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# Recognition and Repair Pathways of Damaged DNA in Higher Plants

Sascha Biedermann[1,2], Sutton Mooney[1] and Hanjo Hellmann[1]
[1]*Washington State University Pullman*
[2]*Angewandte Genetik, Berlin*
[1]*United States of America*
[2]*Germany*

## 1. Introduction

Living organisms are continuously exposed to factors that threaten the integrity of their cells. This includes structural and enzymatic components like lipids or proteins, but also their genomes. Damage to genetic material can be critical as unrecognized and unrepaired DNA damage may cause fatal mutations not only threatening the organism's immediate survival but also that of its descendants. These genotoxic factors can derive from their surrounding environment and may include chemicals or ionizing radiation; but DNA damage can also be caused by reactive oxygen species (ROS) that are byproducts of daily metabolism or result from insufficient protection against abiotic stress conditions.
UV light can cause direct DNA damage by generating 6-4 and CPD photoproducts (example given in Fig. 1 is a thymine dimer). UV like most abiotic stress conditions can also generate ROS production in the cell. ROS have a high potential to damage single bases by oxidation (example give is 8-oxoG (Fig. 1)), but are also capable of introducing single or double strand breaks.
In contrast to most animals, plants are sessile organisms that cannot change their location when exposed to unfavorable conditions such as drought or salinity. Plants also face the difficult situation that they depend on sunlight for photosynthesis, a process that on its own constitutively generates ROS (Asada, 1999; Krieger-Liszkay, 2005; Triantaphylides and Havaux, 2009). Sunlight also contains significant amounts of UV-B light, which can contribute to both ROS production in the nucleus as well as directly affecting the DNA structure. Sunlight and high production rates of ROS are two of the main factors that lead to many mutations in plants. Consequently, the current review will focus on mechanisms that plants have in place to recognize and repair damaged DNA caused by either of these factors. We will provide a brief overview on the different classifications of DNA damage that can be expected, how these damages are repaired, and what is known about regulatory and physiological mechanisms that are in place in plants to recognize and respond to DNA damage. Because plants have taken a different evolutionary path than animals and possess some unique features not found in animals, we will compare selected repair and regulatory pathways in animals and plants. Despite their differences, plants and animals share many aspects in damaged DNA recognition and repair, and for this reason we will conclude this chapter by elaborating on some opinions for using plants as powerful and valuable model organisms for animals to understand the underlying processes of DNA repair.

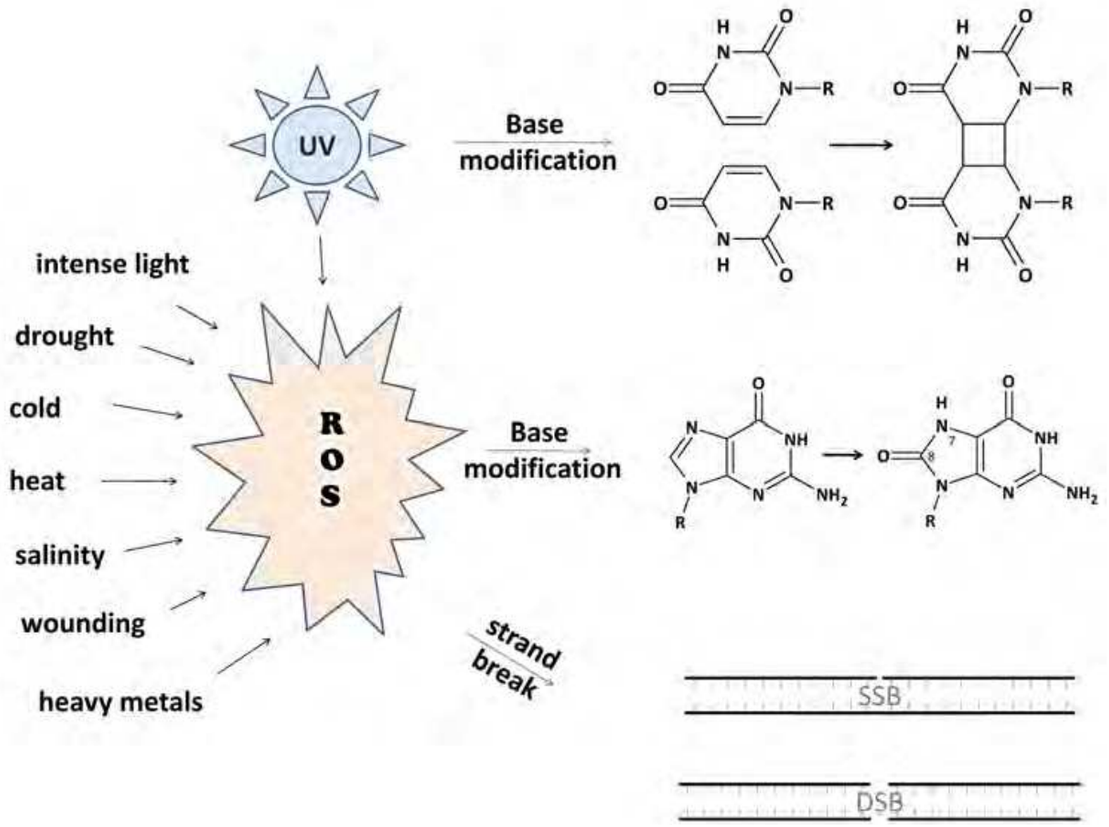


Fig. 1. UV light and ROS as genotoxic stress factors.

## 2. DNA damage caused by exposure to sunlight and abiotic stress

Ironically, although sunlight is obligatory for photosynthesis and survival of plants, it also represents one of the major threats to their genomic integrity. This can be ascribed to at least three reasons:

First, sunlight contains energy rich UV-C (280 to 100 nm), UV-B (290 to 320 nm) and UV-A (320–400 nm) light. Whereas UV-C is filtered out in the atmosphere, UV-B and UV-A can reach earth's surface. Although the amount strongly depends on the latitude and elevation, as well as cloud cover and canopy density, due to their sessile nature plants are exposed throughout the day to this genotoxic stress. UV-light is a strong mutagen that is absorbed by the DNA and may lead to the generation of cyclobutane pyrimidine dimers (CPD) and to a lesser extent pyrimidine (6,4) pyrimidone dimers (Friedberg EC et al., 2006). Both photoproducts are DNA lesions that affect transcriptional processes and result in error-prone replication (Fig. 1) (Friedberg EC et al., 2006). Solar UV light can also indirectly cause DNA damage by ROS production in the nucleus (Iovine et al., 2009). ROS induce a broad range of DNA damage, which includes base and nucleotide modifications, especially in sequences with a high guanosine content, and may even cause strand breaks (Wiseman and Halliwell, 1996; Tuteja et al., 2001; Tuteja and Tuteja, 2001). Although the precise nature of ROS generated by UV-light is not fully resolved, it is well established that oxygenated nucleotides like 8-oxo-guanine that can be caused by the accumulation of hydroxyl radicals (•OH) after prolonged UV exposure in the cell (Yamamoto et al., 1992; Hattori et al., 1996).

Second, ROS are commonly produced as metabolic byproducts in the chloroplasts, peroxisomes, and mitochondria (Foyer and Noctor, 2003). In fact it is estimated for mammals that per day ~180 guanines are oxidized to 8-hydroxyguanine in a single cell (Lindahl, 1993); and it is likely that this rate is even higher in photosynthetically active plants where chloroplasts continuously produce ROS. Furthermore, excessive light exposure as it may occur in mid-day under non-shaded conditions can overexcite the photosynthetic machinery. As a consequence, singlet oxygen ($^1O_2$) can be produced from triplet-state chlorophyll in the light- harvesting complex of photosystem II (PSII). In addition, byproducts of photosynthetic activities are superoxide ($O_2^-$) and hydrogen peroxide ($H_20_2$) that can derive from water-splitting activities of the oxygen-evolving complex of PSII, and superoxide can be generated on the reducing side of PSI by the Mehler reaction (Noctor et al., 2002) (Fig. 1).

Third, heat from the sunlight can lead to failure of the structural composition and enzymatic machinery within the cell. To prevent cellular collapse, plants have developed a variety of protective mechanisms, the most important being the cooling effect of water transpiration through stomata. However, this dependency on water availability, together with their immobility, make plants highly susceptible to water stress conditions that derive from drought, salinity, or cold. Abiotic stress unbalances metabolic processes including photosynthesis, which ultimately causes a general increase in ROS concentration in the cell (Vinocur and Altman, 2005; Jaspers and Kangasjarvi, 2010). Although ROS detoxifying defense mechanisms are in place in the organelles and the cytosol, under the stress conditions described above, these mechanisms may not provide sufficient protection. To avoid excessive mutations over prolonged exposure to abiotic stress, plant cells depend on efficient repair pathways.

