucleotidyltransferase) and Pol σ [137]. Pol λ and Pol μ [89,138] play specialized roles during nonhomologous end joining (NHEJ) [139].

Knowledge about how plants cope with unrepaired DNA lesions remains quite limited, although DNA damage tolerance may have important consequences for plants due to their lifestyle. Unlike most higher eukaryotes they lack a reserved germline, and produce meiotic cells late in development, so mutations arising in somatic cells may be represented in gametes [3]. The existence of specialized DNA polymerases in plants has been inferred from the analysis of genome sequences, which reveals genes encoding putative orthologs of several polymerases from other organisms [7]. Only recently have the functions and physiological roles of these genes begun to be revealed, although studies of specialized DNA polymerases in plants are not abundant. An Arabidopsis mutation that confers sensitivity to UV-B and various DNA damaging has been mapped to AtREV3, a gene encoding the putative catalytic subunit of Arabidopsis DNA polymerase ξ [140]. A recent study by the same group has reported that mutations in Arabidopsis homologs of REV1 and REV7 (a putative regulatory subunit of pol ξ) render plants moderately sensitive to UV-B and DNA cross-linking agents [141]. A cDNA encoding a putative Arabidopsis homolog of mammalian Pol λ has been reported [89] and it has been suggested that the corresponding *Oryza sativa* homolog performs DNA repair functions in plant meristematic and meiotic tissues [90]. AtPOLK, is an Arabidopsis homolog of *E. coli* pol IV and human pol κ, and belongs to the DinB subfamily [142]. AtPOLK is a template-directed DNA polymerase endowed with limited processivity, that is able to extend mispaired primer ends [142]. Alternative splicing of the primary AtPOLK transcript gives rise to different mRNAs that have distinct patterns of expression in different organs, and AtPOLK promoter is active in a variety of tissues, with a possible association with endoreduplication cycles [142]. I

Most studies concerning translesion synthesis of oxidative damage have concentrated on the predominant lesion 8-oxoG. The miscoding potential of 8-oxoG arises from its ability to form stable base pairs with either a C or an A residue [42]. Most replicative DNA polymerases preferentially insert A opposite 8-oxoG [42], causing G:C→T:A transversions [46]. Insertion preferences among Y-family DNA polymerases vary considerably. Yeast and human pol η [143,144], and archaeal Dpo4 [145,146] preferentially insert C opposite the lesion. In contrast, human pol κ inserts A more efficiently than C opposite 8-oxodG [147-149], and human pol ι is significantly blocked by the lesion [150,151].

AtPOLK is the only plant DNA polymerase examined so far for the capacity to bypass DNA oxidative damage. AtPOLK is able to insert nucleotides opposite 8-oxoG and moderately extend from the resulting primer end [152]. Interestingly, the ability of AtPOLK to bypass 8-oxoG is influenced by its C terminus. While full-length AtPOLK shows a relative incorporation efficiency for A opposite 8-oxoG twice that of C, a truncated version lacking 193 amino acids from its C terminus (AtPOLKΔC) inserts both A and C with similar efficiency and shows ~10-fold higher catalytic efficiency than the wild-type enzyme for nucleotide insertion opposite 8-oxoG. [152]. It has been suggested that the C-terminal domain of AtPOLK may modulate the catalytic activity of the protein, affecting its catalytic efficiency and fidelity during synthesis on non-damaged DNA templates, its capacity to extend mismatches through misalignment and its bypass efficiency through error-prone and error-free bypass [152].

Specialized DNA polymerases may play other roles in addition to tolerance of oxidative DNA lesions though translesion synthesis. Recent evidence in mouse cells suggest that mammalian pol κ may participate in NER [153], but a similar role in plants has not been reported so far.

9. Cellular responses to oxidative DNA damage in plants

Cells respond to DNA damage by activating complex signaling pathways that minimize its deleterious consequences. These pathways initiate a series of appropriate measures that include delaying cell cycle progress, thus allowing time for DNA repair, and activation of genes required for repair and cellular protection [2]. Although the identity of the sensors that directly recognize DNA damage is not accurately known in most cases, in yeast and mammalian cells two protein kinases of the phosphoinositide-3-OH-kinase-related (PI3KK) family are involved in the early signaling process: ATM (ataxia telangiectasia-mutated) and ATR (ATM-Rad3-related) [154].

Homologs of ATM and ATR have been found to be encoded in the genome of Arabidopsis and other plants [155-157]. Mutant *atatm* Arabidopsis plants are hypersensitive to ionizing radiation but not to UV-B light, thus suggesting that AtATM activation occurs primarily in response to DSB [158]. In contrast, *atatr* mutants are only mildly sensitive to ionizing radiation and hypersensitive to replication blocking agents such as UV-B light, hydroxyurea or aphidicolin [159]. This suggests that, similarly to mammalian cells, the DNA damage signal resulting in AtATR activation is probably ssDNA, such as that resulting from collapsed replication forks or excision repair [160]. Also, like its homologs in mammals, AtATR is required for the G2-phase checkpoint in response to replication blocks [159].

Presumably, the activation of both AtATM and AtATR in response to DNA damage initiates a protein phosphorylation cascade resulting in the transcriptional activation of effector proteins. Recent studies have shown that the transcriptional response of Arabidopsis plants to ionizing radiation comprises genes that regulate cell cycle transitions and DNA repair, and is primarily dependent on AtATM, but not AtATR [161,162]. This is not surprising, given the great significance of DSB in the types of damage induced by ionizing radiation. Similar

transcriptional responses elicited in plants by other sources of oxidative DNA damage are yet to be explored.

Other signaling pathways triggered by ROS in plants originate outside the nucleus and involve activation of mitogen-activated protein (MAP) kinases. The implication of MAP kinases in genotoxic stress signaling in plants is well documented [163] and some of them, such as AtMPK6, are specifically activated by oxidative stress [164].

10.Conclusions and perspectives

Recent advances in plant DNA repair studies clearly illustrate the viability of elucidating the molecular mechanisms of plant cells responses to oxidative insults to DNA. Remarkably, the comparative analysis of plant and animal responses to oxidative DNA damage has revealed many similarities and some characteristic differences. In fact, in some instances the plant mechanisms are closer to mammalian processes than other well-established eukaryotic models in the field of DNA repair and mutagenesis. This proximity highlights the advantages of plant studies in the elucidation of highly conserved pathways of DNA damage repair and tolerance. In some species, such as Arabidopsis, the advantages of a fully sequenced genome and extremely powerful tools for genetics and molecular analysis will undoubtedly help to bring plants to the forefront of research in oxidative DNA damage and repair.

Acknowledgments

We apologize to colleagues whose work was not cited due to space limitations. Our sincere thanks to two anonymous reviewers for their suggestions and comments on an earlier version of this article. Work in our laboratory is supported by grants from the Ministerio de Educación y Ciencia, Spain, and the Junta de Andalucía, Spain.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

References

[1] M. Dizdaroglu, P. Jaruga, M. Birincioglu and H. Rodriguez, Free radical-induced damage to DNA: mechanisms and measurement, Free Radic Biol Med 32 (2002) 1102-1115.

