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UV Damaged DNA Repair & Tolerance in Plants

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1. Introduction

In both natural and agricultural conditions, plants are frequently subjected to unfavourable environments, resulting in varying degrees of stress. UV irradiation, drought, heat shock, chilling/freezing, salinity and oxygen deficiency are a few of the major abiotic factors restricting plant growth and development. An important consequence of stratospheric ozone depletion is increased transmission of solar Ultra Violet (UV) radiation through the earth's atmosphere. This increased incidence of UV irradiation causes detrimental effects to all life forms on earth.

1.1 UV irradiation

The spectrum of solar electromagnetic radiation striking the earth's atmosphere ranges from 100 nm to 1 mm. This includes the UV spectrum (100-400 nm), visible spectrum (380-780 nm) and infrared spectrum (700 nm-1 mm). The UV spectrum is further subdivided into three catogories: UV-C (100-280 nm), UV-B (280-315 nm), and UV-A (315-400 nm) (Ballaré, 2003). The shortest of these wavelengths, UV-C, is blocked completely by the ozone layer and atmospheric oxygen. In contrast, UV-A is weakly absorbed and directly transmitted to the earth's surface. Wavelengths in the UV-B range are absorbed efficiently though not completely by ozone, as a very small percentage may pass through holes in the ozone. UV-C is extremely harmful, followed by UV-B, while UV-A has milder effects (Batschauer et al., 1999).

1.2 Plants and UV radiation

Plants, due to their non-motile nature, generally have a higher rate of UV tolerance than animals. Plant secondary metabolites aid in defence against both abiotic and biotic stress factors. Plants are capable of reflecting or absorbing harmful UV rays via thick layers of waxy cutin or submerin on the cell walls and intracellular accumulation of chemical substances such as flavanols or phenolics. The biological effects of UV radiation on plants include altered growth responses, reproductive deformities, epigenetic variations, plant susceptibly to biotic factors, premature senescence, damage to the photosynthetic apparatus, and altered conformation of membrane structures. A wide array of genes were found to be induced upon prolonged exposure to low doses of UV-B in the model plant *Arabidopsis thaliana* (Frohnmeyer & Staiger, 2003; Mackerness, 2000; Ries et al., 2000). Upregulated transcripts include: antioxidant/free radical scavenging enzymes, proteins involved in: DNA repair, translation, E3 ligase system, cell cycle, signal transduction, and secondary

metabolites, as well as several other genes with unknown function (Brosché et al., 2002; Jansen et al., 2008). UV-B also results in numerous changes in plant morphology. This signalling cascade is well reviewed elsewhere (Jenkins, 2009). Here we focus on plant responses to UV-induced DNA damage.

1.3 UV induced DNA damage

UV-C/B radiation is directly absorbed by DNA, inducing lesions which inhibit vital cellular functions such as transcription and DNA replication. UV-A is comparatively less efficient in lesion induction but triggers the production of reactive oxygen species (ROS) (Kunz et al., 2006). The primary UV induced DNA lesions include cyclobutane pyrimidine dimers (adjacent pyrimidines covalently linked between C-5 and C-6 carbon atoms) and secondary lesions 6-4 pyrimidine-pyrimidone photoproducts (6-4 PP) (covalent linkage between the C-4 position of a pyrimidine to the C-6 position of an adjacent pyrimidine) (Fig. 1). In order to respond to this damage, plants employ specific mechanisms (Britt, 1999). In light conditions, photoreactivation catalyses dimer monomerizations while during dark conditions, Nucleotide Excision Repair (NER) excises these helix-distorting lesions. Finally, residual lesions are bypassed via translesion synthesis (TLS).
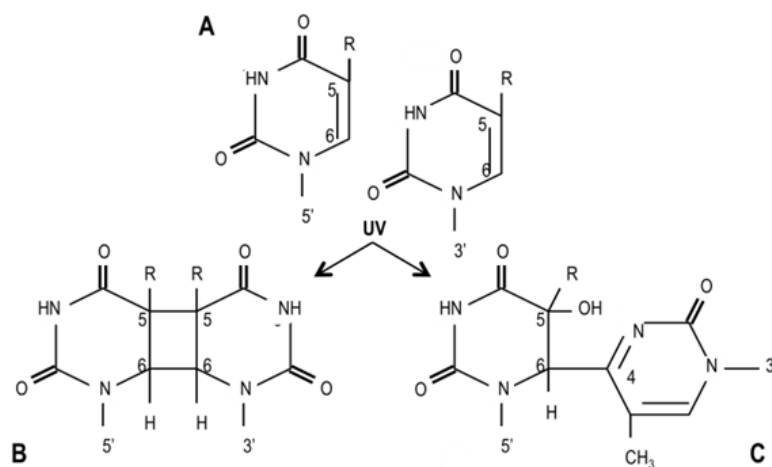

Fig. 1. A) Normal adjacent pyrimidine residues. B) UV-induced Cyclobutane Pyrimidine Dimer (CPD) and C) 6-4 Pyrimidine-Pyrimidone photoproduct (6-4 PP).

2. Photoreactivation

Photoreactivation is a blue light dependant DNA repair mechanism catalysed by the photolyase (E.C 4.1.99.3) class of enzymes. Pyrimidine dimers are split by the action of two photoactive damage specific DNA repair enzymes – CPD photolyase and 6-4 PP photolyase. Both classes of photolyase require two co-factors, one being the two electron reduced form of Flavin Adenine Dinucleotide (FAD) and the second chromophore, a blue light harvesting photoantenna, being either 5,10- methenyltretrahydrofolate (MTHF) or 8-hydroxy-7,8-didemethyl-5-deazariboflavin (8-HDF). FAD is an essential co-factor for regulating DNA binding and repair. In contrast, the second chromophore has a higher extinction co-efficient and an absorption maximum at longer wavelengths, hence regulates the rate of repair depending on the external light intensity. MTHF or 8-HDF absorbs the photoreactivating blue light photons and transfers this excitation energy to the reduced FAD. The FADH- in