## 3. Major repair mechanisms in plants

### 3.1 Photoreactivation by photolyases

In plants the main repair pathway for direct DNA damage caused by UV-light that leads to the generation of CPDs and (6–4) photoproducts is based on the activity of photolyases (Jiang et al., 1997). Two types of photolyases have evolved that specifically recognize and repair either type of photodamage. Based on sequence homology, CPD photolyases are grouped into two different classes: while class I CPD photolyases are present in microorganisms, class II enzymes can be found in archaea, eubacteria, some animals (excluding placental mammals), and plants (Kanai et al., 1997). In comparison, (6-4) photolyases have been found in metazoans and plants, and they share sequence similarities with class I CPD photolyases (Kanai et al., 1997).

The structure and reaction mechanisms of photolyases have been intensively studied in the last decade, providing us with plentiful data on their function. Photolyases have two types of chromophoric co-factors that are used for photoreactivation (Huang et al., 2006; Ozturk et al., 2008; Hitomi et al., 2009). One chromophore is $FADH^-$, the two electron reduced form of FAD, while the second one can be either methenyltetrahydrofolate (MTHF) or 7,8-didemethyl-8-hydroxy-5-deazariboflavin (8-HDF). MTHF or 8-HDF function as the light harvesting chromophores that absorb blue light (300-600 nm), and transfer the energy to $FADH^-$ (Moldt et al., 2009; Li et al., 2010; Okafuji et al., 2010). Photolyases bind directly to CPD and (6-4) photoproducts, where an electron is transferred from the excited $FADH^-$ to

the dimers generating pyrimidine monomers, upon which the enzyme is released (Li et al., 2010; Okafuji et al., 2010) (Fig. 2).

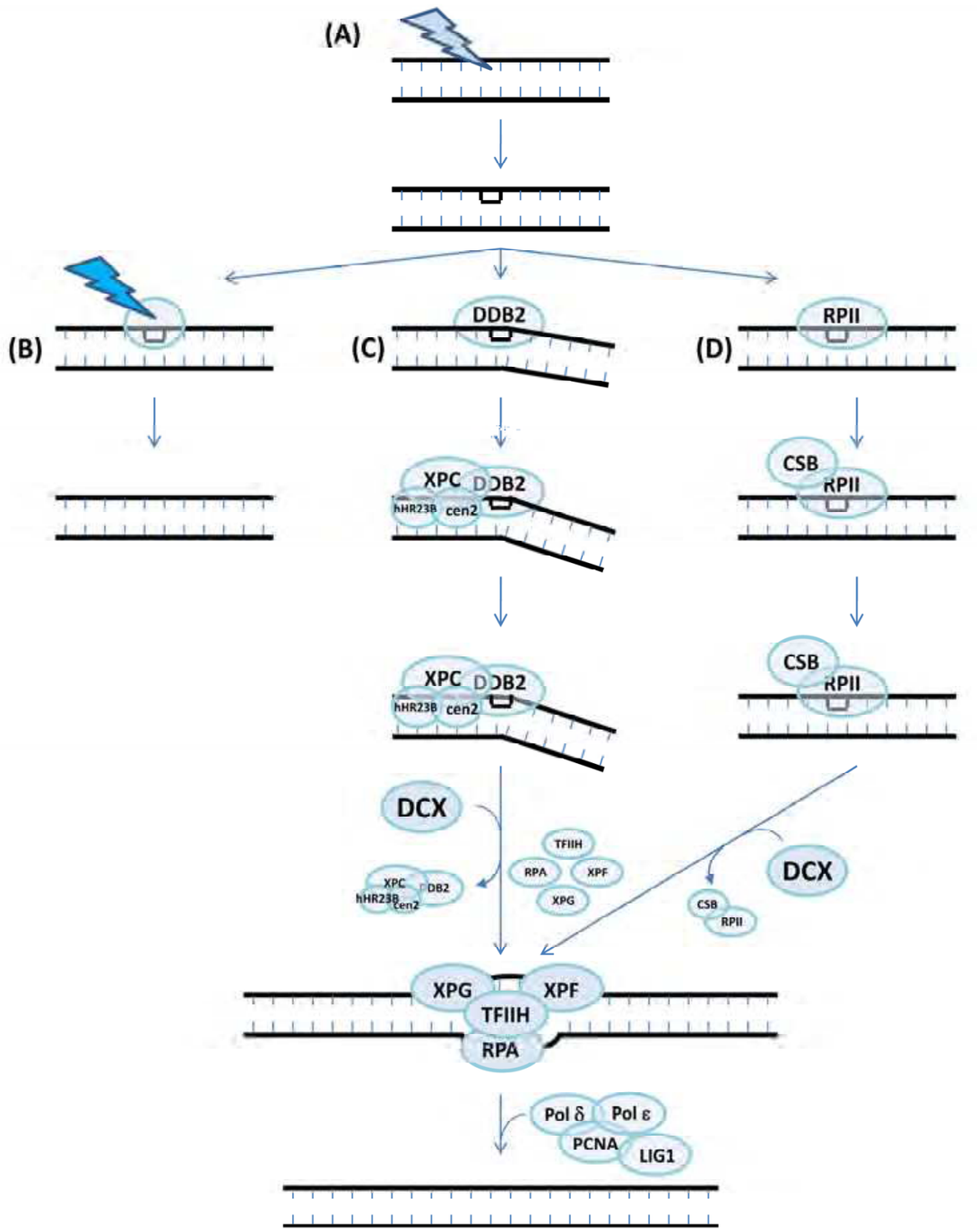


Fig. 2. Photodamage and potential repair pathways in plants.
**(A)** Direct DNA damage caused by UV can be recognized and repaired by **(B)** photolyases in a light-dependent reaction. Alternatively, repair can follow **(C)** the global genome nucleotide excision repair (GGR) or **(D)** the transcription coupled NER (TCR).

Photolyases have been widely described in plants and may often comprise small gene families like, for example, in *Arabidopsis*, which encodes for five members (http://www.arabidopsis.org/). While loss of single members can lead to increased UV-sensitivity (Jiang et al., 1997; Landry et al., 1997; Nakajima et al., 1998; Teranishi et al., 2004), the constitutive expression of CPD photolyases has been demonstrated to markedly improve UV tolerance in higher plants (Hidema et al., 2007; Kaiser et al., 2009). Although not much is known about their regulatory aspects, it has been demonstrated in rice that phosphorylation may play a role in regulating photolyase activities (Teranishi et al., 2008) and a few reports show that light increases photolyase expression (Chen et al., 1994; Waterworth et al., 2002). It was recently indicated that in darkness basal transcription of the photolyase genes *UVR3* and *PHR1* is sustained by the light signaling transcription factors HY5 and HYH and is limited by the actions of COP1 and DET1 dependent E3 ligases (Castells et al., 2010). Upon light exposure and during photomorphogenesis, COP1 leaves the nucleus and expression of *PHR1* is greatly induced by HY5 and HYH while the repression through DET1 remains in place. These observations suggest that photoreactivation is controlled by the photomorphogenisis pathway, and the activation of the PHR1 is dependent on photomorphogenetic regulators.

### 3.2 Nucleotide excision repair

A mechanism that can substitute for photolyase activities in plants, and which is required for photodamage repair in mammals, is the nucleotide excision repair (NER) pathway. NER is light-independent and, hence, sometimes referred to as dark repair. In contrast to photoreactivation, which reduces CPDs and 6-4 photoproducts back to pyrimidine monomers, NER is based on a complex recognition and repair machinery that excises and *de novo* synthesizes single DNA strands between 24-32 bp around the lesions. NER is highly conserved among eukaryotes and has two sub-pathways: transcription coupled NER (TCR) and global genome NER (GGR). NER has been intensively studied in animals, but the findings are a model for what is being found in plants, and will be briefly summarized in the following paragraph.