[2] E.C. Friedberg, G.C. Walker, W. Siede, R.D. Wood, R.A. Schultz and T. Ellenberger, DNA Repair and Mutagenesis, ASM Press, Washington, D.C., 2006.

[3] V. Walbot and M.M. Evans, Unique features of the plant life cycle and their consequences, Nat Rev Genet 4 (2003) 369-379.

[4] A.B. Britt, Repair of damaged bases, in: C. Somerville and E.M. Meyerowitz (Eds.), The Arabidopsis Book, American Society of Plant Biologists, Rockville, MD, 2002.

[5] J.B. Hays, *Arabidopsis thaliana*, a versatile model system for study of eukaryotic genome-maintenance functions, DNA Repair 1 (2002) 579-600.

[6] C.M. Bray and C.E. West, DNA repair mechanisms in plants: crucial sensors and effectors for the maintenance of genome integrity, New Phytol 168 (2005) 511-528.

[7] B.A. Kunz, H.J. Anderson, M.J. Osmond and E.J. Vonarx, Components of nucleotide excision repair and DNA damage tolerance in Arabidopsis thaliana, Environ Mol Mutagen 45 (2005) 115-127.

[8] C.H. Foyer and G. Noctor, Redox sensing and signalling associated with reactive oxygen in chloroplasts, peroxisomes and mitochondria, Physiologia Plantarum 119 (2003) 355-364.

[9] K. Asada, Production and scavenging of reactive oxygen species in chloroplasts and their functions, Plant Physiol 141 (2006) 391-396.

[10] L.A. del Rio, L.M. Sandalio, F.J. Corpas, J.M. Palma and J.B. Barroso, Reactive oxygen species and reactive nitrogen species in peroxisomes. Production, scavenging, and role in cell signaling, Plant Physiol 141 (2006) 330-335.

[11] D.P. Maxwell, Y. Wang and L. McIntosh, The alternative oxidase lowers mitochondrial reactive oxygen production in plant cells, Proc Natl Acad Sci USA 96 (1999) 8271-8276.

[12] I.M. Moller, P.E. Jensen and A. Hansson, Oxidative modifications to cellular components in plants, Annu Rev Plant Biol 58 (2007) 459-481.

[13] C. Gapper and L. Dolan, Control of plant development by reactive oxygen species, Plant Physiol 141 (2006) 341-345.

[14] K. Apel and H. Hirt, Reactive oxygen species: metabolism, oxidative stress, and signal transduction, Annu Rev Plant Biol 55 (2004) 373-399.

[15] H. Mehlhorn, B.J. Tabner and A.R. Wellburn, Electron-spin-resonance evidence for the formation of free-radicals in plants exposed to ozone, Physiologia Plantarum 79 (1990) 377-383.

[16] L.G. Landry, C.C. Chapple and R.L. Last, Arabidopsis mutants lacking phenolic sunscreens exhibit enhanced ultraviolet-B injury and oxidative damage, Plant Physiol 109 (1995) 1159-1166.

[17] J.F. Ward, DNA damage produced by ionizing radiation in mammalian cells: identities, mechanisms of formation, and reparability, Prog Nucleic Acid Res Mol Biol 35 (1988) 95-125.

[18] J.M. Cheeseman, Hydrogen peroxide concentrations in leaves under natural conditions, J Exp Bot 57 (2006) 2435-2444.

[19] F. Haber and J. Weiss, The catalytic decomposition of hydrogen peroxide by iron salts, Proc R Soc Lond Ser A 147 (1934) 332-351.

[20] F. Hutchinson, The distance that a radical formed by ionizing radiation can diffuse in a yeast cell, Radiat Res 7 (1957) 473-483.

[21] R.G. Alscher and J.L. Hess, Antioxidants in higher plants, CRC Press, Boca Raton, 1993.
[22] P.L. Conklin, E.H. Williams and R.L. Last, Environmental stress sensitivity of an ascorbic acid-deficient Arabidopsis mutant, Proc Natl Acad Sci USA 93 (1996) 9970-9974.
[23] M. Dizdaroglu, Chemistry of free radical damage to DNA and nucleoproteins, in: B. Halliwell and O.I. Aruoma (Eds.), DNA and Free Radicals, Ellis Horwood, London, 1993, pp. 19-39.
[24] E.A. Furlong, T.J. Jorgenson and W.D. Henner, Production of dihydrothymine stereoisomers in DNA by gamma-radiation, Biochemistry 25 (1986) 4344-4349.
[25] S. Nishimoto, H. Ide, T. Wada and T. Kagiya, Radiation-induced hydroxylation of thymine promoted by electron-affinic compounds, Int J Radiat Biol 44 (1983) 585-600.
[26] R. Téoule, Radiation-induced DNA damage and its repair, Int J Radiat Biol 51 (1987) 589.
[27] M. Dizdaroglu, J. Laval and S. Boiteux, Substrate specificity of the Escherichia coli endonuclease III: excision of thymine- and cytosine-derived lesions in DNA produced by radiation-generated free radicals, Biochemistry 32 (1993) 12105-12111.
[28] C. von Sonntag, The Chemical Basis of Radiation Biology, Taylor and Francis, London, 1987.
[29] M. Dizdaroglu, Formation of an 8-hydroxyguanine moiety in deoxyribonucleic acid on gamma-irradiation in aqueous solution, Biochemistry 24 (1985) 4476-4481.
[30] H. Kasai and S. Nishimura, Hydroxylation of deoxyguanine at the C-8 position by ascorbic acid and other reducing agents, Nucleic Acids Res 12 (1984) 2137-2145.
[31] H. Kasai, H. Tanooka and S. Nishimura, Formation of 8-hydroxyguanine residues in DNA by X-irradiation, Gann 75 (1984) 1037-1039.
[32] A.F. Fuciarelli, B.J. Wegher, W.F. Blakely and M. Dizdaroglu, Yields of radiation-induced base products in DNA: effects of DNA conformation and gassing conditions, Int J Radiat Biol 58 (1990) 397-415.
[33] C.J. Chetsanga and C. Grigorian, A dose-response study on opening of imidazole ring of adenine in DNA by ionizing radiation, Int J Radiat Biol 44 (1983) 321-331.
[34] L.J. Marnett, Oxyradicals and DNA damage, Carcinogenesis 21 (2000) 361-370.
[35] S.P. Fink, G.R. Reddy and L.J. Marnett, Mutagenicity in Escherichia coli of the major DNA adduct derived from the endogenous mutagen malondialdehyde, Proc Natl Acad Sci U S A 94 (1997) 8652-8657.
[36] M. Saparbaev and J. Laval, 3,N4-ethenocytosine, a highly mutagenic adduct, is a primary substrate for Escherichia coli double-stranded uracil-DNA glycosylase and human mismatch-specific thymine-DNA glycosylase, Proc Natl Acad Sci U S A 95 (1998) 8508-8513.
[37] M.D. Evans, M. Dizdaroglu and M.S. Cooke, Oxidative DNA damage and disease: induction, repair and significance, Mutat Res 567 (2004) 1-61.
[38] H. Ide, Y.W. Kow and S.S. Wallace, Thymine glycols and urea residues in M13 DNA constitute replicative blocks in vitro, Nucleic Acids Res 13 (1985) 8032-8052.
[39] J. Evans, M. Maccabee, Z. Hatahet, J. Courcelle, R. Bockrath, H. Ide and S. Wallace, Thymine ring saturation and fragmentation products: lesion bypass, misinsertion and implications for mutagenesis, Mutat Res 299 (1993) 147-156.
[40] K.I. Takata, T. Shimizu, S. Iwai and R.D. Wood, Human DNA polymerase N (POLN) is a low-fidelity enzyme capable of error-free bypass of 5S-thymine glycol, J Biol Chem 282 (2006) 23445-23455.