turn transfers electrons to the lesions, catalyzing the cleavage of the cyclobutane rings and dimer monomerization (Deisenhofer, 2000; Sancar, 2003, 2008). Multiple sequence alignment reveals that conserved homology between prokaryotic and eukaryotic CPD photolyases is limited to the C-terminal FAD binding site. It has been suggested that a common ancestor gave rise to both type I and type II photolyases but diverged at an early evolutionary stage (Yasui et al., 1994). CPD photolyases have been classified into Class I (microbial) and Class II (higher eukaryotes excluding placental mammals) groups, respectively. The 6–4 photolyases from *Drosophila* and *Arabidopsis* have strong sequence similarity to class I CPD photolyases (Nakajima et al., 1998; Todo et al., 1996). Similarly cryptochromes, the plant blue light photoreceptors, are 30% similar to the class I microbial photolyases, but demonstrate no photolyase activity (Ahmad & Cashmore, 1993). Thus, microbial Class I CPD photolyases, eukaryotic 6–4 photolyases, and blue light photoreceptors constitute the class I photolyase/photoreceptor family.

Genes encoding CPD photolyases and 6-4 PP photolyases have been identified and characterized in a range of prokaryotic and eukaryotic systems (Sancar, 2003). In plants genes encoding CPD photolyases have been identified in *Arabidopsis thaliana* (Ahmed et al., 1997), cucumber (Takahashi et al., 2002), rice (Hirouchi et al., 2003), spinach (Yoshihara et al., 2005), and soybean (Yamamoto et al., 2008). Genes encoding 6-4 PP photolyases have been identified in *Arabidopsis* and rice (Chen et al., 1994; Singh et al., 2010). In *Arabidopsis*, the highest levels of both photolyases are associated with floral tissues, which may presumably serve to minimize lesions in germline cells. While expression of the CPD photolyase is light/UV-B regulated, 6-4 PP photolyase is constitutively expressed (Takahashi et al., 2002; Waterworth et al., 2002). The *Arabidopsis* CPD photolyase gene (*AtPHR1*) encodes a class II CPD photolyase. An *Arabidopsis* mutant (*uvr2*) lacking this gene is hypersensitive to UV. AtPHR1 is efficient in CPD photoreactivation but deficient in 6-4 photoproduct repair (Ahmed et al., 1997; Landry et al., 1997). *AtPHR1* is upregulated several fold in a UV insensitive mutant of *Arabidopsis* (*uvi1*) irrespective of light conditions, conferring constitutive protection (Tanaka et al., 2002). Overexpression of CPD photolyase in *Arabidopsis* and rice resulted in enhanced CPD removal (Hidema et al., 2007; Kaiser et al., 2009; Ueda et al., 2005). Genetic complementation of photolyase deficient *E.coli* strains with soybean, rice, spinach and *Arabidopsis* CPD photolyase genes restored photoreactivation activity (Yamamoto et al., 2007, 2008; Yoshihara et al., 2005). CPD photolyase activity in *Arabidopsis* (Pang & Hays, 1991; Waterworth et al., 2002), soybean (Yamamoto et al., 2008) and rice (Hidema et al., 2000) has been reported to be temperature sensitive. Rice CPD photolyase, encoded by a single copy gene in the nuclear genome, translocates to chloroplasts, mitochondria and nuclei to repair UV-induced CPDs in all three genomes (Takahashi et al., 2011), a phenomenon not observed in spinach chloroplasts (Hada et al., 2000) or young *Arabidopsis* seedlings (Chen et al., 1996). However, upon exposure to photoreactivating blue light, *Arabidopsis* seedlings did exhibit efficient repair of CPDs in the extracellular organelles (Draper & Hays, 2000). The *Arabidopsis* 6-4 PP photolyase, encoded by the *UVR3* gene, encodes a 62 kDa protein with 45% identity to *Drosophila* 6-4 PP photolyase and 17% identity to the Class II CPD photolyases. AtUVR3 is proficient in 6-4 photoproduct removal but deficient in CPD repair. Both *uvr2* and *uvr3* are nonsense mutations, and the double mutants are extremely sensitive to UV relative to the single mutants (Nakajima et al., 1998). Photolyases appear to be the sole repair mechanism active in non-proliferating plant tissues (Kimura et al., 2004). Hence, photolyases play an important role in plant repair of UV damaged DNA.

3. Nucleotide excision repair

Nucleotide excision repair (NER) is a light independent repair process involving a series of reactions: initial damaged DNA recognition, DNA unwinding, dual incision bracketing the lesion, repair synthesis and final ligation to seal the repaired site. NER initiates with specific sub-pathways for transcriptionally active (Transcription Coupled Repair (TC-NER)) or silent (Global Genomic Repair (GG-NER)) DNA. TC-NER and GG-NER exhibit different damage recognition strategies followed by a common repair pathway (Gillet & Scharer, 2006) (Fig. 2). Defects in human NER genes result in the photosensitive syndromes Xeroderma pigmentosum (XP) or Cockayne syndrome (CS). Eight genetic complementation groups for XP have been identified (XPA-G, V) as well as two for CS (CSA and CSB). While XP-V mutation uniquely results in defects in translesion synthesis, XP -A, -B, -D, -F, and -G mutation results in both TC-NER and GG-NER defects, while XP –C and -E mutation results in GG-NER defects only. CSA and CSB mutation results exclusively in TC-NER defects (Hoeijmakers, 2001; Svejstrup, 2002). Bioinformatic analysis of the plant NER protein machinery suggests the molecular mechanisms are largely but not entirely conserved with that of the extensively studied yeast *S. cerevisiae* and mammalian cells (Kimura & Sakaguchi, 2006; Kunz et al., 2005, 2006). NER in plants has been studied primarily in rice and *Arabidopsis* (Singh et al., 2010). Many *Arabidopsis* NER related genes were initially isolated by analysis of UV hypersensitive (*uvh*) and UV repair defective (*uvr*) mutants which were subsequently mapped to homologues of the human XP genes (Table 1).