GGR and TCR recruit the same repair proteins; however, they mainly differ in their initial steps of damaged DNA recognition. GGR is genome-wide active, and its initial steps include the xeroderma pigmentosum group C factor (XPC), which is able to sense thermodynamic destabilizations of the Watson-Crick duplex caused by a flipping-out of the affected bases from the strands (Min and Pavletich, 2007). XPC in itself is capable of detecting most bulky DNA lesions, but for the recognition of CPDs it is supported by WD-40 protein Damaged DNA Binding 2 (DDB2) (Aboussekhra et al., 1995; Mu et al., 1995; Mu et al., 1996; Moser et al., 2005; Min and Pavletich, 2007; Scrima et al., 2008). DDB2 binds with high affinity to photoproducts, induces a bending of the DNA to approximately 40° and facilitates the flipping of the affected bases that are recognized and bound by the XPC/hHR23B complex, which further introduces structural changes into the DNA (Min and Pavletich, 2007; Scrima et al., 2008). DDB2 is part of a DDB1-CUL4-RBX1 (DCX) E3 ligase that mediates the polyubiquitination of histones, XPC and DDB2 itself (Rapic-Otrin et al., 2002; Fitch et al., 2003; Sugasawa et al., 2005; Chen et al., 2006; Kapetanaki et al., 2006; Wang et al., 2006). As a consequence, DDB2 is degraded via the 26S proteasome clearing the way for later repair stages (Rapic-Otrin et al., 2002; Fitch et al., 2003; Chen et al., 2006). Interestingly ubiquitination has the opposite effect on XPC leading to its stabilization and activation (Sugasawa et al., 2005). The DDB2-dependent ubiquitination of histones H2A, H3, and H4

may be necessary for the loosening of the DNA structure to allow the binding of other repair proteins (Kapetanaki et al., 2006; Wang et al., 2006). In a similar way the recently observed ability of DDB2 to recruit histone modifying proteins to specific DNA sequences could contribute to accessibility of the DNA for XPC and other factors (Minig et al., 2009; Roy et al., 2010). XPC is then needed for the recruitment of the core NER repair factors XPA, TFIIH, and RPA (Evans et al., 1997; Araujo et al., 2001; Thoma and Vasquez, 2003). XPA and the basal transcription factor complex TFIIH bind to the damaged site and unwind the DNA around the lesion (Reardon and Sancar, 2003; Maltseva et al., 2006; Yang et al., 2006; Kesseler et al., 2007; Krasikova et al., 2008). Unwinding is specifically performed by two subunits of TFIIH, the helicases XPB (ERCC3) and XPD (ERCC2). RPA is a heterotrimeric DNA binding protein, and while it prevents incision of the non-damaged DNA strand, together with XPA, it stabilizes the opened double helix (Blackwell et al., 1996; Camenisch et al., 2006; Maltseva et al., 2006; Yang et al., 2006). Incisions are performed by the endonucleases XPF (ERCC1) and XPG which nick the damaged DNA strand 5′ and 3′ around the lesion. After the damaged strand is excised, the gap is filled and ligated by the concerted activities of replication factors Proliferating Cell Nuclear Antigen (PCNA), Replication Factor C (RFC), Replication Protein A (RPA), DNA polymerases δ and ε, and DNA ligase 1 (LIG1) (Nichols and Sancar, 1992; Shivji et al., 1992; Green and Almouzni, 2003; Ogi et al., 2010). In contrast to GGR, TCR is specifically connected to DNA lesions in transcriptionally active regions. Here, RNA polymerase 2 (RP2) becomes stalled at CPD or (6-4) photoproduct containing sites (Selby and Sancar, 1997; Tornaletti and Hanawalt, 1999). Recognition of stalled RP2 has not been fully resolved. However, a critical role has been shown for Cockayne Syndrome factor B (CSB), a member of the SWI/SNF family of helicases (Selby and Sancar, 1997; van Gool et al., 1997; Citterio et al., 2000; Kamiuchi et al., 2002; Fousteri et al., 2006; Cazzalini et al., 2008). CSB binds to the stalled RP2, and this binding is a necessary trigger for recruitment of the same core repair proteins as described for GGR. Comparable to DDB2, CSB becomes a target of the DCX E3 ligase, which is mediated by another WD-40 protein, CSA. This interaction ultimately results in degradation of CSA, CSB and possibly also RP2 (Groisman et al., 2006).

Most of the proteins that play a role in GGR or TCR can be found in animals and plants, while only a few members, like XPA and TF2H3, a subunit of TFIIH, appear to be absent in plants (Kimura and Sakaguchi, 2006). It is currently open whether plants encode for functional analogs of XPA and TF23H that would perform tasks similar to these proteins. For most of the other NER proteins that are conserved among animals and plants, a role in DNA repair has been demonstrated, frequently by reverse genetic studies in *Arabidopsis thaliana*. Here, proteins shown to be involved in damaged DNA recognition in animals, such as DCX-E3 ligases, DDB2 and CSA, have also been recently described by several groups in plants (Bernhardt et al., 2006; Molinier et al., 2008; Al Khateeb and Schroeder, 2009; Bernhardt et al., 2010; Biedermann and Hellmann, 2010; Zhang et al., 2010; Zhang and Schroeder, 2010; Castells et al., 2011). While plants affected in ATCSA-1, the Arabidopsis CSA ortholog, do not display an abnormal development (Biedermann and Hellmann, 2010), loss of CUL4 or DDB2 cause a dwarf-like phenotype (Bernhardt et al., 2006; Koga et al., 2006). Interestingly, Arabidopsis *ddb2* or *atcsa-1* mutants are UV-hypersensitive but only when brought into the dark right after UV treatment, demonstrating that plants primarily rely on photoreactivation rather than NER (Biedermann and Hellmann, 2010). However, when kept in the dark both mutants have reduced repair activities when compared to wild type (Biedermann and Hellmann, 2010). CSB-like helicases are also present in plants

(Kimura et al., 2004; Shaked et al., 2006), and although they are not biochemically characterized, studies in Arabidopsis demonstrate their critical role for UV tolerance (Shaked et al., 2006). Other mutants directly affected in NER factors such as Arabidopsis mutants *atcen2* and *uvh3–1/xpg,* also show decreased repair activities *in vitro* and behave hypersensitive towards UV-C exposure, respectively (Liu et al., 2000; Molinier et al., 2004b). Loss of the TFIIH transcription factor complex subunits XPB/UVH6 and XPD is lethal; however, *uvh6-1* plants expressing a mutated but potentially partially functional XPB protein already show decreased repair rates of UV-induced 6–4 photoproducts (Liu et al., 2003). Overall the current findings strongly indicate that the basic mechanisms of UV-induced damaged DNA recognition and NER based repair are comparable and highly conserved among plants and animals.

### 3.3 Base excision repair

Not all nucleotide modifications can be repaired by NER, and many DNA lesions generated by reactive oxygen species (ROS) are not recognized by the NER proteins. Thus as an additional mechanism to ensure genomic integrity, cells utilize other repair mechanisms like base excision repair (BER). Because ROS are continuously produced as metabolic byproducts or by ionizing radiation, they represent a considerable source of the daily DNA damage. ROS-induced DNA lesions include for example 8-hydroxyguanine (8-oxoG), formamidopyrimidines, and 5-hydroxyuracil, which can potentially lead to miscoding during replication and transcription.

As a general rule BER requires the activities of DNA glycosylases, which cleave the N-glycosyl bond between the base and the sugar at the lesion site. This releases the base and leaves an abasic or apurinic/apyrimidinic (AP) site. In bacteria, fungi, plants and animals, several DNA glycosylases have been described that either specifically or broadly recognize certain lesions. For example, the mammalian DNA glycosylase OGG1 has a high affinity to 8-oxoG and some formamidopyrimidines, while another mammalian DNA glycosylase, NEIL1, efficiently repairs formamidopyrimidines but only poorly 8-oxoG (Morland et al., 2002; Parsons et al., 2005). DNA glycosylases are classified as either being mono- or bifunctional. Monofunctionally they only perform the cleavage reaction of the glycosylic bond between the deoxyribose and the target base to generate an AP site. Bifunctional DNA glycosylases/lyases, to which OGG1 and NEIL1 belong, are able to catalyze the release of the oxidized base and the cleavage of the DNA backbone at the AP site (Hazra et al., 2001).

Although there is currently no evidence that plants have NEIL1 orthologs, which are common in bacteria and animals and required in part for excision of oxidized purines and pyrimidines, most other DNA glycosylases have been found. For example, plants encode for orthologs of OGG1 (Roldan-Arjona and Ariza, 2009), and their activity in excising oxidized purines has been demonstrated for the *Arabidopsis* AtOGG1 (Dany and Tissier, 2001; Garcia-Ortiz et al., 2001; Morales-Ruiz et al., 2003). In addition to OGG1, plants also encode for proteins related to the bifunctional Endonuclease III/Nth from *E. coli*, yeast, and animals, which remove a broad range of damaged pyrimidines (Breimer and Lindahl, 1980; Boorstein et al., 1989; Hatahet et al., 1994; Phadnis et al., 2006; Guay et al., 2008). Like their bacterial counterparts, *Arabidopsis* AtNTH1 also shows a broad substrate specificity and DNA glycosylase activity for DNA lesions containing modified pyrimidines (Krokan et al., 1997; Roldan-Arjona et al., 2000). Furthermore, plants encode for proteins related to MutM/Fpg, an original model DNA glycosylase/lyase from *E. coli* that excises 8-oxo-guanine and other oxidized purines from damaged DNA (Tchou et al., 1991; Tchou et al., 1993; Bhagwat and

Gerlt, 1996; Ohtsubo et al., 1998; Murphy and Gao, 2001; Roldan-Arjona and Ariza, 2009). Although enzymatic function for all three types of plant DNA glycosylases is established, there is unfortunately no information available on how loss of these proteins affects development or ROS sensitivity of mutant plants.