[41] P.L. Fischhaber, V.L. Gerlach, W.J. Feaver, Z. Hatahet, S.S. Wallace and E.C. Friedberg, Human DNA polymerase κ bypasses and extends beyond thymine glycols during translesion synthesis *in vitro*, preferentially incorporating correct nucleotides, J Biol Chem 277 (2002) 37604-37611.

[42] S. Shibutani, M. Takeshita and A.P. Grollman, Insertion of specific bases during DNA synthesis past the oxidation-damaged base 8-oxodG, Nature 349 (1991) 431-434.

[43] M.L. Wood, M. Dizdaroglu, E. Gajewski and J.M. Essigmann, Mechanistic studies of ionizing radiation and oxidative mutagenesis: genetic effects of a single 8-hydroxyguanine (7-hydro-8-oxoguanine) residue inserted at a unique site in a viral genome, Biochemistry 29 (1990) 7024-7032.

[44] M. Moriya, C. Cu, V. Bodepudi, F. Johnson, M. Takeshita and A.P. Grollman, Site-specific mutagenesis using a gapped duplex vector: a study of translesion synthesis past 8-oxodeoxyguanosine in E. coli, Mutat Res 254 (1991) 281-288.

[45] K.C. Cheng, D.S. Cahill, H. Kasai, S. Nishimura and L.A. Loeb, 8-Hydroxyguanine, an abundant form of oxidative DNA damage, causes G→T and A→C substitutions, J Biol Chem 267 (1992) 166-172.

[46] M. Moriya, Single-stranded shuttle phagemid for mutagenesis studies in mammalian cells: 8-oxoguanine in DNA induces targeted G·C→T·A transversions in simian kidney cells, Proc Natl Acad Sci USA 90 (1993) 1122-1126.

[47] B. Tudek, S. Boiteux and J. Laval, Biological properties of imidazole ring-opened N7-methylguanine in M13mp18 phage DNA, Nucleic Acids Res 20 (1992) 3079-3084.

[48] T.R. O'Connor, S. Boiteux and J. Laval, Ring-opened 7-methylguanine residues in DNA are a block to in vitro DNA synthesis, Nucleic Acids Res 16 (1988) 5879-5894.

[49] M. Dizdaroglu, Base-excision repair of oxidative DNA damage by DNA glycosylases, Mutat Res 591 (2005) 45-59.

[50] D.E. Barnes and T. Lindahl, Repair and genetic consequences of endogenous DNA base damage in mammalian cells, Annu. Rev. Genet. 38 (2004) 445-476.

[51] R.J. Boorstein, T.P. Hilbert, J. Cadet, R.P. Cunningham and G.W. Teebor, UV-induced pyrimidine hydrates in DNA are repaired by bacterial and mammalian DNA glycosylase activities, Biochemistry 28 (1989) 6164-6170.

[52] L. Breimer and T. Lindahl, A DNA glycosylase from Escherichia coli that releases free urea from a polydeoxyribonucleotide containing fragments of base residues, Nucleic Acids Res 8 (1980) 6199-6211.

[53] Z. Hatahet, Y.W. Kow, A.A. Purmal, R.P. Cunningham and S.S. Wallace, New substrates for old enzymes. 5-hydroxy-2'-deoxycytidine and 5- hydroxy-2'-deoxyuridine are substrates for Escherichia coli endonuclease III and formamidopyrimidine DNA N-glycosylase, while 5- hydroxy-2'-deoxyuridine is a substrate for uracil DNA N-glycosylase, J Biol Chem 269 (1994) 18814-18820.

[54] T. Roldan-Arjona, M.V. Garcia-Ortiz, M. Ruiz-Rubio and R.R. Ariza, cDNA cloning, expression and functional characterization of an Arabidopsis thaliana homologue of the Escherichia coli DNA repair enzyme endonuclease III, Plant Mol Biol 44 (2000) 43-52.

[55] H.E. Krokan, R. Standal and G. Slupphaug, DNA glycosylases in the base excision repair of DNA, Biochem J 325 (1997) 1-16.

[56] P.M. Girard and S. Boiteux, Repair of oxidized DNA bases in the yeast Saccharomyces cerevisiae, Biochimie 79 (1997) 559-566.

[57] D.R. Denver, S.L. Swenson and M. Lynch, An evolutionary analysis of the helix-hairpin-helix superfamily of DNA repair glycosylases, Mol Biol Evol 20 (2003) 1603-1611.

[58] I. Alseth, L. Eide, M. Pirovano, T. Rognes, E. Seeberg and M. Bjoras, The Saccharomyces cerevisiae homologues of endonuclease III from Escherichia coli, Ntg1 and Ntg2, are both required for efficient repair of spontaneous and induced oxidative DNA damage in yeast, Mol Cell Biol 19 (1999) 3779-3787.

[59] D. Jiang, Z. Hatahet, J.O. Blaisdell, R.J. Melamede and S.S. Wallace, Escherichia coli endonuclease VIII: cloning, sequencing, and overexpression of the nei structural gene and characterization of nei and nei nth mutants, J Bacteriol 179 (1997) 3773-3782.

[60] J. Tchou, H. Kasai, S. Shibutani, M.H. Chung, J. Laval, A.P. Grollman and S. Nishimura, 8-oxoguanine (8-hydroxyguanine) DNA glycosylase and its substrate specificity, Proc Natl Acad Sci USA 88 (1991) 4690-4694.

[61] S. Boiteux, E. Gajewski, J. Laval and M. Dizdaroglu, Substrate specificity of the Escherichia coli Fpg protein (formamidopyrimidine-DNA glycosylase): excision of purine lesions in DNA produced by ionizing radiation or photosensitization, Biochemistry 31 (1992) 106-110.

[62] M. Bhagwat and J.A. Gerlt, 3'- and 5'-strand cleavage reactions catalyzed by the Fpg protein from Escherichia coli occur via successive beta- and delta-elimination mechanisms, respectively, Biochemistry 35 (1996) 659-665.

[63] M.L. Michaels, C. Cruz, A.P. Grollman and J.H. Miller, Evidence that MutY and MutM combine to prevent mutations by an oxidatively damaged form of guanine in DNA, Proc Natl Acad Sci USA 89 (1992) 7022-7025.

[64] J.A. Eisen and P.C. Hanawalt, A phylogenomic study of DNA repair genes, proteins, and processes, Mutat Res 435 (1999) 171-213.

[65] P.A. van der Kemp, D. Thomas, R. Barbey, R. de Oliveira and S. Boiteux, Cloning and expression in Escherichia coli of the OGG1 gene of Saccharomyces cerevisiae, which codes for a DNA glycosylase that excises 7,8-dihydro-8-oxoguanine and 2,6-diamino-4-hydroxy-5-N-methylformamidopyrimidine, Proc Natl Acad Sci USA 93 (1996) 5197-5202.