3.1 Global genomic repair
3.1.1 Damage recognition

3.1.1.1 DDB1 & DDB2

In mammalian systems, damage detection in the GG-NER pathway involves UV-Damaged DNA Binding protein 1 and 2 (DDB1 and DDB2) followed by the XPC-HR23B-CEN2 complex. In humans DDB2 complements the *XPE* mutation and plays a role in recognition of the UV-induced lesion, while DDB1 is required for high affinity interaction of the DDB1-DDB2 complex (Groisman et al., 2003; Luijsterburg et al., 2007; Rapic-Otrin et al., 2002). *S. pombe* Ddb1 knockouts result in chromosomal segregation defects, UV sensitivity and slow S phase progression leading to defects in meiosis (Holmberg et al., 2005). DDB1 and DDB2 homologues have been identified in rice, where they are UV-induced in proliferating tissues (Ishibashi et al., 2003). *Arabidopsis thaliana* encodes two homologs of DDB1 – DDB1A and DDB1B. These proteins are 91% identical with redundant function. Although *ddb1b* null alleles appear lethal, a viable partial loss of function allele exhibits no developmental or UV sensitive phenotypes (Bernhardt et al., 2010; Schroeder et al., 2002). Overexpression of DDB1A in *Arabidopsis* confers enhanced UV resistance and *ddb1a* knockouts exhibit mild UV sensitivity (Al Khateeb & Schroeder, 2009; Molinier et al., 2008). *AtDDB2* encodes a 48 kDa nuclear localized protein with upregulated expression upon UV-induction. *AtDDB2* loss of function results in UV sensitivity while overexpression increases UV tolerance (Biedermann & Hellmann, 2010; Koga et al., 2006; Molinier et al., 2008).

3.1.1.2 Cullin based E3 ligases

The 127 kDa DDB1 homologs function as substrate adaptors for CULLIN4 based E3 ubiquitin (Ub) ligases (Groisman et al., 2003). E3 Ub ligases are multimeric complexes that add ubiquitin moieties to target proteins and contain CULLIN proteins as scaffolding
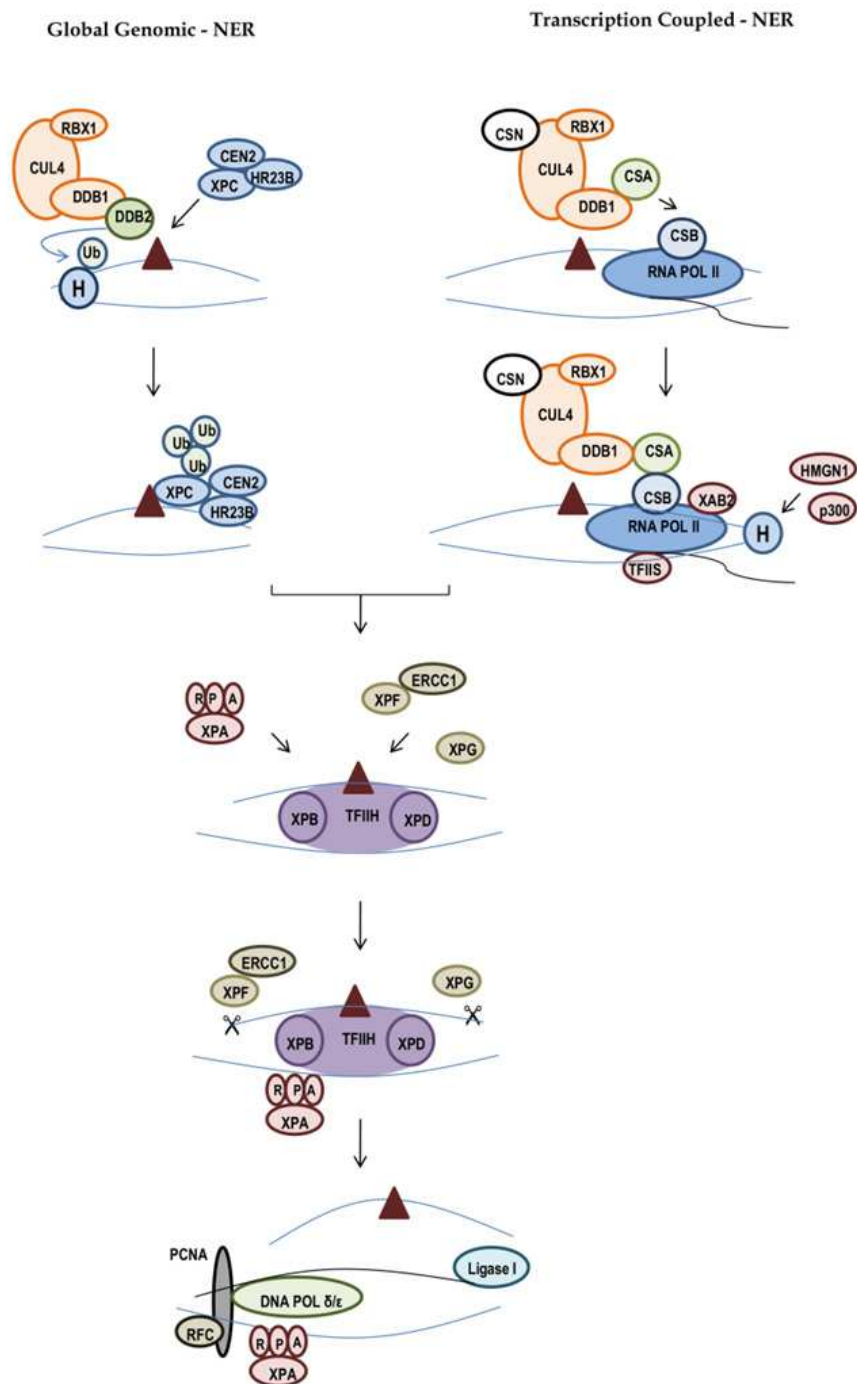
Fig. 2. Overview of mammalian nucleotide excision repair. In GG-NER, DDB2-CUL4 mediated histone (H) and XPC ubiquitination facilitates lesion binding. In TC-NER, stalled RNA POL II recruits CSB and the CSA-CUL4-CSN complex, followed by recruitment of other TC-NER specific factors. In both cases, NER core players follow suit: XPB and XPD helicases of the TFIIH complex, XPF-ERCC1 and XPG endonucleases, and the ssDNA binding XPA-RPA complex. The fragment encompassing the lesion is excised, followed by repair synthesis and ligation. Repair synthesis requires DNA POL δ/ε in concert with accessory proteins PCNA, RFC and RPA. See text for details.