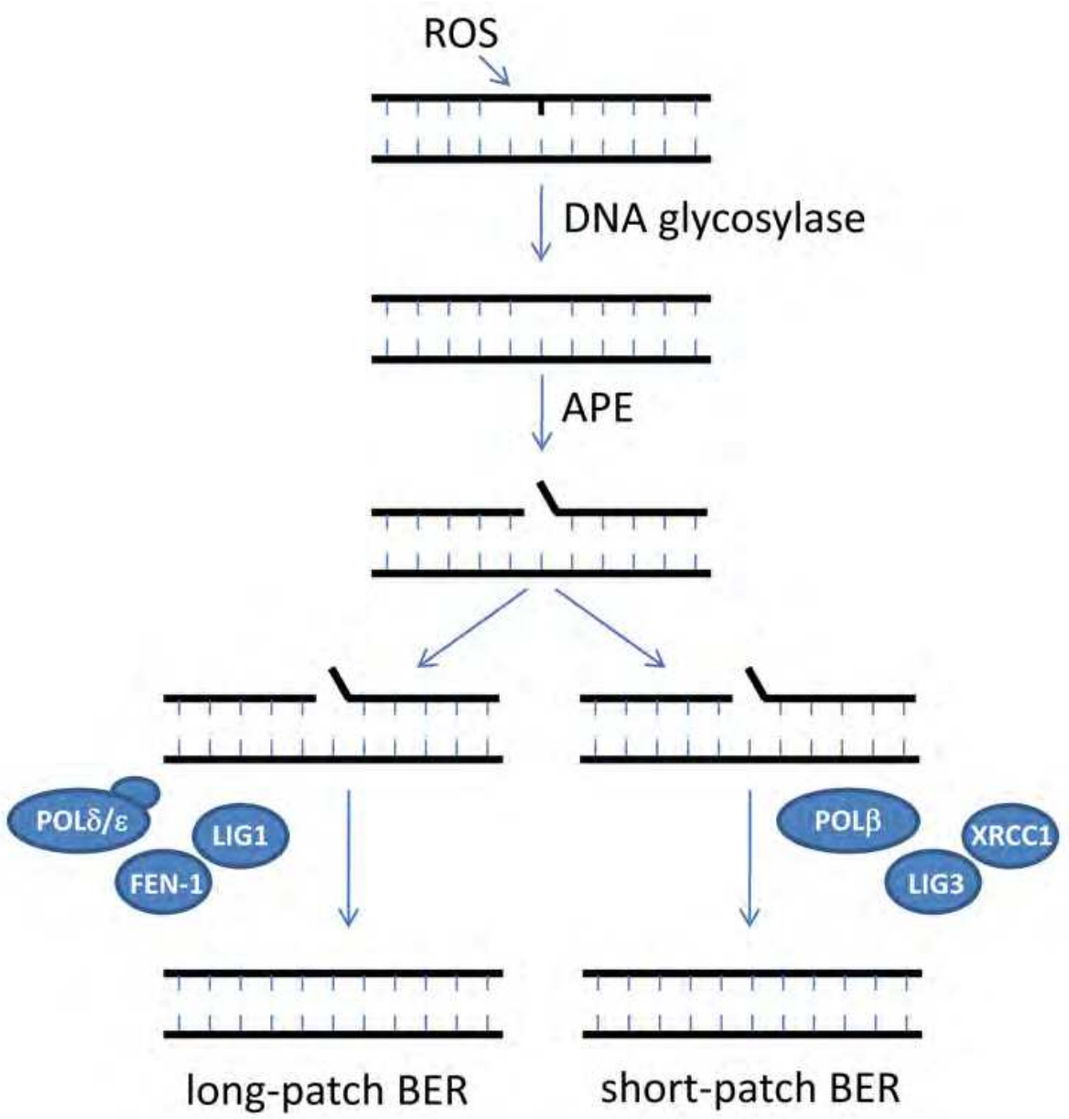


Fig. 3. Schematic model for base excision repair (BER).

DNA lesions caused by ROS are recognized and modified by the concerted activities of a DNA glycosylase and APE, after which cells can either take the route of long-patch repair or alternatively the short-patch repair pathway. Currently evidence indicates for plants that the long-patch repair is employed for BER.

Plant OGG1 and NTH proteins generate 3′ phospho α,β-unsaturated aldehydes (3′ dRP) at the strand breaks, and these need to be removed to generate free 3′ hydroxyl ends to allow

gap-filling repair mediated by a DNA polymerase (Demple and Harrison, 1994; Roldan-Arjona et al., 2000; Garcia-Ortiz et al., 2001). Removal of 3'dRP is mediated in plants and animals by AP endonucleases (APE) which also work on AP sites generated by either monofunctional DNA glycosylases or those that occurred through spontaneous degradation of the DNA (Babiychuk et al., 1994; Demple et al., 1997; Pascucci et al., 2002) (Fig. 3).

Subsequently to APE, two separate BER repair pathways can become active in mammalian cells. First, the short-patch repair pathway, which relies on the concerted activities of DNA polymerase β (Polβ), X-ray repair cross-complementing protein 1 (XRCC1), and the DNA ligase 3 (LIG3). Polβ has an intrinsic 3'dRP activity and can remove deoxyribose sugar itself if required (Caldecott, 2001). XRCC1 interacts with LIG3 and other BER proteins and may function as a repair coordinating protein (Vidal et al., 2001) (Fig. 3). Alternatively, the long patch-repair pathway can be employed in mammalian cells, which requires activities of DNA polymerases δ and ε, RFC, PCNA, and flap endonuclease 1 (FEN1) to remove and resynthesize up to 10 nucleotides 3' to the AP site, while the nick is ligated by LIG1 (Matsumoto, 2001) (Fig. 3).

While most proteins are present in plants that can participate in long-patch repair (Kimura and Sakaguchi, 2006), it is currently open whether a short-patch pathway exists in plants since no obvious homologs of POLβ and LIG3 are identified so far (Kimura and Sakaguchi, 2006; Roldan-Arjona and Ariza, 2009). In addition, plant XRCC1-like proteins lack domains that are necessary for complex assembly with POLβ and LIG3, and it is therefore currently open whether the protein participates in BER (Vidal et al., 2001; Taylor et al., 2002). Although no POLβ proteins are described in plants so far, it is possible that their function is conducted by POLλ. Both polymerases belong to the X superfamily of DNA polymerases and several amino acid residues are conserved between POLβ and λ (Garcia-Diaz et al., 2000; Uchiyama et al., 2004). In addition, POLλ has been demonstrated in rice to possess intrinsic 3'dRP activity and its expression is mainly found in meristematic and proliferating tissues (Uchiyama et al., 2004).

An important role in the recognition and repair of SSB and activation of BER involves poly(ADP-ribose) polymerases (PARP). PARP proteins belong to small protein families with, for example, 18 members in human, and they are highly conserved among eukaryotes (Ame et al., 2004); however, it is PARP1 and PARP2 that have been brought in context with damaged DNA recognition and DNA repair processes. PARP1 is a 113 kDa protein that contains a modular set of domains that enable it to fulfill multiple functions in the cell. At its N-terminal region PARP1 contains a DNA break recognition fold that is composed of a duplicated zinc finger similar to DNA ligase III. A BRCT motif is present in the center that can be found in many proteins connected with maintenance of genomic integrity and cell cycle checkpoints. The motif also functions as the main interface for protein–protein interactions. Finally, at its COOH-terminal region, PARP1 has motifs with different catalytic activities including $NAD^+$ hydrolysis as well as initiation, elongation, branching and termination of ADP-ribose polymers (Citarelli et al., 2010). It has been shown in mammalian cells that, upon binding a DNA lesion PARP1 poly(ADP)ribosylates itself as well as nearby histones (H1 and H2B), which relaxes the chromatin structure allowing better access for XRCC1 and other repair proteins to the damaged site (Poirier et al., 1982; Masson et al., 1998; Pleschke et al., 2000). Plant PARP1 and PARP2 are nuclear localized like their animal counterparts, and they become transcriptionally activated upon genotoxic stress conditions such as ionizing radiation or oxidative stress (Puchta et al., 1995; Babiychuk et al., 1998;

Doucet-Chabeaud et al., 2001; Chen et al., 2003). However, although a similar role of plant PARP1 and PARP2 in damaged DNA recognition and initiation of DNA repair is likely, a detailed *in planta* functional description is still missing for these proteins.