[66] H.M. Nash, S.D. Bruner, O.D. Scharer, T. Kawate, T.A. Addona, E. Spooner, W.S. Lane and G.L. Verdine, Cloning of a yeast 8-oxoguanine DNA glycosylase reveals the existence of a base-excision DNA-repair protein superfamily, Curr. Biol. 6 (1996) 968-980.

[67] T. Roldan-Arjona, Y.F. Wei, K.C. Carter, A. Klungland, C. Anselmino, R.P. Wang, M. Augustus and T. Lindahl, Molecular cloning and functional expression of a human cDNA encoding the antimutator enzyme 8-hydroxyguanine-DNA glycosylase, Proc Natl Acad Sci USA 94 (1997) 8016-8020.

[68] J.P. Radicella, C. Dherin, C. Desmaze, M.S. Fox and S. Boiteux, Cloning and characterization of hOGG1, a human homolog of the OGG1 gene of Saccharomyces cerevisiae, Proc Natl Acad Sci USA 94 (1997) 8010-8015.

[69] T.A. Rosenquist, D.O. Zharkov and A.P. Grollman, Cloning and characterization of a mammalian 8-oxoguanine DNA glycosylase, Proc Natl Acad Sci USA 94 (1997) 7429-7434.

[70] P.M. Girard, N. Guibourt and S. Boiteux, The Ogg1 protein of Saccharomyces cerevisiae: a 7,8-dihydro-8-oxoguanine DNA glycosylase/AP lyase whose lysine 241 is a critical residue for catalytic activity, Nucleic Acids Res 25 (1997) 3204-3211.

[71] T. Ohtsubo, O. Matsuda, K. Iba, I. Terashima, M. Sekiguchi and Y. Nakabeppu, Molecular cloning of AtMMH, an Arabidopsis thaliana ortholog of the Escherichia coli mutM gene, and analysis of functional domains of its product, Mol Gen Genet 259 (1998) 577-590.

[72] A.L. Dany and A. Tissier, A functional OGG1 homologue from Arabidopsis thaliana, Mol Genet Genomics 265 (2001) 293-301.

[73] M.V. Garcia-Ortiz, R.R. Ariza and T. Roldan-Arjona, An OGG1 orthologue encoding a functional 8-oxoguanine DNA glycosylase/lyase in *Arabidopsis thaliana*, Plant Mol. Biol. 47 (2001) 795-804.

[74] T.M. Murphy and M.J. Gao, Multiple forms of formamidopyrimidine-DNA glycosylase produced by alternative splicing in Arabidopsis thaliana, J Photochem Photobiol B 61 (2001) 87-93.

[75] K.C. Scortecci, A.F. Lima, F.M. Carvalho, U.B. Silva, L.F. Agnez-Lima and S.R. Batistuzzo de Medeiros, A characterization of a MutM/Fpg ortholog in sugarcane--A monocot plant, Biochem Biophys Res Commun 361 (2007) 1054-1060.

[76] T. Morales-Ruiz, M. Birincioglu, P. Jaruga, H. Rodriguez, T. Roldan-Arjona and M. Dizdaroglu, Arabidopsis thaliana Ogg1 protein excises 8-hydroxyguanine and 2,6-diamino-4-hydroxy-5-formamidopyrimidine from oxidatively damaged DNA containing multiple lesions, Biochemistry 42 (2003) 3089-3095.

[77] T.M. Murphy, What is base excision repair good for? knockout mutants for FPG and OGG glycosylase genes in Arabidopsis, Physiologia Plantarum 123 (2005) 227-232.

[78] O. Leprince, N.M. Atherton, R. Deltour and G. Hendry, The involvement of respiration in free radical processes during loss of desiccation tolerance in germinating *Zea mays* L., Plant Physiol 104 (1994) 1333-1339.

[79] C. Reuzeau and G. Cavalie, Activities of free-radical processing enzymes in dry sunflower Seeds, New Phytol 130 (1995) 59-66.

[80] B. Demple and L. Harrison, Repair of oxidative damage to DNA: enzymology and biology, Annu Rev Biochem 63 (1994) 915-948.

[81] D.R. Marenstein, M.K. Chan, A. Altamirano, A.K. Basu, R.J. Boorstein, R.P. Cunningham and G.W. Teebor, Substrate specificity of human endonuclease III (hNth1): Effect of human AP endonuclease 1 (APE1) on hNth1 activity, J Biol Chem 278 (2003) 9005-9012.

[82] B. Pascucci, G. Maga, U. Hubscher, M. Bjoras, E. Seeberg, I.D. Hickson, G. Villani, C. Giordano, L. Cellai and E. Dogliotti, Reconstitution of the base excision repair pathway for 7,8-dihydro-8-oxoguanine with purified human proteins, Nucleic Acids Res 30 (2002) 2124-2130.

[83] E. Babiychuk, S. Kushnir, M. Van Montagu and D. Inze, The Arabidopsis thaliana apurinic endonuclease Arp reduces human transcription factors Fos and Jun, Proc Natl Acad Sci USA 91 (1994) 3299-3303.

[84] M.Z. Hadi, K. Ginalski, L.H. Nguyen and D.M. Wilson, 3rd, Determinants in nuclease specificity of Ape1 and Ape2, human homologues of Escherichia coli exonuclease III, J Mol Biol 316 (2002) 853-866.

[85] L. Wiederhold, J.B. Leppard, P. Kedar, F. Karimi-Busheri, A. Rasouli-Nia, M. Weinfeld, A.E. Tomkinson, T. Izumi, R. Prasad, S.H. Wilson, S. Mitra and T.K. Hazra, AP endonuclease-independent DNA base excision repair in human cells, Mol Cell 15 (2004) 209-220.

[86] C.J. Whitehouse, R.M. Taylor, A. Thistlethwaite, H. Zhang, F. Karimi-Busheri, D.D. Lasko, M. Weinfeld and K.W. Caldecott, XRCC1 stimulates human polynucleotide kinase activity at damaged DNA termini and accelerates DNA single-strand break repair, Cell 104 (2001) 107-117.

[87] M. Betti, S. Petrucco, A. Bolchi, G. Dieci and S. Ottonello, A plant 3'-phosphoesterase involved in the repair of DNA strand breaks generated by oxidative damage, J Biol Chem 276 (2001) 18038-18045.

[88] S. Petrucco, G. Volpi, A. Bolchi, C. Rivetti and S. Ottonello, A nick-sensing DNA 3'-repair enzyme from Arabidopsis, J Biol Chem 277 (2002) 23675-23683.

[89] M. Garcia-Diaz, O. Dominguez, L.A. Lopez-Fernandez, L.T. de Lera, M.L. Saniger, J.F. Ruiz, M. Parraga, M.J. Garcia-Ortiz, T. Kirchhoff, J. del Mazo, A. Bernad and L. Blanco, DNA polymerase lambda (Pol lambda), a novel eukaryotic DNA polymerase with a potential role in meiosis, J Mol Biol 301 (2000) 851-867.