subunits (Hua & Vierstra, 2011). CUL4 based E3 ubiquitin ligases consist of three core subunits: CULLIN4 (CUL4), RING finger protein REGULATOR OF CULLINS1 (ROC1)/RING-BOX1 (RBX1), and DDB1. The CUL4 – RBX1 – DDB1 complex interacts with a large number of proteins containing WD40 motifs referred to as DCAF proteins (DDB1-CUL4 Associated Factor) or DWD proteins (DDB1 binding WD40 proteins) (Lee & Zhou, 2007). DDB2 is an example of a WD40 domain containing DCAF protein. WD40 motifs are characterized by 40 amino acid repeats initiated by a glycine-histidine dipeptide and terminated by a tryptophan-aspartate (WD) dipeptide facilitating protein-protein interactions. DDB1 is composed of three β propeller domains (BPA, BPB and BPC) and DDB2, in addition to the WD40 domain, contains a helix loop helix (HLX) segment in the N terminal. While the clam shaped BPA-BPC of DDB1 mediates interaction with the HLX motif of DDB2 and other DCAF substrates, BPB exhibits exclusive interactions with CUL4 (Scrima et al., 2008).

AtCUL4 is a 91 kDa protein with a conserved CH motif and an extended N terminal region of 65 amino acids that shares close sequence similarity to its human/mouse orthologs. *AtCUL4* loss of function results in abnormal plant development (Bernhardt et al., 2006; Chen et al., 2006) and UV sensitivity (Molinier et al., 2008). Examples of DCAF proteins interacting with the *Arabidopsis* CUL4–DDB1A/B complex include AtDDB2 (Bernhardt et al., 2006), AtCSA-1&2 (Biedermann & Hellmann, 2010; Zhang et al., 2010), as well as the negative regulator of photomorphogenesis DET1 (De-etiolated1) (Schroeder et al., 2002), and many other DWD proteins (Lee et al., 2008). Recent results have shed light on the cross talk between photomorphogenesis regulation and repair of UV damaged DNA. HY5, a positive regulator of photomorphogenesis, has been shown to regulate gene sets connected to UV tolerance, such as the *UVR3* and *PHR1* photolyases, as well as secondary metabolite transcriptional regulators (Oravecz et al., 2006; Ulm et al., 2004). DET1, initially identified as a nuclear localized negative regulator of photomorphogenesis, exhibits a constitutively light grown phenotype in addition to increased levels of flavanoids (Pepper et al., 1994). Recent papers show that *det1* mutants exhibit enhanced UV tolerance through increased levels of secondary metabolites reflecting/absorbing UV irradiation as well as by upregulation of photolyase genes. Further it appears that DET1 protein dosage influences UV sensitivity of plants as DET1 overexpressing lines exhibit increased UV sensitivity (Castells et al., 2010, 2011).

3.1.1.3 Histone ubiquitination facilitates NER machinery entry

In mammals, in the absence of UV irradiation, DDB2-DDB1-CUL4-RBX1 (DDB2 complex) was found to be associated with the COP9 Signalosome complex (CSN). CSN shares significant structural homology with the 19S lid of 26S proteosome. The CSN deconjugates neddylation (Nedd8) from CULLINs, thereby regulating the activation, stability or the disassembly of CULLIN based E3 ligase activity (Parry & Estelle, 2004; Schwechheimer & Deng, 2001). The DDB2 - CSN complex show no ubiquitin ligase activity, but upon UV irradiation, these complexes disassociate in parallel with increased neddylation and activation of CUL4 (Groisman et al., 2003). Core histone proteins have been identified as potential targets for DDB2-DDB1-CUL4-RBX1 mediated proteosomal degradation. Kapetanaki et al. (2006) and Wang et al. (2006) describe the ubiquitination of H2A, H3 and H4 histone proteins. Reduction of histone H3 and H4 ubiquitination by knockdown of *cul4* impairs recruitment of the repair protein XPC to the damaged foci and inhibits the repair process. Thus biochemical studies indicate that DDB-CUL4-RBX1-mediated histone

Human	Yeast	Function	ATG no.	Arabidopsis
Photoreactivation:				
ND	*ND*	6-4 PP Photolyase	At3g15620	*UVR3*
ND	*PHR1*	Class II CPD Photolyase	At1g12370	*PHR1/UVR2*
Nucleotide Excision Repair:				
DDB1	*ND*	Substrate adaptor for CUL4. Interacts with DCAF proteins	At4g05420 At4g21100	*AtDDB1a* *AtDDB1b*
DDB2/XPE	*ND*	Damaged DNA binding (DCAF)	At5g58760	*AtDDB2*
CUL4	*CUL4*	Scaffolding subunit of E3 Ub ligase	At5g46210	*AtCUL4*
XPC	*RAD4*	GG-NER damage recognition	At5g16630	*AtXPC*
HR23B	*RAD23*	Binds to XPC	At1g79650 At1g16190 At3g02540 At5g38470	*AtRAD23A* *AtRAD23B* *AtRAD23C* *AtRAD23D*
CEN2	*CEN2*	Stabilizes XPC-HR23B complex	At3g50360	*AtCEN2*
XPB	*RAD25*	Subunit of TFIIH. 3'->5' helicase	At5g41370 At5g41360	*AtXPB1* *AtXPB2*
XPD	*RAD3*	Subunit of TFIIH. 5'->3' helicase	At1g03190	*AtXPD/UVH6*
GTF2H1 *GTF2H2* *GTF2H3* *GTF2H4* *GTF2H5*	*TFB1* *SSL1* *TFB4* *TFB2* *TFB5*	Core TFIIH subunits	At1g55750 At3g61420 At1g05055 At1g18340 At4g17020 At1g12400 At1g62886	*AtTFB1-1* *AtTFB1-2* *Atp44* *AtTFB4* *AtTFB2* *AtTFB5-1* *AtTFB5-2*
XPA	*RAD14*	ssDNA binding	ND	*ND*
XPG	*RAD2*	3' endonuclease	At3g28030	*AtXPG/UVH3*
ERCC1	*RAD10*	5' endonuclease with XPF	At3g05210	*AtERCC1/UVR7*
XPF	*RAD1*	5' endonuclease with ERCC1	At5g41150	*AtXPF/UVH1*
PCNA	*PCNA*	RFC dependant sliding clamp	At1g07370 At2g29570	*AtPCNA1* *AtPCNA2*
RFC1 *RFC2* *RFC3* *RFC4* *RFC5*	*RFC1* *RFC2* *RFC3* *RFC4* *RFC5*	DNA-dependent ATPase required for DNA replication and repair	At5g22010 At1g21690 At1g77470 At1g63160 At5g27740	*AtRFC1* *AtRFC2* *AtRFC3* *AtRFC4* *AtRFC5*
RPA70 *RPA32* *RPA14*	*RFA1* *RFA2* *RFA3*	ssDNA binding protein required for architectural role in dual lesion incision and repair synthesis	At2g06510 At4g19130 At5g08020 At5g45400 At5g61000 At2g24490 At3g02920 At3g52630 At4g18590	*AtRPA70A* *AtRPA70B* *AtRPA70C* *AtRPA70D* *AtRPA70E* *AtRPA32A* *AtRPA32B* *AtRPA14A* *AtRPA14B*
CSA	*RAD28*	TC-NER specific DCAF protein	At1g27840 At1g19750	*AtCSA1A* *AtCSA1B*