### 3.4 DSB repair: Nonhomologous end joining and homologous recombination

ROS, especially •OH generated by ionizing radiation or via the Fenton reaction (Karanjawala et al., 2003; Clark, 2008), also have a high potential to cause double-strand breaks (DSB) (Karanjawala et al., 2002; Karanjawala et al., 2003). DSB require repair mechanisms distinct from photolyases, NER and BER. Therefore cells primarily depend on either the nonhomologous DNA end joining pathway (NHEJ) or homologous recombination (HR). NHEJ is an error-prone repair pathway, which directly ligates the free DNA ends together. In animals, the pathway is discussed to start with the binding of the heterodimeric Ku70/Ku80 complex to a DNA end. This step is required for employment of DNA-dependent protein kinase (DNA-PK) and Artemis endonuclease that process the DNA ends (Ma et al., 2002), while rejoining and ligation is performed by the XRCC4/LIG4/XLF complex (Grawunder et al., 1997; Barnes et al., 1998) (Fig. 4). The processing of the DNA ends can result in deletions or insertions and is the reason why NHEJ based repair often results in mutations in the repaired DNA. Current research in plants indicates that the NHEJ pathway is conserved among plants and animals. Ku70 and Ku80 related proteins as well as the Artemis-like protein SNM1/PSO1 are expressed in *Arabidopsis* and rice, and *Arabidopsis* mutants affected in these proteins become hypersensitive to γ-irradiation and the chemotherapeutic agent bleomycin, a double-strand break inducing chemical, which is in agreement with their roles in NHEJ (Tamura et al., 2002; Friesner and Britt, 2003; Gallego et al., 2003; Molinier et al., 2004a; Kimura et al., 2005; Kimura and Sakaguchi, 2006; Charbonnel et al., 2010). Likewise, XRCC4 and Lig4 homologues have been described in plants, and functionally connected to NHEJ (West et al., 2000; Friesner and Britt, 2003; Kimura and Sakaguchi, 2006; Waterworth et al., 2010).

In contrast to the error prone NHEJ pathway, HR is a more accurate repair mechanism that uses homologous DNA strands as templates for repair activities (Boyko et al., 2006a; Boyko et al., 2006b; Li and Ma, 2006; Osman et al., 2011). Several alternative pathways may exist that allow HR based repair of DSBs, however, good evidence is provided for at least two alternative pathways in plants. One is the synthesis-dependent strand annealing (SDSA) mechanism which involves the meiotic recombination11/Rad50/X-ray sensitive 2 (MRN) complex (Waterworth et al., 2007; Ronceret et al., 2009; Amiard et al., 2010). The MRN complex is discussed to function as a first sensor of double strand breaks. It generates single strand DNA at the DSB sites that can be used as templates to mediate HR by RecA and Rad51 homologues (Lin et al., 2006; Li et al., 2007; Markmann-Mulisch et al., 2007; Odahara et al., 2007; Vignard et al., 2007; Waterworth et al., 2007; Odahara et al., 2009; Ronceret et al., 2009; Amiard et al., 2010; Chittela and Sainis, 2010; Devisetty et al., 2010; Ko et al., 2010; Schaefer et al., 2010; Wang et al., 2010; Ko et al., 2011) (Fig. 4). However, the precise subsequent steps of Holliday structure formation, cleavage by endonucleases and dissociation into two DNA chains is only poorly understood in plants. Alternatively to SDSA, plants also use the single strand annealing (SSA) mechanism (Tissier et al., 1995; Ayora et al., 2002; Blanck et al., 2009; Mannuss et al., 2010). SSA requires a double strand break between two repeated sequences that are oriented in the same direction. Adjacent to the break, single-stranded DNA is created so that the repeated sequences can be used as

complementary strands to anneal the ends of the break, after which non-homologous tails are detached and nicks can be ligated (Tissier et al., 1995; Puchta, 2005; Blanck et al., 2009; Mannuss et al., 2010). Because HR is less likely to cause changes in the genetic information than NHEJ, it is likely that the extent to which either NHEJ or HR repair pathways are employed in DSB repair may impact genome evolution in living organisms.

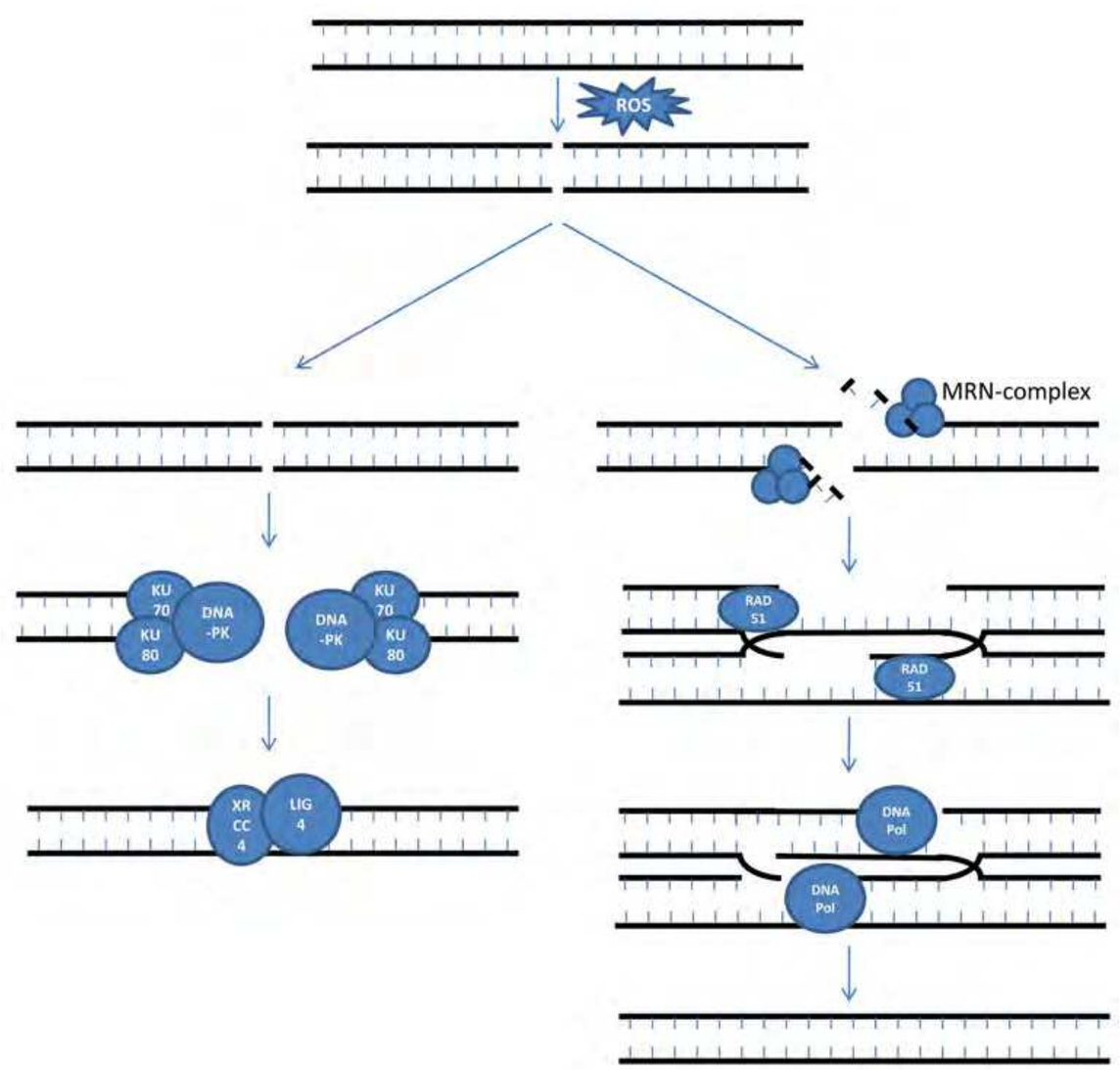


Fig. 4. ROS induced repair of double-strand breaks.

Two alternative pathways for which strong evidence is present to exist in plants are shown. Double-strand breaks can either be repaired by nonhomologous DNA end joining pathway (NHEJ; left hand side), or by homologous recombination (HR; right hand side).

### 3.5 DNA repair in chloroplasts

Based on their high metabolic activities in respiration and photosynthesis, organelles are centers of ROS production. Both mitochondria and chloroplasts possess their own repair

pathways, and it appears to be that they have most of the repair pathways that are also found in the nucleus (for an excellent review about mitochondrial repair see (Boesch et al., 2011). We will focus here on chloroplast repair and briefly summarize recent findings.