[90] Y. Uchiyama, S. Kimura, T. Yamamoto, T. Ishibashi and K. Sakaguchi, Plant DNA polymerase lambda, a DNA repair enzyme that functions in plant meristematic and meiotic tissues, Eur J Biochem 271 (2004) 2799-2807.

[91] Y. Mori, S. Kimura, A. Saotome, N. Kasai, N. Sakaguchi, Y. Uchiyama, T. Ishibashi, T. Yamamoto, H. Chiku and K. Sakaguchi, Plastid DNA polymerases from higher plants, Arabidopsis thaliana, Biochem Biophys Res Commun 334 (2005) 43-50.

[92] R. Takeuchi, S. Kimura, A. Saotome and K. Sakaguchi, Biochemical properties of a plastidial DNA polymerase of rice, Plant Mol Biol 64 (2007) 601-611.

[93] A.E. Vidal, S. Boiteux, I.D. Hickson and J.P. Radicella, XRCC1 coordinates the initial and late stages of DNA abasic site repair through protein-protein interactions, EMBO J 20 (2001) 6530-6539.

[94] R.M. Taylor, A. Thistlethwaite and K.W. Caldecott, Central role for the XRCC1 BRCT I domain in mammalian DNA single-strand break repair, Mol Cell Biol 22 (2002) 2556-2563.

[95] C.E. West, W.M. Waterworth, Q. Jiang and C.M. Bray, Arabidopsis DNA ligase IV is induced by gamma-irradiation and interacts with an Arabidopsis homologue of the double strand break repair protein XRCC4, Plant J 24 (2000) 67-78.

[96] H. van Attikum, P. Bundock, R.M. Overmeer, L.Y. Lee, S.B. Gelvin and P.J. Hooykaas, The Arabidopsis AtLIG4 gene is required for the repair of DNA damage, but not for the integration of Agrobacterium T-DNA, Nucleic Acids Res 31 (2003) 4247-4255.

[97] R.M. Taylor, M.J. Hamer, J. Rosamond and C.M. Bray, Molecular cloning and functional analysis of the Arabidopsis thaliana DNA ligase I homologue, Plant J 14 (1998) 75-81.

[98] Y.Q. Wu, B. Hohn and A. Ziemienowic, Characterization of an ATP-dependent type I DNA ligase from Arabidopsis thaliana, Plant Mol Biol 46 (2001) 161-170.

[99] P.A. Sunderland, C.E. West, W.M. Waterworth and C.M. Bray, An evolutionarily conserved translation initiation mechanism regulates nuclear or mitochondrial targeting of DNA ligase 1 in Arabidopsis thaliana, Plant J 47 (2006) 356-367.

[100] D. Bonatto, L.F. Revers, M. Brendel and J.A. Henriques, The eukaryotic Pso2/Snm1/Artemis proteins and their function as genomic and cellular caretakers, Braz J Med Biol Res 38 (2005) 321-334.

[101] G. Slupphaug, B. Kavli and H.E. Krokan, The interacting pathways for prevention and repair of oxidative DNA damage, Mutat Res 531 (2003) 231-251.

[102] R.D. Wood, S.J. Araujo, R.R. Ariza, D.P. Batty, M. Biggerstaff, E. Evans, P.H. Gaillard, D. Gunz, B. Koberle, I. Kuraoka, J.G. Moggs, J.K. Sandall and M.K. Shivji, DNA damage recognition and nucleotide excision repair in mammalian cells, Cold Spring Harb Symp Quant Biol 65 (2000) 173-182.

[103] G.R. Harlow, M.E. Jenkins, T.S. Pittalwala and D.W. Mount, Isolation of uvh1, an Arabidopsis mutant hypersensitive to ultraviolet light and ionizing radiation, Plant Cell 6 (1994) 227-235.

[104] A.L. Fidantsef, D.L. Mitchell and A.B. Britt, The Arabidopsis UVH1 gene is a homolog of the yeast repair endonuclease RAD1, Plant Physiol 124 (2000) 579-586.

[105] Z. Liu, G.S. Hossain, M.A. Islas-Osuna, D.L. Mitchell and D.W. Mount, Repair of UV damage in plants by nucleotide excision repair: Arabidopsis UVH1 DNA repair gene is a homolog of Saccharomyces cerevisiae Rad1, Plant J 21 (2000) 519-528.

[106] E.J. Vonarx, N.G. Howlett, R.H. Schiestl and B.A. Kunz, Detection of Arabidopsis thaliana AtRAD1 cDNA variants and assessment of function by expression in a yeast rad1 mutant, Gene 296 (2002) 1-9.
[107] E. Hefner, S.B. Preuss and A.B. Britt, Arabidopsis mutants sensitive to gamma radiation include the homologue of the human repair gene ERCC1, J Exp Bot 54 (2003) 669-680.
[108] J. Molinier, M.E. Stamm and B. Hohn, SNM-dependent recombinational repair of oxidatively induced DNA damage in Arabidopsis thaliana, EMBO Rep 5 (2004) 994-999.
[109] L. Liang, S. Flury, V. Kalck, B. Hohn and J. Molinier, CENTRIN2 interacts with the Arabidopsis homolog of the human XPC protein (AtRAD4) and contributes to efficient synthesis-dependent repair of bulky DNA lesions, Plant Mol Biol 61 (2006) 345-356.
[110] D.T. Ribeiro, C.R. Machado, R.M. Costa, U.M. Praekelt, M.A. Van Sluys and C.F. Menck, Cloning of a cDNA from Arabidopsis thaliana homologous to the human XPB gene, Gene 208 (1998) 207-213.
[111] R.M. Costa, P.G. Morgante, C.M. Berra, M. Nakabashi, D. Bruneau, D. Bouchez, K.S. Sweder, M.A. Van Sluys and C.F. Menck, The participation of AtXPB1, the XPB/RAD25 homologue gene from Arabidopsis thaliana, in DNA repair and plant development, Plant J 28 (2001) 385-395.
[112] P.G. Morgante, C.M. Berra, M. Nakabashi, R.M. Costa, C.F. Menck and M.A. Van Sluys, Functional XPB/RAD25 redundancy in Arabidopsis genome: characterization of AtXPB2 and expression analysis, Gene 344 (2005) 93-103.
[113] E.J. Vonarx, E.K. Tabone, M.J. Osmond, H.J. Anderson and B.A. Kunz, Arabidopsis homologue of human transcription factor IIH/nucleotide excision repair factor p44 can function in transcription and DNA repair and interacts with AtXPD, Plant J 46 (2006) 512-521.
[114] A. Li, D. Schuermann, F. Gallego, I. Kovalchuk and B. Tinland, Repair of damaged DNA by Arabidopsis cell extract, Plant Cell 14 (2002) 263-273.
[115] A. Koga, T. Ishibashi, S. Kimura, Y. Uchiyama and K. Sakaguchi, Characterization of T-DNA insertion mutants and RNAi silenced plants of Arabidopsis thaliana UV-damaged DNA binding protein 2 (AtUV-DDB2), Plant Mol Biol 61 (2006) 227-240.
[116] K.B. Beckman and B.N. Ames, Oxidative decay of DNA, J Biol Chem 272 (1997) 19633-19636.
[117] T. Lindahl, M.S. Satoh, G.G. Poirier and A. Klungland, Post-translational modification of poly(ADP-ribose) polymerase induced by DNA strand breaks, Trends Biochem Sci 20 (1995) 405-411.
[118] L.H. Thompson and M.G. West, XRCC1 keeps DNA from getting stranded, Mutat Res 459 (2000) 1-18.
[119] E. Babiychuk, P.B. Cottrill, S. Storozhenko, M. Fuangthong, Y. Chen, M.K. O'Farrell, M. Van Montagu, D. Inze and S. Kushnir, Higher plants possess two structurally different poly(ADP-ribose) polymerases, Plant J 15 (1998) 635-645.
[120] G. Doucet-Chabeaud, C. Godon, C. Brutesco, G. de Murcia and M. Kazmaier, Ionising radiation induces the expression of PARP-1 and PARP-2 genes in Arabidopsis, Mol Genet Genomics 265 (2001) 954-963.
[121] H. Puchta, P. Swoboda and B. Hohn, Induction of intrachromosomal homologous recombination in whole plants, Plant J 7 (1995) 203-210.
[122] I.P. Chen, U. Haehnel, L. Altschmied, I. Schubert and H. Puchta, The transcriptional response of Arabidopsis to genotoxic stress - a high-density colony array study (HDCA), Plant J 35 (2003) 771-786.