Human	Yeast	Function	ATG no.	Arabidopsis
CSB	RAD26	SWI/SNF2 like ATPase	At2g18760	AtCSB
XAB2	SYF1	Complex stabilization	At5g28740	AtXAB2
TFIIS	TFIIS	TC-NER elongation factor	At2g38560	AtTFIIS
HMGN1	ND	Nucleosome binding	ND	ND
EP300/CBP	ND	Histone acetyl transferase	At1g79000 At1g67220 At1g55970 At3g12980 At1g16710	HAC1 HAC2 HAC4 HAC5 HAC12
Translesion Synthesis				
POLH/XPV	RAD30	Y-family DNA polymerase	At5g44740	AtPOLH
REV1	REV1	Y-family DNA polymerase	At5g44750	AtREV1
POLZ	REV3	B-family DNA polymerase	At1g67500	AtREV3
REV7	REV7	REV3 accessory subunit	At1g16590	AtREV7
POLK	ND	Y-family DNA polymerase	At1g49980	AtPOLK

Table 1. Genes involved in UV damaged DNA repair and tolerance. ND=not detected.

ubiquitination weakens the interaction between histones and DNA to further facilitate the recruitment of repair proteins to damaged DNA (Guerrero-Santoro et al., 2008; Higa et al., 2006). The activated DDB2 complex recruits XPC via protein-protein interactions, followed by ubiquitination of XPC and DDB2. Polyubiquitinated DDB2 exhibits reduced affinity for damaged DNA and is subsequently displaced from the damaged foci, whereas polyubiquitinated XPC enhances its binding to DNA (Sugasawa et al., 2005). In *Arabidopsis*, DDB2 turnover is abrogated in *cul4, ddb1a, atr* and *det1* mutants suggesting that ATR and DET1 may co-operate with the CUL4-DDB1 E3 ligase complex in regulating NER (Castells et al., 2011; Molinier et al., 2008).

3.1.1.4 XPC-HR23B-CEN2

The next step in GG-NER involves the homologous heterodimers hXPC-hHR23B (in Humans) and RAD4-RAD23 (in yeast). In addition to hXPC-hHR23B, Araki et al. (2001) identified hCEN2, a Ca^{2+} binding protein contributing to the stability of the hXPC-hHR23B complex. Hence in mammalian systems the identified protein recognition complex is hXPC-hHR23B-hCEN2, however neither hHR23B nor hCEN2 bind to damaged DNA but enhance both the affinity and specificity of hXPC binding to damaged DNA (Fitch et al., 2003; Nishi et al., 2005). AtCEN2 shares 49% identity with hCEN2, *Atcen2* mutants are UV sensitive, and AtCEN2 overexpression resulted in enhanced repair. Upon UV irradiation, AtCEN2 level increases and it rapidly translocates to the nucleus. AtCEN2-AtXPC interaction in *Arabidopsis thaliana* has also been demonstrated (Liang et al., 2006; Molinier et al., 2004). Potential homologs of HR23B/RAD23 have been identified in *Arabidopsis thaliana*, *Oryza sativa* and *Daucus carota* (Schultz & Quatrano, 1997; Sturm & Leinhard, 1998). The *Arabidopsis* genome has 4 loci encoding RAD23 homologs (RAD23a, RAD23b, RAD23c, RAD23d), and although mutants exhibit multiple pleotrophic developmental defects (Farmer et al., 2010), UV sensitivity or complex interactions with the *Arabidopsis* NER machinery have not yet been reported.

3.1.2 DNA unwinding complex assembly

Following recognition, the damaged region is unwound by the TFIIH transcription factor which joins the XPC-CEN2-HR23B complex. TFIIH is a complex of 10 proteins, seven of which are players in the NER pathway (helicases XPB and XPD, p62, p44, p34, p52, and p8). The last five proteins are encoded by GTF2H1, GTF2H2, GTF2H3, GTF2H4, GTF2H5 (Frit et al., 1999). TFIIH not only participates in NER of transcriptionally active and inactive DNA, but also in RNA POL II dependant transcription, cell cycle control and regulation of nuclear receptor activity (Chen & Suter, 2003). ATP dependant 5′–>3′ and 3′–>5′ helicase activities associated with XPD/RAD3 and XPB/RAD25 respectively unwind the DNA encompassing the lesion with the concomitant release of the recognition complex. Human XPB and the corresponding yeast RAD25 knockouts are lethal. *Arabidopsis thaliana,* unlike the sugarcane, rice or mammalian genomes, encodes two homologs of XPB – AtXPB1 and AtXPB2. These proteins are 95% identical with redundant functions and are expressed constitutively throughout plant development (Morgante et al., 2005; Ribeiro et al., 1998). Despite this redundancy, *xpb1* mutants exhibit delayed germination and flowering phenotypes but are not UV sensitive (Costa et al., 2001). Phenotypes of *Arabidopsis xpb2* or double mutants have not yet been reported. *Arabidopsis* XPD is 56% and 50% identical to human and yeast sequences. *Arabidopsis XPD/RAD3* null mutations are lethal, however viable point mutation alleles are UV sensitive and were identified as *uvh6* (*uv hypersensitive 6*) mutants. (Jenkins et al., 1997; Liu et al., 2003). Another component of the of TFIIH complex, p44, was identified in *Arabidopsis* as ATGTF2H2 and was found to interact in vivo with AtXPD (Vonarx et al., 2006).