The chloroplast genome is in general relative small, but gene numbers can vary significantly between species ranging from, for example, 54 in *Helicosporidium sp. ex Simulium jonesii* and up to 301 in *Pinus koraiensis* (http://chloroplast.cbio.psu.edu/); (Cui et al., 2006). These genes and their corresponding proteins are crucial for proper functioning of the organelle and hence survival of the plant and it is not surprising that chloroplasts have several repair pathways.

A recent report described a rice CPD photolyase to mediate repair of direct DNA damage caused by UV light (Takahashi et al., 2011), and also an earlier report describes PHR2, a class II photolyase predicted to be in chloroplasts of *C. reinhardtii* (Petersen et al., 1999). There is also strong evidence in *Arabidopsis* for two bifunctional DNA glycosylase/lyase of the *E. coli* Endonuclease III/Nth type and an APE to be involved in repair of ROS based DNA damage (Gutman and Niyogi, 2009). The authors can show specific localization of the three proteins to the chloroplast and specific activities *in vitro*. However, single or even triple mutants affected in the three proteins do not display any apparent developmental defects or increased sensitivities to photo-oxidative stress (e.g. UV- and high light or methyl viologen), from which the authors concluded that additional, yet unknown BER repair pathways exist in chloroplast (Gutman and Niyogi, 2009).

Currently no clear data are available for NER activities in the chloroplasts and only poor evidence is currently present on whether or how chloroplasts repair DSBs. Work on the green algae *Chlamydomonas reinhardtii* showed presence of a chloroplast-located RecA homolog, which is inducible in expression by DNA-damaging reagents (Nakazato et al., 2003). In addition, *Arabidopsis* T-DNA insertion mutants affected in a chloroplast localized RecA (*cpRecA*) homolog have increased amounts of single-strand DNA, altered structures of chloroplast DNA, and chloroplasts showed signs of reduced function after four generations post T-DNA insertion (Rowan et al., 2010). Yet, further data for additional repair proteins is still missing, as well as strong evidence for HR or NHEJ activities in chloroplasts of higher plants. Recent findings, however, indicate that chloroplasts repair DSBs using microhomology-mediated end joining (MMEJ) (Kwon et al., 2010). This repair mechanism requires only very short (2–14 bp) regions of homology, and is discussed as a potential backup to NHEJ in eukaryotes (Heacock et al., 2004; Bennardo et al., 2008). Although Kwon and co-workers provide strong evidence for MMEJ in chloroplasts, it is currently open which proteins mediate this repair.

### 3.6 Physiological responses after UV and ROS exposure

Besides immediate repair processes, it is also critical for plant cells to generate a physiological environment in which further DNA damage is prevented or at least reduced. A common physiological response to UV exposure in plants appears to be the accumulation of anthocyanin and flavonoids, potentially as a photoprotective or ROS quenching mechanism (Ng et al., 1964 ; Yatsuhashi et al., 1982; Takeda and Abe, 1992; Ye et al., 2010). It is interesting to note that some plants like grape vine (*Vitis vinifera*) or common bean (*Phaseolus vulgaris*) accumulate resveratrol or coumestrol, respectively, in response to UV exposure (Langcake and Pryce, 1977; Beggs et al., 1985). Resveratrol is a protective phytoalexin that is produced primarily under biotic stress conditions, while coumestrol is a

phytoestrogen with unknown function. Both compounds are associated with effecting cell proliferation, cell cycle, and apoptosis of mammalian cells (Ndebele et al., 2010; Delmas et al., 2011) and may be signaling molecules in plants to trigger specific responses upon UV exposure.

A critical factor that is discussed as a regulator of DNA repair pathways in response to increased ROS accumulation in the cell appears to be ADP-Ribose/NADH Pyrophosphohydrolase AtNUDX7 (Ishikawa et al., 2009). AtNUDX7 belongs to the family of Nudix hydrolyases, which catalyze the hydrolysis of dinucleoside polyphosphates, nucleoside di- and triphosphates, nucleotide sugars, and coenzymes in plants and animals (McLennan, 2006; Kraszewska, 2008). AtNUDX7 substrates are ADP-Ribose (ADP-Rib) and NADH which are converted to AMP plus ribose 5-phosphate and nicotinamide mononucleotide (NMNH) plus AMP, respectively (Ogawa et al., 2005). The protein may have a central function for the homeostasis of $NAD^+$ pools by supplying ATP via nucleotide recycling from free ADP-Ribose molecules. This may be critical for the cell since substantial PARP activity can significantly lower $NAD^+$ and ATP levels; such a depletion of cellular energy can result in necrotic cell death (Ha and Snyder, 1999; Virag and Szabo, 2002; De Block et al., 2005). As discussed for BER, DNA damaged-induced, PARP-dependent poly(ADP)-ribosylation of proteins is considered a critical step for recognition of damage to be converted into intracellular signals that can trigger DNA repair programs or cell death. Consequently, AtNUDX7 is up-regulated upon abiotic stress (salinity, drought, high light, paraquat), and plants constitutively overexpressing AtNUDX7 become less susceptible to these stress conditions (Ishikawa et al., 2009).

A microarray study has shown that UV-C, bleomycin, or biotic stress factors elicit a hypersensitive response and increased $H_20_2$ levels in the cell (Molinier et al., 2005). Although each stress elicited specific responses, the authors could also find 209 genes that were commonly up-regulated, while 54 were similarly down-regulated by all three stress treatments. Among the commonly regulated genes were components of signaling pathways, transcription factors, and genes connected with an oxidative stress or defense response. Cell-cycle genes were also down-regulated after genotoxic stress exposure, as was earlier noted for animals (Dasika et al., 1999). However, the authors also noted that in Arabidopsis expression of only a comparably few number of repair genes was induced, and concluded that the plant must be mainly relying on existing synthesized proteins. It will be interesting to see whether results are broadly applicable to other plant species or whether the tested conditions and responses are specific for Arabidopsis.

### 3.7 ATM/ATR dependent regulation of DNA repair

A central regulator of the fate of damaged cells between apoptosis or cell cycle arrest and DNA repair in animals is the tumor-suppressing p53, sometimes dubbed the "guardian of the genome". This transcription factor controls not only cell cycle genes like p21 and apoptosis factors like PUMA, NOXA, and BAX but also various components of major DNA repair pathways such as CSB, DDB2 and XPC (NER); FANCC (DNA crosslink repair) and MSH2, MLH1, and PMS2 (mismatch repair) (Gatz and Wiesmuller, 2006; Brady and Attardi, 2010). There is also evidence that it has a more direct role in BER, interacting with APE1 and OGG1 and thereby enhancing the excision of oxidized DNA bases (Gatz and Wiesmuller, 2006; Vigneron and Vousden, 2010). Additionally p53 seems to recognize and bind directly to certain DNA structures e.g. Holliday junctions and mismatches where it represses the

activities of HR and NHEJ (Bakalkin et al., 1994; Subramanian and Griffith, 2005; Gatz and Wiesmuller, 2006).

Activation of p53 after DNA damaging conditions is achieved by phosphorylation by the checkpoint kinases ATAXIA TELANGIECTASIA MUTATED (ATM) and ATAXIA TELANGIECTASIA AND RAD3 RELATED (ATR) (Canman et al., 1998; Tibbetts et al., 1999). While recent studies imply that ATM is a sensor for the redox state of the cell, it is mainly known to be activated by the above-mentioned DSB sensing MRN-complex (Bakkenist and Kastan, 2003; Falck et al., 2005; Kruger and Ralser, 2011; Perry and Tainer, 2011). ATR, on the other hand, is recruited to RPA-coated UV-induced lesions by the ATR INTERACTING PROTEIN (ATRIP) (Wright et al., 1998; Cortez et al., 2001; Ball and Cortez, 2005; Warmerdam et al., 2010). Once activated both kinases phosphorylate p53 and the effector kinases CHK1 and CHK2 regulating cell cycle and DNA repair (Brady and Attardi, 2010).

Curiously no plant homologues of p53 have been identified in any of the model organisms. This is probably linked to the absence of the core apoptotic machinery as we know it from animals. In contrast most of the DNA repair targets of p53, as well as ATM and ATR, are very well conserved in plants. Where loss of one of the checkpoint kinases in animals is lethal, the existence of viable *atr* and *atm* mutant plants in Arabidopsis make it an ideal model for their investigation. Both are involved in the response to ionizing radiation (IR) and necessary for the IR-induced transcription activation of many genes participating in DNA repair, cell cycle control, transcription, and replication (Culligan et al., 2006; Ricaud et al., 2007; Yoshiyama et al., 2009; Furukawa et al., 2010).