[123] Y. Amor, E. Babiychuk, D. Inze and A. Levine, The involvement of poly(ADP-ribose) polymerase in the oxidative stress responses in plants, FEBS Lett 440 (1998) 1-7.
[124] M. De Block, C. Verduyn, D. De Brouwer and M. Cornelissen, Poly(ADP-ribose) polymerase in plants affects energy homeostasis, cell death and stress tolerance, Plant J 41 (2005) 95-106.
[125] S. Petrucco, Sensing DNA damage by PARP-like fingers, Nucleic Acids Res 31 (2003) 6689-6699.
[126] J.Y. Bleuyard, M.E. Gallego and C.I. White, Recent advances in understanding of the DNA double-strand break repair machinery of plants, DNA Repair (Amst) 5 (2006) 1-12.
[127] H. Puchta, The repair of double-strand breaks in plants: mechanisms and consequences for genome evolution, J Exp Bot 56 (2005) 1-14.
[128] E.C. Friedberg, Suffering in silence: the tolerance of DNA damage, Nat Rev Mol Cell Biol 6 (2005) 943-953.
[129] E.C. Friedberg, G.C. Walker and W. Siede, DNA Repair and Mutagenesis, ASM Press, Washington, D.C., 1995.
[130] S. Prakash, R.E. Johnson and L. Prakash, Eukaryotic translesion synthesis DNA polymerases: specificity of structure and function, Annu Rev Biochem 74 (2005) 317-353.
[131] A.R. Lehmann, Replication of damaged DNA by translesion synthesis in human cells, FEBS Lett 579 (2005) 873-876.
[132] A.J. Rattray and J.N. Strathern, Error-prone DNA polymerases: when making a mistake is the only way to get ahead, Annu Rev Genet 37 (2003) 31-66.
[133] H. Ohmori, E.C. Friedberg, R.P. Fuchs, M.F. Goodman, F. Hanaoka, D. Hinkle, T.A. Kunkel, C.W. Lawrence, Z. Livneh, T. Nohmi, L. Prakash, S. Prakash, T. Todo, G.C. Walker, Z. Wang and R. Woodgate, The Y-family of DNA polymerases, Mol Cell 8 (2001) 7-8.
[134] T.A. Kunkel, DNA replication fidelity, J Biol Chem 279 (2004) 16895-16898.
[135] R. Woodgate, A plethora of lesion-replicating DNA polymerases, Genes Dev 13 (1999) 2191-2195.
[136] C.W. Lawrence, P.E. Gibbs, R.S. Murante, X.D. Wang, Z. Li, T.P. McManus, W.G. McGregor, J.R. Nelson, D.C. Hinkle and V.M. Maher, Roles of DNA polymerase ζ and Rev1 protein in eukaryotic mutagenesis and translesion replication, Cold Spring Harb Symp Quant Biol 65 (2000) 61-69.
[137] U. Hübscher, G. Maga and S. Spadari, Eukaryotic DNA polymerases, Annu Rev Biochem 71 (2002) 133-163.
[138] O. Dominguez, J.F. Ruiz, T. Lain de Lera, M. Garcia-Diaz, M.A. Gonzalez, T. Kirchhoff, A.C. Martinez, A. Bernad and L. Blanco, DNA polymerase mu (Pol mu), homologous to TdT, could act as a DNA mutator in eukaryotic cells, EMBO J 19 (2000) 1731-1742.
[139] S. Gonzalez-Barrera, A. Sanchez, J.F. Ruiz, R. Juarez, A.J. Picher, G. Terrados, P. Andrade and L. Blanco, Characterization of SpPol4, a unique X-family DNA polymerase in Schizosaccharomyces pombe, Nucleic Acids Res 33 (2005) 4762-4774.
[140] A. Sakamoto, V.T. Lan, Y. Hase, N. Shikazono, T. Matsunaga and A. Tanaka, Disruption of the *AtREV3* gene causes hypersensitivity to ultraviolet B light and gamma-rays in *Arabidopsis*: implication of the presence of a translesion synthesis mechanism in plants, Plant Cell 15 (2003) 2042-2057.
[141] S. Takahashi, A. Sakamoto, S. Sato, T. Kato, S. Tabata and A. Tanaka, Roles of Arabidopsis AtREV1 and AtREV7 in translesion synthesis, Plant Physiol 138 (2005) 870-881.