3.1.3 Endonuclease recruitment following unwinding

TFIIH further recruits additional factors such as XPA and heterotrimeric Replication Protein A (RPA), composed of 70, 32 and 14 kDa subunits, to promote and stabilize the formation of an open intermediate essential for the dual incision by XPG and XPF-ERCC1 (Excision Repair Complementing defective repair in Chinese hamster 1) (RAD1/RAD10) endonucleases at the 3′ and 5′ sites respectively (Tapais et al., 2004). The RPA-XPA complex exhibits interactions with both endonucleases (He et al., 1995; Wold, 1997), however the specific function of XPA is still not evident. Initially it was thought to function as a lesion recognition complex in concert with XPC, but was later determined to be recruited after TFIIH entry and facilitate XPC complex departure (Hey et al., 2002; Volker et al., 2001). In addition, XPA homologues do not exist in plants (Kunz et al., 2005). The dual incisions catalyzed by the endonucleases excise oligonucleotides of about 20-30 bases containing the lesion (Reidl et al., 2003).

Potential homologs of ERCC1, XPF, XPG and RPA have been identified in plants. Although ERCC1 was first cloned from male germ line cells of *Lilium longiforum*, southern blots confirmed the presence of ERCC1 across diverse plant species such as *A. thaliana*, *B. napus*, *Z. mays*, *L. esculentum*, *N. tobacum*, and *O. sativa* (Xu et al., 1998). Hefner et al. (2003) mapped the *Arabidopsis uvr7* mutant to *AtERCC1*. *Atercc1* knockouts are phenotypically normal in contrast to the lethal mammalian counterparts (Weeda et al., 1997). *Atercc1* mutants are extremely sensitive to DNA damaging chemicals such as mitomycin and ionizing agents such as UV and γ – radiation (Hefner et al., 2003). More recent studies in *Arabidopsis* indicate significant roles of *AtERCC1* in concert with *AtXPF* in homologous recombination and chromosomal stability (Dubest et al., 2002, 2004; Vannier et al., 2009). Gallego et al. (2000) and Liu et al. (2000) characterized the single copy AtXPF which is 37% and 29% identical to

human XPF and *S. cerevisiae* RAD1 respectively. *AtXPF* is homogenously expressed, was mapped to the *uvh1* mutant in *Arabidopsis,* and partially complements the yeast *rad1* mutant (Gallego et al., 2000). *AtXPF* point mutations result in sensitivity to ionizing radiation and mitomycin C, and impaired removal of photoproducts (Fidanstef et al., 2000; Vonarx et al., 2002). *AtXPG* was mapped to the *UVH3* locus and knockouts result in UV sensitivity as well as premature senescence and reduced seed production (Liu et al., 2001). The *XPG* rice homolog, *OsSEND-1*, exhibits upregulated mRNA levels in response to UV and DNA damaging agents (Furukawa et al., 2003a).

ssDNA binding RPA proteins in plants were first identified in rice (Ishibashi et al., 2001). Unlike most eukaryotic organisms, *Arabidopsis* and rice possess multiple copies of the RPA homologs. In addition to participating in DNA repair, RPA proteins play a role in homologous recombination and DNA replication in humans and yeast (Sakaguchi et al., 2009). The rice genome encodes three OsRPA70 (OsRPA70A, OsRPA70B, OsRPA70C), three OsRPA32 (OsRPA32-1, OsRPA32-2, OsRPA32-3) and one OsRPA14. *In vivo* interactions in rice confirms three different complex formations: OsRPA70A-OsRPA32-2-OsRPA14 (Type1); OsRPA70B-OsRPA32-1-OsRPA14 (Type2); and OsRPA70C-OsRPa32-3-OsRPA14 (Type3). Subcellular localization of all three OsRPA32 was detected in both the nucleus and chloroplasts. OsRPA70A was only in the chloroplast whereas OsRPA70B and OsRPA70C were exclusively to the nucleus. This data suggest that while the Type1 complex may participate in chloroplast DNA repair, Type2 and Type3 complexes concentrate on nuclear DNA repair (Ishibashi et al., 2006). OsRPA70A and OsRPa70B share only 33% sequence homology and exhibit differences in expression pattern (Ishibashi et al., 2001). A T-DNA insertion in *OsRPA70A* resulted in partial male sterility, complete female sterility and hypersensitivity to DNA mutagens (Chang et al., 2009). OsRPA32 protein abundance is regulated by both UV irradiation and cell cycle phase (Marwedal et al., 2002). *Arabidopsis*, on the other hand, encodes five putative RPA70 genes and two copies each of RPA32 and RPA14 (Shultz et al., 2007). *Arabidopsis* RPA70A interacts preferentially with AtRPA32A rather than AtRPA32B. Knockouts of both AtRPA70A and AtRPA70B exhibited UV sensitivity when irradiated, but exhibited wildtype characteristics under normal conditions (Ishibashi et al., 2005; Takashi et al., 2009).