This raises the question if there is a factor that is functioning as a p53 analog mediating the DNA damage response between ATM/ATR and the downstream repair factors. An answer to that could be SUPPRESSOR OF GAMMA RESPONSE 1 (SOG1). Though unrelated to p53 and unique to plants, this transcription factor, discovered in a screen for suppressor mutants of the γ-irradiation induced cell cycle arrest of Arabidopsis *uvh1* seeds, is necessary for the activation of genes downstream of both ATM and ATR in response to γ-irradiation (Preuss and Britt, 2003; Yoshiyama et al., 2009; Furukawa et al., 2010). SOG1, ATM, and ATR were also found to trigger plant programmed cell death (PCD) in root meristems after γ- or UV-B irradiation, a mechanism that was recently shown to be distinct from animal apoptosis (Fulcher and Sablowski, 2009; Furukawa et al., 2010). Hence, SOG1 is a good candidate to control repair processes in a p53-like fashion, at least by activating transcription of the plant homologues of factors like DDB2, MSH2 and XPC in response to UV and IR stresses.

Current research indicates that plants and animals share roughly similar repair pathways. But for some repair proteins that have been described in animals no homologues have been found in plants, as yet. However, with ongoing research, it seems plausible that plant counterparts will be identified that can substitute for missing animal orthologs as it appears to be the case with p53 and SOG1.

## 4. Plants as model organisms to study DNA repair

Plants and animals share a surprisingly high degree of conservation among their abilities to repair damaged DNA (please also see Table 1 at the end of this passage for an overview of genes involved in DNA repair in the model plant *Arabidopsis thaliana*). While mammalian researchers have very valid and scientifically relevant reasons to use animal subjects, plants

can and should be considered as excellent and viable alternatives to investigate the fundamentals of DNA repair processes. Tolerance towards mutations and abiotic stresses along with the relative ease of upkeep and propagation of the research organisms are two factors that we will briefly discuss in this final section of the review.

Due to their inability to elude many constantly damaging influences, plants need to utilize efficient ways to cope with these stresses. One strategy plants seem to have adopted to manage the higher demands on DNA repair is redundancy. For instance, genes of every pathway discussed here were found to be duplicated in Arabidopsis or rice (Singh et al., 2010). Additionally the existence of both 8-oxo-guanine glycosylases, OGG1, as well as MutM/Fpg in Arabidopsis demonstrate functional redundancy of independent, alternative repair pathways, which may have originated from the incorporation of chloroplast and mitochondrial genes into the nuclear genome (Boesch et al., 2009; Singh et al., 2010; Rowan et al., 2010).

Probably because of these gene duplications, functional redundancies, and more efficient or alternative pathways in comparison to animals, plants often have greater flexibilities in how they can respond to and potentially tolerate damaged DNA and mutations. For example a homozygous mutant in ATR kinase, which would be lethal in mammals, can in plants be investigated for the impact on DNA repair, control of apoptosis or gene expression profiles. In order to see the global effects of genotoxic stressors on a model organism, the subjects need to be exposed to different degrees of damaging agents. Here, plants are ideal models because of their sessile nature. They can be cultivated under very steady and reproducible conditions, while stress exposure is highly controlled. In addition, from an ethical point of view, plants can be taken to the edge of survival with very harsh treatments such as high levels of UV-light or toxin applications that for some may be not comfortable to perform on animals.

In comparison to animals, plants are low cost organisms that only require minimal monitoring along with water and occasionally fertilizer. Small plants like the moss *Physcomitrella patens* or *Arabidopsis thaliana* can be cultivated to great numbers within in a few square feet while by comparison animals require adequate space and regular food, water, and cleaning. While mutant lines are readily available for many animal and plant systems, shipment and propagation of plant resources can be quite straightforward. Seeds can be harvested for immediate propagation of the next generation or stored long-term, even at room temperature, before use months or even years later. Sending seed material to colleagues around the world is technically simple since no special transport accommodations need to be made. Generating transgenic *Arabidopsis* lines using *Agrobacterium* infection is a standard lab procedure, and allows for rapid complementation of mutant lines to verify protein functionality and observation of response and recovery. Also generation time of Arabidopsis plants is very short with just two months from seed to seed.

In addition to using plants as basic models to understand DNA repair processes, there are also practical reasons why this area of research urgently needs to be expanded. With the increase in food shortages for increasing populations, the recognition of environmental toxins and the growing evidence of impending and occurring climate changes across the world, it becomes critical to rapidly develop plants that can better cope with environmental stress. As such, stress tolerant crop plants generated either by genetic engineering or classical breeding will become increasingly important resources to guarantee stable food supplies to the human population in an expected changing environment.

| Repair pathway | Representative Gene Model | Gene in Arabidopsis | Function | Acc. No. | Reference |
|---|---|---|---|---|---|
| **Photore-activation** | | *PHR1/UVR2* | repair of CPDs | AT1G12370 | Ahmad et al., 1997; Landry et al., 1997 |
| | | *PHR2* | repair of CPDs | AT2G47590 | Ahmad et al., 1998; Petersen et al., 1999 |
| | | *UVR3* | repair of 6-4PPs | AT3G15620 | Jiang et al., 1997; Nakajima et al., 1998 |
| **NER** | *XPC* | *AtRAD4* | recognition of CPDs and 6-4PPs, GGR | AT5G16630 | Kunz et al., 2005; Liang et al., 2006 |
| | *HHR23A,B/RAD23* | *RAD23A* | recognition of CPDs and 6-4PPs, GGR | AT1G16190 | Molinier et al., 2005; Kunz et al., 2005; Farmer et al., 2010 |
| | | *RAD23B* | | AT1G79650 | Molinier et al., 2004b Kunz et al., 2005; Farmer et al., 2010 |
| | | *RAD23C* | | AT3G02540 | Molinier et al., 2004b; Kunz et al., 2005; Farmer et al., 2010 |
| | | *RAD23D* | | AT5G38470 | Molinier et al., 2004b; Kunz et al., 2005; Farmer et al., 2010 |
| | *CEN2* | *AtCEN2* | recognition of CPDs and 6-4PPs, GGR | AT4G37010 | Molinier et al., 2004b; Liang et al., 2006 |
| | *ROC1/RBX1* | *RBX1A* | activation of CUL4-dependent ligases | AT5G20570 | Lechner et al., 2002; Gray et al., 2002 |
| | | *RBX1B* | | AT3G42830 | Lechner et al., 2002; Gray et al., 2002 |
| | *CUL4* | *CUL4* | Ubiquitylation of targets | AT5G46210 | Molinier et al., 2008; (Biedermann and Hellmann, 2010 |
| | *DDB1* | *AtDDB1a* | Ubiquitylation of targets | AT4G05420 | Molinier et al., 2008; (Biedermann and Hellmann, 2010 |
| | | *AtDDB1b* | | AT4G21100 | Bernhardt et al., 2006; Bernhardt et al., 2010 |
| | *DDB2* | *DDB2* | recognition of CPDs and 6-4PPs, GGR, substrate recognition for CUL4-dependent ubiquitination | At5g58760 | Koga et al., 2006; Molinier et al., 2008 |
| | *TFIIH1* | *AtTFB1-1* | TFIIH subunit p62 | At1g55750 | Kunz et al., 2005; Singh et al., 2010 |
| | | *AtTFB1-2* | | At1g55680 | Kunz et al., 2005; Singh et al., 2010 |
| | | *AtTFB1-3* | | At3g61420 | Kunz et al., 2005; Singh et al., 2010 |