[142] M.V. Garcia-Ortiz, R.R. Ariza, P.D. Hoffman, J.B. Hays and T. Roldan-Arjona, *Arabidopsis thaliana AtPOLK* encodes a DinB-like DNA polymerase that extends mispaired primer termini and is highly expressed in a variety of tissues, Plant J 39 (2004) 84-97.
[143] L. Haracska, S.L. Yu, R.E. Johnson, L. Prakash and S. Prakash, Efficient and accurate replication in the presence of 7,8-dihydro-8-oxoguanine by DNA polymerase η, Nat Genet 25 (2000) 458-461.
[144] F. Yuan, Y. Zhang, D.K. Rajpal, X. Wu, D. Guo, M. Wang, J.S. Taylor and Z. Wang, Specificity of DNA lesion bypass by the yeast DNA polymerase η, J Biol Chem 275 (2000) 8233-8239.
[145] O. Rechkoblit, L. Malinina, Y. Cheng, V. Kuryavyi, S. Broyde, N.E. Geacintov and D.J. Patel, Stepwise translocation of Dpo4 polymerase during error-free bypass of an oxoG lesion, PLoS Biol 4 (2006) e11.
[146] H. Zang, A. Irimia, J.Y. Choi, K.C. Angel, L.V. Loukachevitch, M. Egli and F.P. Guengerich, Efficient and high fidelity incorporation of dCTP opposite 7,8-dihydro-8-oxodeoxyguanosine by Sulfolobus solfataricus DNA polymerase Dpo4, J Biol Chem 281 (2006) 2358-2372.
[147] L. Haracska, L. Prakash and S. Prakash, Role of human DNA polymerase κ as an extender in translesion synthesis, Proc Natl Acad Sci USA 99 (2002) 16000-16005.
[148] Y. Zhang, F. Yuan, X. Wu, M. Wang, O. Rechkoblit, J.S. Taylor, N.E. Geacintov and Z. Wang, Error-free and error-prone lesion bypass by human DNA polymerase κ in vitro, Nucleic Acids Res 28 (2000) 4138-4146.
[149] P. Jaloszynski, E. Ohashi, H. Ohmori and S. Nishimura, Error-prone and inefficient replication across 8-hydroxyguanine (8-oxoguanine) in human and mouse ras gene fragments by DNA polymerase κ, Genes Cells 10 (2005) 543-550.
[150] Y. Zhang, F. Yuan, X. Wu, J.S. Taylor and Z. Wang, Response of human DNA polymerase ι to DNA lesions, Nucleic Acids Res 29 (2001) 928-935.
[151] R.E. Johnson, L. Haracska, L. Prakash and S. Prakash, Role of hoogsteen edge hydrogen bonding at template purines in nucleotide incorporation by human DNA polymerase ι, Mol Cell Biol 26 (2006) 6435-6441.
[152] M.V. Garcia-Ortiz, T. Roldan-Arjona and R.R. Ariza, The noncatalytic C-terminus of AtPOLK Y-family DNA polymerase affects synthesis fidelity, mismatch extension and translesion replication, Febs J 254 (2007) 3340-3350.
[153] T. Ogi and A.R. Lehmann, The Y-family DNA polymerase kappa (pol kappa) functions in mammalian nucleotide-excision repair, Nat Cell Biol 8 (2006) 640-642.
[154] P.J. Hurley and F. Bunz, ATM and ATR: components of an integrated circuit, Cell Cycle 6 (2007) 414-417.
[155] V. Garcia, M. Salanoubat, N. Choisne and A. Tissier, An ATM homologue from Arabidopsis thaliana: complete genomic organisation and expression analysis, Nucleic Acids Res 28 (2000) 1692-1699.
[156] AGI, Analysis of the genome sequence of the flowering plant *Arabidopsis thaliana*, Nature 408 (2000) 796-815.
[157] G.W. Templeton and G.B. Moorhead, The phosphoinositide-3-OH-kinase-related kinases of Arabidopsis thaliana, EMBO Rep 6 (2005) 723-728.
[158] V. Garcia, H. Bruchet, D. Camescasse, F. Granier, D. Bouchez and A. Tissier, AtATM is essential for meiosis and the somatic response to DNA damage in plants, Plant Cell 15 (2003) 119-132.
[159] K. Culligan, A. Tissier and A. Britt, ATR regulates a G2-phase cell-cycle checkpoint in Arabidopsis thaliana, Plant Cell 16 (2004) 1091-1104.

[160] L. Zou and S.J. Elledge, Sensing DNA damage through ATRIP recognition of RPA-ssDNA complexes, Science 300 (2003) 1542-1548.
[161] K.M. Culligan, C.E. Robertson, J. Foreman, P. Doerner and A.B. Britt, ATR and ATM play both distinct and additive roles in response to ionizing radiation, Plant J 48 (2006) 947-961.
[162] L. Ricaud, C. Proux, J.P. Renou, O. Pichon, S. Fochesato, P. Ortet and M.H. Montane, ATM-Mediated Transcriptional and Developmental Responses to gamma-rays in Arabidopsis, PLoS ONE 2 (2007) e430.
[163] R. Ulm, Molecular genetics of genotoxic stress signalling in plants, in: H. Hirt and K. Shinozaki (Eds.), Plant Responses to Abiotic Stress, Springer-Verlag, Heidelberg, 2003, pp. 217-240.
[164] T. Yuasa, K. Ichimura, T. Mizoguchi and K. Shinozaki, Oxidative stress activates ATMPK6, an Arabidopsis homologue of MAP kinase, Plant Cell Physiol 42 (2001) 1012-1016.
[165] L. Lepiniec, E. Babiychuk, S. Kushnir, M. Van Montagu and D. Inze, Characterization of an Arabidopsis thaliana cDNA homologue to animal poly(ADP-ribose) polymerase, FEBS Lett 364 (1995) 103-108.
[166] M. Garcia-Diaz, K. Bebenek, R. Sabariegos, O. Dominguez, J. Rodriguez, T. Kirchhoff, E. Garcia-Palomero, A.J. Picher, R. Juarez, J.F. Ruiz, T.A. Kunkel and L. Blanco, DNA polymerase lambda, a novel DNA repair enzyme in human cells, J Biol Chem 277 (2002) 13184-13191.

Figure legends

Figure 1. Diagram showing major steps during base excision repair of oxidized bases in plants. AtOGG1 and AtNTH1 DNA glycosylases carry out a β-elimination, leaving a 3′-dRP residue that is subsequently removed by an AP endonuclease (such as AtArp, AtAPE1 or AtAPE2). AtMMH DNA glycosylase performs a β, δ-elimination and the resulting 3′-phosphate may be a substrate of AtZDP. Gap filling could be performed by AtPOLL and ligation carried out by AtLIG1. AtXRCC1 probably acts as a scaffold protein during initial and late steps of BER. Other proteins possibly involved are not shown.

Roldan-Arjona, T. and R. R. Ariza (2009). "Repair and tolerance of oxidative DNA damage in plants." Mutat. Res. 681(2-3): 169-179.