3.1.4 Repair synthesis and ligation

In mammals, the gap formed by the excision is filled via PCNA (Proliferating Cell Nuclear Antigen) and RFC dependant DNA synthesis by DNA POL δ/ϵ. These components are likely recruited by XPG and RPA as RFC exhibits interaction with RPA (Yuzhakov et al., 1999). RFC catalyzes the ATP dependant loading of PCNA to DNA at the 3' OH. PCNA is a homotrimeric protein which forms a sliding clamp-like complex (Gulbis et al., 1996) and interacts with the DNA POL to ensure replication occurs processively (Mocquet et al., 2008). The final phase of NER is completed by phosphodiester backbone rejoining of the repaired DNA strand by DNA Ligase I.

Although PCNA and RFC homologues have been identified in plants, their specific role in nucleotide excision repair has not yet been elucidated (Furukawa et al., 2003b; Strzalka & Ziemienowicz, 2011). Recently, Roy et al. (2011) cloned and characterized a homolog of mammalian DNA POLλ in *Arabidopsis.* AtPOLλ was upregulated upon UV induction under dark conditions, and *Atpolλ* mutants exhibited UV sensitivity and decreased DNA repair. Thus, this report suggests a role for DNA POLλ in plant NER.

3.2 Transcription coupled repair

The emerging picture of mammalian TC-NER is of a complex mechanism requiring two essential assembly factors (CSA and CSB), certain TC-NER specific proteins (P300, HMGN1, XAB2 and TFIIS), as well as core NER proteins. UV induced DNA damage is initially recognised by RNA POL II, which stalls when it encounters helix-distorting lesions on the template strand during transcription. Stalled RNA POL II backtracks a few nucleotides and is recognised by the CSB protein which in turn co-ordinates the recruitment of the repair factors required to accomplish Transcription Coupled NER (Mellon, 2005).

Cloning and characterization of the mammalian CSB gene revealed a nuclear protein of 168 kDa with a region of homology to the SWI2/SNF2 family of helicases. CSB has been shown to interact with RNA POL II and this interaction is enhanced and prolonged by UV exposure (van den Boom et al., 2004). Studies propose that functional CSB in the absence of UV could also serve as a component of the transcriptional machinery promoting elongation (Fousteri & Mullenders, 2008; Hanawalt & Spivak, 2008). Further, CSB facilitates the entry of the core NER factors XPA, XPG and TFIIH through complex interactions (Laine & Egly, 2006; Saxowsky & Doetsch, 2006; Svejstrup, 2002). Mammalian CSA on the other hand is a 46 kDa DWD protein containing seven WD40 repeats that associates with DDB1-CUL4 type E3 ligases and is recruited to the damaged site after CSB. CSA physically interacts with the CSB-RNA POL II complex in a UV dependant manner (Groisman et al., 2003; Fousteri et al., 2006). Interestingly, unlike the DDB2 complex, the CSA-CUL4 Ub ligase complex is active under normal conditions but is rapidly inactivated upon UV irradiation by CSN. Hence CSN plays a differential and dynamic role in regulating both pathways of Nucleotide Excision Repair. The stable CSN-CSA-CSB complex is required for the recruitment of the other NER factors. Following repair, CSN dissociates, reactivating CSA Ub ligase activity and resulting in CSB degradation. Clearance of CSB is required for the reinitiation of transcription by RNA POL II (Groisman et al., 2003, 2006).

Several papers over the years propose the fate of RNA POL II during the coupling process: either ubiquitinated and degraded, translocated or bypassed from the lesion site, or simply stalled during the entire repair process, is still a matter of debate (Reviewed in Tornaletti, 2009). XAB2 (XPA binding protein 2) is a RNA-binding protein with 15 tetratricopeptide repeats. In addition to interacting with XPA, XAB2 is capable of interacting with CSA, CSB and RNA POL II (Nakatsu et al., 2000). XAB2 is thought to stabilize protein assemblies by functioning as a scaffolding subunit. XAB2 knockouts in mammalian cells exhibit hypersensitivity and decreased recovery of mRNA synthesis post UV irradiation (Kuraoka et al., 2008). Increased amounts of histone acetyl transferase p300 and High Mobility Group Nucleosome binding domain containing protein 1 (HMGN1) interact with RNA POL II in a CSB-dependant manner upon UV irradiation but exhibit weak interactions under normal conditions (Fousteri et al., 2006). Both HMGN1 and p300 are nucleosome interacting proteins which remodel the chromatin structure behind the arrested polymerase and facilitating the backward translocation of RNA POL II (Hanawalt & Spivak, 2008). TFIIS, functioning as a transcription elongation factor, stimulates the arrested RNA POL II to restart elongation. This TFIIS-RNA POL II interaction is significantly increased upon UV irradiation (Fousteri et al., 2006). Hence it is proposed that TFIIS facilitates resumption of transcription post DNA lesion removal in a CSA/B-dependent manner.

Elucidation of the TC-NER mechanism in plants is still at its infancy. While there is no plant homologue for HMGN1, the *Arabidopsis* genome encodes homologues of XAB2,

TFIIS, and five p300/CBP homologues, however the role of these genes in DNA repair has not been assessed (Grasser et al., 2009; Kunz et al., 2005; Pandey et al., 2002). Only recently was the homolog of human CSA cloned and characterized in *Arabidopsis*. In contrast to mammalian systems, the *Arabidopsis* genome encodes two homologs of CSA – AtCSA1A and AtCSA1B, 92% identical DWD proteins with overlapping subcellular localization and expression patterns. These proteins exist as heterotetramers in planta and are capable of interacting with the DDB1-CUL4 E3 complex. Knockouts of either gene result in UV sensitivity and decreased photoproduct removal (Zhang et al., 2010). Concurrently, another group overexpressed AtCSA1A, which surprisingly also resulted in increased UV sensitivity. This result is hypothesised to be due to competition between CSA and with other DWD proteins to interact with the DDB1-CUL4 complex. Interestingly AtCSA1A levels remained constant upon UV induction (Biedermann & Hellmann, 2010). RNAi of a putative *Arabidopsis* CSB homolog resulted in a UV sensitive phenotype (Shaked et al., 2006). Hence, taken as a whole, these results confirm the role of the CUL4-DDB1-CSA and CSB pathway in plants.