| Repair pathway | Representative Gene Model | Gene in Arabidopsis | Function | Acc. No. | Reference |
|---|---|---|---|---|---|
| | *TFIIH2* | *AtGTF2H2* | TFIIH subunit p44 | At1g05050 | Kunz et al., 2005; Singh et al., 2010 |
| | *TFIIH3* | *AtTFB4* | TFIIH subunit p34 | AT1G18340 | Kunz et al., 2005; Singh et al., 2010 |
| | *TFIIH4* | *AtTFB2* | TFIIH subunit p52 | At4g17020 | Kunz et al., 2005; Singh et al., 2010 |
| | *TFIIH5* | *AtTFB5* | TFIIH subunit | AT1G12400 | Kunz et al., 2005; Singh et al., 2010 |
| | | | | AT1G62886 | Singh et al., 2010 |
| | *CDK7* | *CAK3AT/CDKD1;1* | cyclin activating kinase-subcomplex of THIIH | AT1G73690 | Singh et al., 2010 |
| | | *CAK4AT/CDKD1;2* | | AT1G66750 | Singh et al., 2010 |
| | | *CAK2AT/CDKD1;3* | | AT1G18040 | Singh et al., 2010 |
| | *XPB/RAD25/ERCC3* | *AtXPB1* | helicase subunit of TFIIH | AT5G41370 | Costa et al., 2001 |
| | | *AtXPB2* | | AT5G41360 | Morgante et al., 2005 |
| | *XPD/RAD3/ERCC2* | *AtXPD/UVH6* | helicase subunit of TFIIH | AT1G03190 | Jenkins et al., 1995; Liu et al., 2003 |
| | *XPF/RAD1/ERCC4* | *AtRAD1/UVH1* | 5'-endonuclease | AT5G41150 | Harlow et al., 1994; Jenkins et al., 1995 |
| | *XPG/RAD2/ERCC5* | *UVH3/UVR1* | 3'-endonuclease | AT3G28030 | Jenkins et al., 1995; Liu et al., 2003 |
| | *CSA/RAD28/ERCC8* | *ATCSA-1/CSAat1A* | substrate recognition for CUL4-dependent ubiquitination, TCR | AT1G27840 | Biedermann and Hellmann, 2010; Zhang et al., 2010 |
| | | *ATCSA-2/CSAat1B* | | AT1G19750 | Kunz et al., 2005; Zhang et al., 2010 |
| | *CSB/RAD26/ERCC6* | *CHR8* | binding of stalled RNA polymerase, recruitment of repair machinery, TCR | AT2G18760 | Shaked et al., 2006 |
| | | *CHR24* | | AT5G63950 | Shaked et al., 2006 |
| **BER** | *OGG1* | *AtOGG1* | 8-oxoguanine DNA glycosylase | AT1G21710 | Garcia-Ortiz et al., 2001; Dany and Tissier, 2001 |
| | *MutM* | *AtFPG/MMH* | formamidopyrimidine DNA glycosylase | AT1G52500 | Ohtsubo et al., 1998 |
| | *NTH* | *AtNTH1* | DNA glycosylase and apyrimidinic (AP) lyase/endonuclease | AT2G31450 | Gutman and Niyogi, 2009 |
| | | *AtNTH2* | | AT1G05900 | Gutman and Niyogi, 2009 |

| Repair pathway | Representative Gene Model | Gene in Arabidopsis | Function | Acc. No. | Reference |
|---|---|---|---|---|---|
| | *APE* | *ARP/APE1* | apurinic/apyrimidinic (AP) endonuclease | AT2G41460 | Babiychuk et al., 1994; Gutman and Niyogi, 2009 |
| | | *APE2* | | AT4G36050 | Singh et al., 2010 |
| | *XRCC1* | *AtXRCC1* | co-factor of DNA ligase 3 | AT1G80420 | Petrucco et al., 2002; Singh et al., 2010 |
| | *FEN* | *FEN1* | flap endonuclease | AT5G26680 | Singh et al., 2010 |
| **NHEJ/HR** | *KU70/XRCC6* | *AtKU70* | binding of DNA double strand break ends | AT1G16970 | Riha et al., 2002 |
| | *KU80/XRCC5* | *AtKU80* | binding of DNA double strand break ends | AT1G48050 | Riha et al., 2002 |
| | *XRCC4* | *XRCC4* | co-factor of DNA ligase 4 | AT3G23100 | West et al., 2000 |
| | *LIG4* | *AtLIG4* | DNA ligation | AT5G57160 | West et al., 2000 |
| | *MRE11* | *AtMRE11* | subunit of the MRN complex, damage recognition, generation of single-stranded DNA | AT5G54260 | Hartung and Puchta, 1999; Daoudal-Cotterell et al., 2002 |
| | *RAD50* | *AtRAD50* | subunit of the MRN complex, damage recognition, generation of single-stranded DNA | AT2G31970 | Gallego and White, 2001 |
| | *NBS1* | *AtNBS1* | subunit of the MRN complex, damage recognition, generation of single-stranded DNA | AT3G02680 | Bleuyard et al., 2006; Waterworth et al., 2007 |
| | *RECA (E. Coli)* | *AtRECA1/cp RecA* | DNA binding, mediation of inter-strand-pairing | AT1G79050 | Cerutti et al., 1992; Cao Cao et al., 1997; Shedge et al., 2007; Rowan et al., 2010 |
| | | *AtRECA2* | | AT2G19490 | Shedge et al., 2007 |
| | | *AtRECA3* | | AT3G10140 | Khazi et al., 2003; Shedge et al., 2007 |
| | | | | AT3G32920 | Shedge et al., 2007 |
| | | *DRT100* | | AT3G12610 | Pang et al., 1992; Pang et al., 1993 |
| | *RAD51* | *AtRAD51/RAD51A* | DNA binding, mediation of inter-strand-pairing | AT5G20850 | Doutriaux et al., 1998 |
| | | *RAD51B* | | AT2G28560 | Bleuyard et al., 2005; Osakabe et al., 2005 |
| | | *RAD51C* | | AT2G45280 | Bleuyard et al., 2005 |
| | | *RAD51D/SSN1* | | AT1G07745 | Bleuyard et al., 2005; Osakabe et al., 2006 |
| | *BRCA1* | *AtBRCA1* | supports homology pairing | AT4G21070 | Lafarge and Montane, 2003 |

| Repair pathway | Representative Gene Model | Gene in Arabidopsis | Function | Acc. No. | Reference |
|---|---|---|---|---|---|
| | *BRCA2* | *AtBRCA2A* | supports homology pairing | AT4G00020 | Siaud et al., 2004; Dray et al., 2006 |
| | | *AtBRCA2B* | | AT5G01630 | Siaud et al., 2004; Dray et al., 2006 |
| **Other** | *ATM* | *AtATM* | checkpoint kinase | AT3G48190 | Garcia et al., 2000) |
| | *ATR/RAD3* | *AtATR/AtRAD3* | checkpoint kinase | AT5G40820 | Culligan et al., 2004 |
| | *PCNA* | *AtPCNA1* | DNA polymerase processivity factor activity | AT1G07370 | Strzalka et al., 2009 |
| | | *AtPCNA2* | | AT2G29570 | Strzalka et al., 2009 |
| | *LIG1* | *AtLIG1* | DNA ligation | AT1G08130 | Taylor et al., 1998 |
| | | | | AT1G49250 | Singh et al., 2010 |
| | *PARP* | *AtPARP1* | damage recognition, poly(ADP)ribosylation | AT4G02390 | Lepiniec et al., 1995 |
| | | *AtPARP2* | | AT2G31320 | Doucet-Chabeaud et al., 2001 |
| | | *AtPARP3* | | AT5G22470 | Singh et al., 2010 |
| | *RPA1* | *AtRPA1A/AtRPA1-3/RPA70A* | stabilization of single-stranded DNA intermediates | AT2G06510 | Ishibashi et al., 2005; Chang et al., 2009 |
| | | *AtRPA1-1* | | AT4G19130 | Kunz et al., 2005; Singh et al., 2010 |
| | | *AtRPA1-5/RPA70B* | | AT5G08020 | Kunz et al., 2005; Singh et al., 2010 |
| | | *AtRPA1-2/RPA70C* | | AT5G45400 | Kunz et al., 2005; Singh et al., 2010 |
| | | *AtRPA1-4/RPA70D* | | AT5G61000 | Kunz et al., 2005; Singh et al., 2010 |
| | *RPA2* | *AtRPA2-1/ATRPA32A* | | AT2G24490 | Kunz et al., 2005 |
| | | *AtRPA2-2/ATRPA32B* | | AT3G02920 | Kunz et al., 2005 |
| | *RPA3* | | | AT3G52630 | Singh et al., 2010 |
| | | | | AT4G18590 | Singh et al., 2010 |

Table 1. Overview of genes involved in DNA repair in the model plant *Arabidopsis thaliana*.

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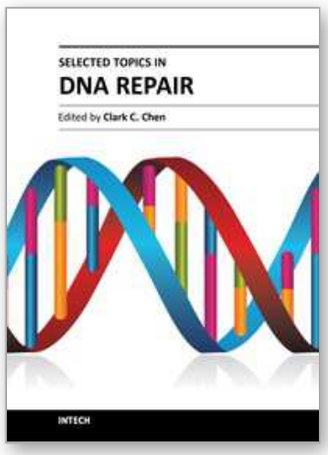


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This book is intended for students and scientists working in the field of DNA repair, focusing on a number of topics ranging from DNA damaging agents and mechanistic insights to methods in DNA repair and insights into therapeutic strategies. These topics demonstrate how scientific ideas are developed, tested, dialogued, and matured as it is meant to discuss key concepts in DNA repair. The book should serve as a supplementary text in courses and seminars as well as a general reference for biologists with an interest in DNA repair.

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