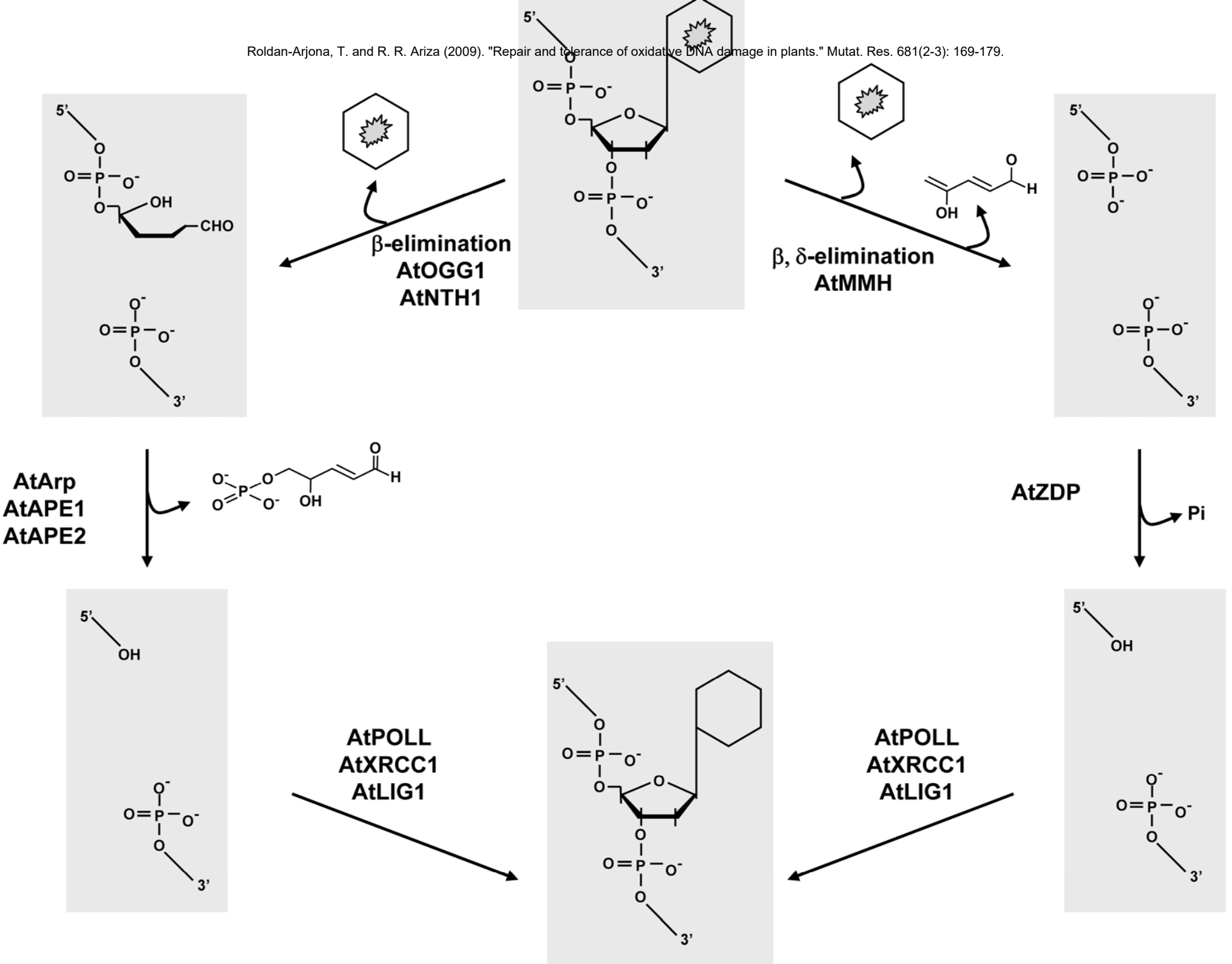

Table 1. Proteins involved in repair of oxidative base damage and single-strand breaks in bacteria, yeast, humans and *Arabidopsis thaliana*.

	E. coli	*S. cerevisiae*	*H. sapiens*	*A. thaliana*	References[a]
LESION RECOGNITION AND/OR STRAND INCISION					
Excision of oxidized pyrimidines	Nth	Ntg1p, Ntg2p	NTH1	AtNTH1, AtNTH2	[54]
Excision of oxidized purines	MutM	-	-	AtMMH	[71]
	-	Ogg1p	OGG1	AtOGG1	[72,73]
Excision of oxidized purines and pyrimidines	Nei	-	NEIL1, NEIL2, NEIL3	-	
Excision of adenine paired to 8-oxoG	MutY	-	MYH	AtMUTY	
Excision of etheno-A and etheno-C generated by lipid peroxidation	MUG	-	TDG	-	
DNA GAP TAILORING					
Removal of 3′-dRP after β-elimination	Xth	Apn2p	APEX1, APEX2	AtArp, AtAPE1,AtAPE2	[83]
Removal of 3′phosphate after β,δ-elimination	-	Tpp1p	PNKP	AtZDP	[88]
Single-strand break sensing	-	-	PARP-1, PARP-2	AtPARP1, AtPARP2, AtPARP3	[120,165]
Scaffold protein	-	-	XRCC1	AtXRCC1	[94]
DNA SYNTHESIS AND LIGATION					
Family A DNA polymerases	PolI	-	-	-	
Family X DNA polymerases	-	-	POLB	-	
	-	Pol4p	POLL	AtPOLL	[166]
NAD^+-dependent DNA ligases	LigA	-	-	-	
ATP-dependent DNA ligases	-	Cdc9p	LIG1	AtLIG1	[97]

[a] Articles reporting the identification and/or characterization of Arabidopsis genes

Table 2. Conservation of oxidative DNA repair proteins in five plant species with sequenced genomes[a]

	A. thaliana	*V. vinifera* (grapevine)	*O. sativa* (rice plant)	*P. patens* (moss)	*C. reinhardtii* (unicellular green alga)
LESION RECOGNITION AND/OR STRAND INCISION	AtMMH (At1G52500)[b] 274[d]	CAO62687[c] 410[d] (75)[e]	BAF20093 400 (70)	EDQ52568 496 (55)	XP_001702534 297 (43)
	AtNTH1 (At2G31450) 379	CAO64783 291 (68)	ABA92590 362 (59)	XP_001763953 226 (41)	XP_001701499 292 (29)
	AtNTH2 (At1G05900) 386	CAN69482 377 (48)	X96284 373 (50)	XP_001763953 226 (39)	XP_001701499 292 (29)
	AtOGG1 (At1G21710) 365	CAO61897 399 (67)	BAD15490 399 (53)	XP_001775305 303 (57)	XP_001700241 155 (43)
	AtMUTY (At4G12740) 630	CAO41069 476 (57)	ABA96714 474 (49)	XP_001772500 629 (39)	XP_001701896 793 (40)
DNA GAP TAILORING	AtArp (At2G41460) 536	CAO23347 263 (74)	NP_001044537 499 (57)	EDQ64693 363 (57)	XP_001703445 437 (44)
	AtAPE1 (At3G48425) 364	CAO64180 357 (74)	BAF29592 379 (67)	XP_001768323 369 (59)	-
	AtAPE2 (At4G36050) 610	CAN69587 632 (56)	BAF25697 619 (46)	EDQ53323 591 (40)	XP_001692908 264 (31)
	AtZDP (At3G14890) 694	CAO39403 404 (61)	BAD87018 463 (45)	EDQ56656 187 (61)	XP_001694924 242 (39)
	AtPARP1 (At2G31320) 983	CAO70689 947 (69)	BAC84104 977 (62)	EDQ65830 989 (52)	-
	AtPARP2 (At4G02390) 637	-	BAD52929 633 (59)	EDQ52960 661 (53)	-
	AtPARP3 (At5G22470) 814	CAO48763 828 (66)	EAZ23301 840 (56)	XP_001763226 865 (41)	-
	AtXRCC1 (At1G80420) 353	CAO45954 344 (54)	BAF18694 347 (48)	XP_001777620 367 (37)	-
DNA SYNTHESIS AND LIGATION	AtPOLL (At1G10520) 529	CAO40943_4 549 (66)	BAD18976 552 (61)	XP_001776483 535 (49)	XP_001700433 1599 (30)
	AtLIG1 (At1G08130) 790	CAO16749 783 (65)	EAZ16500 810 (63)	XP_001777550 656 (64)	XP_001702891 813 (46)

[a] Data are from pre-computed BLAST searches against the protein non-redundant (nr) database using the BLink resource available at www.ncbi.nlm.nih.gov.
[b] Locus tag (www.arabidopsis.org).
[c] Accession number.
[d] Protein length (amino acids).
[e] Percent of identical amino acids shared with the *A. thaliana* protein sequence showed in the first column.