4. Translesion synthesis

Despite the available repair mechanisms, there are times when UV damage persists and DNA replication proceeds past UV lesions via translesion synthesis (TLS). This synthesis proceeds via one of several DNA polymerases: Polη, Rev1, Polζ, Polκ or Polι. Polη (eta) is encoded by the *POLH* locus in humans and is homologous to yeast RAD30. Polη performs error-free bypass of CPDs, and loss of function results in increased mutation and xeroderma pigmentosa (XP-V) in humans. REV1 exhibits dCMP transferase activity but is required for 6-4 PP bypass independent of this activity, suggesting its role may be in recruitment of other polymerases. Polζ is composed of REV3 and REV7 and exhibits error prone repair. REV3 is a B-family polymerase (unlike the other TLS polymerases which are all Y-family polymerases) and REV7 an accessory subunit that enhances REV3 activity (Waters et al., 2009). Polκ activity is specific to N2-dG lesions in both animals and plants, while plants do not have a Polι homologue (Garcia-Diaz & Bebenek, 2007; Garcia-Ortiz et al., 2007).

Homologues of REV1, REV3 and REV7 as well as Polη have been identified in *Arabidopsis* (Sakamoto et al., 2003; Santiago et al., 2006; Takahashi et al., 2005). Mutant alleles of *REV3*, *REV1* and *REV7* all result in UV sensitivity, although *rev1* only weakly and *rev7* only to long-term UV exposure (Sakamoto et al., 2003; Takahashi et al., 2005). Interestingly, AtREV1 cannot insert nucleotides across from UV-induced DNA lesions, suggesting that its role is primarily in the recruitment of other TLS polymerases (Takahashi et al., 2007). The UV sensitivity of the *rev1 rev3* double mutant is similar to that of *rev3*, additional evidence that the role of REV1 may be in REV3 recruitment (Takahashi et al., 2005). Analysis of mutation frequency in *rev1* and *rev3* mutants shows a reduction relative to wildtype rate, evidence that these genes contribute to error-prone repair (Nakagawa et al., 2011).

Polη is encoded by the *Arabidopsis POLH* gene. The *POLH* transcript is ubiquitously expressed and alternatively spliced, and AtPolη exhibits similar levels of activity *in vitro* as the human protein (Hoffman et al., 2008; Santiago et al., 2008a, 2009). *AtPOLH* overexpression results in increased UV tolerance, while *AtPOLH* loss of function results in weak UV sensitivity, but enhances the sensitivity of the *rev3* mutant, evidence that Polη is acting independently of Polζ (Curtis & Hays, 2007; Santiago et al., 2008b). *POLH* mutants

exhibit an increased mutation frequency, indicating a role in error-free repair. Interestingly, this increased mutation rate is suppressed in the *rev3 polh* double mutant, indicating that REV3 is required for the increased mutations in *polh* (Nakagawa et al., 2011). AtPolη interacts with the *Arabidopsis* PCNA homologues PCNA1 and PCNA2. In yeast the interaction with PCNA2 was found to be functionally important and require the PCNA-interacting protein (PIP) box and Ubiquitin-binding motif (UBM) of AtPolη (Anderson et al., 2008).

In other systems, PCNA monoubiquitination by RAD6/RAD18 is implicated in polymerase switching during translesion synthesis (Waters et al., 2009). While the *Arabidopsis* genome contains *RAD6* homologues (*AtUBC1-3*), no obvious *RAD18* homologue exists (Kraft et al., 2005). Interestingly, in mammalian cells, the CUL4-DDB1-CDT2 E3 ubiquitin ligase was recently shown to also monoubiquitinate PCNA and promote translesion synthesis (Terai et al., 2010). The CUL4-DDB1-CDT2 complex also ubiquitinates Polη (Kim & Micheal, 2008; Soria & Gottifredi, 2010), suggesting that this complex may be a key regulator of translesion synthesis (Abbas & Dutta, 2011). All components of the CUL4-DDB1-CDT2 complex exist in plants (Lee et al., 2008), so it will be interesting to examine the role of this complex in translesion synthesis.

5. Other responses

In addition to DNA repair and TLS, UV-damaged DNA also triggers other cellular responses such as cell cycle arrest and cell death (Batista et al., 2009). In general, relatively little is known about the molecular basis of these responses in plants. As in mammalian systems, in plants the initial damage sensors include ATM (double strand breaks), ATR (ssDNA) and ATR-interacting protein ATRIP (Culligan et al., 2004; Furukawa et al., 2010; Sakamoto et al., 2009). Plants do not have a p53 homologue, in contrast damage signalling pathways converge on the SOG1 transcription factor, resulting in cell cycle arrest and cell death (Furukawa et al., 2010; Preuss & Britt, 2003; Yoshiyama et al., 2009). UV-induced cell death in plants also involves topoisomerase I (Balestrazzi et al., 2010), metacaspase-8 and caspase-3-like activities (Danon et al., 2004; He et al., 2008; Zhang et al., 2009), as well as changes in reactive oxygen species and mitochrondria (Gao et al., 2008).

6. Conclusions

Thus, despite the barrage of damage resulting from solar UV exposure plants face every day, they have a variety of mechanisms which allow them to survive. UV induced DNA damage is repaired by direct photoreactivation via photolyases, or by dark repair (NER) in both transcribed (TC-NER) or non-transcribed regions (GG-NER). Finally, rather than repair UV damage, plants can tolerate its presence and proceed with DNA replication via translesion synthesis, although there can be mutagenic consequences of this activity. The continued study of these pathways and the interplay between them in plants is sure to bring additional insight.

7. Acknowledgements

8. References

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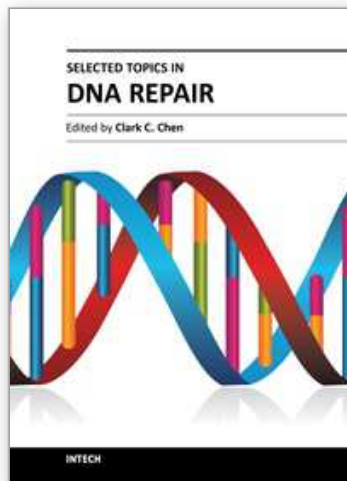
Selected Topics in DNA Repair

Edited by Prof. Clark Chen

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.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

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