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DNA Damage Tolerance in Plants via Translesion Synthesis

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ABSTRACT

Arrest of replication forks at sites of DNA damage may disrupt the cellular replication machinery leading to cell death. Consequently, cells have evolved damage tolerance mechanisms that do not remove damage but allow replication through or around DNA lesions, which can be repaired subsequently. Damaged templates can be copied by translesion synthesis (TLS), or the damaged segment may be avoided by template switching during replication. Non-essential, low fidelity DNA polymerases catalyse TLS in yeast and mammalian cells. Mechanisms for targeting TLS polymerases to stalled replication forks include interaction with the sliding clamp proliferating cell nuclear antigen (PCNA). Regulation of this interaction and the mode of damage tolerance involves post-translational modification of PCNA, TLS polymerase stability and DNA damage surveillance genes. SUMOylation of PCNA at lysine-164 prevents recombination at blocked forks and so may participate in tolerance pathway selection. Monoubiquitylation of the same residue is necessary for TLS, and polyubiquitylation at lysine-164 promotes damage avoidance. Surprisingly, much less is known about damage tolerance and its importance in plants despite their obligate exposure to a major environmental source of DNA damage, solar ultraviolet (UV) radiation. Recent isolation and functional characterisation of cDNAs encoding *Arabidopsis thaliana* homologues of TLS polymerases or PCNA-modifying enzymes suggest that plants may rely in part on damage tolerance to help combat the onslaught of UV photoproducts.

Keywords: Arabidopsis, damage avoidance, ubiquitylation, ultraviolet radiation, yeast
Abbreviations: (6-4) photoproducts, pyrimidine (6-4) pyrimidone photoproducts; **aa**, amino acids; **CPDs**, cyclobutane pyrimidine dimers; **D-loop**, displacement-loop; **HECT**, homology to the E6-AP C terminus; **K**, lysine; **PCNA**, proliferating cell nuclear antigen; **PHD**, plant homeodomain; **PIP**, PCNA interaction peptide; **Pol(s)**, polymerase(s); **RFC**, replication factor C; **RPA**, replication protein A; **RING**, really interesting new gene; **TT**, thymine-thymine; **SUMO**, small ubiquitin-related modifier; **UBM**, ubiquitin-binding motif; **UBZ**, ubiquitin-binding zinc finger; **UEV**, ubiquitin E2 variant; **UV**, ultraviolet

CONTENTS

INTRODUCTION

Their sessile lifestyle and reliance on sunlight for photosynthesis has required plants to evolve highly effective mechanisms to cope with the toxicity of solar ultraviolet (UV) radiation. In particular, UV-B (280-320 nm) wavelengths induce the formation of cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6-4) pyrimidone photoproducts [(6-4) photoproducts] in DNA. This damage blocks replication and transcription of chromosomal templates, and leads to gaps in nascent strands (Friedberg *et al*. 2006; Lopes *et al*. 2006). Consequently, unrepaired UV photoproducts can inhibit plant growth and cause plant death (Britt and Fiscus 2003). To reduce their damage load, plants produce UV-absorbing compounds in epidermal cells, photoreactivate UV-induced CPDs and (6-4) photoproducts, and excise UV photoproducts from their DNA (Britt 2004). However, shielding and DNA repair do not prevent or eliminate all UV-induced lesions, and cell death may result if replication forks stall at sites of damage, or strand gaps accumulate. As additional insurance, other organisms also employ processes to restart blocked replication forks, or fill strand gaps left behind moving forks, thereby allowing bypass of UV photoproducts which can then be repaired postreplicatively. The

Received: 16 February, 2007. Accepted: 24 April, 2007.

Invited Review

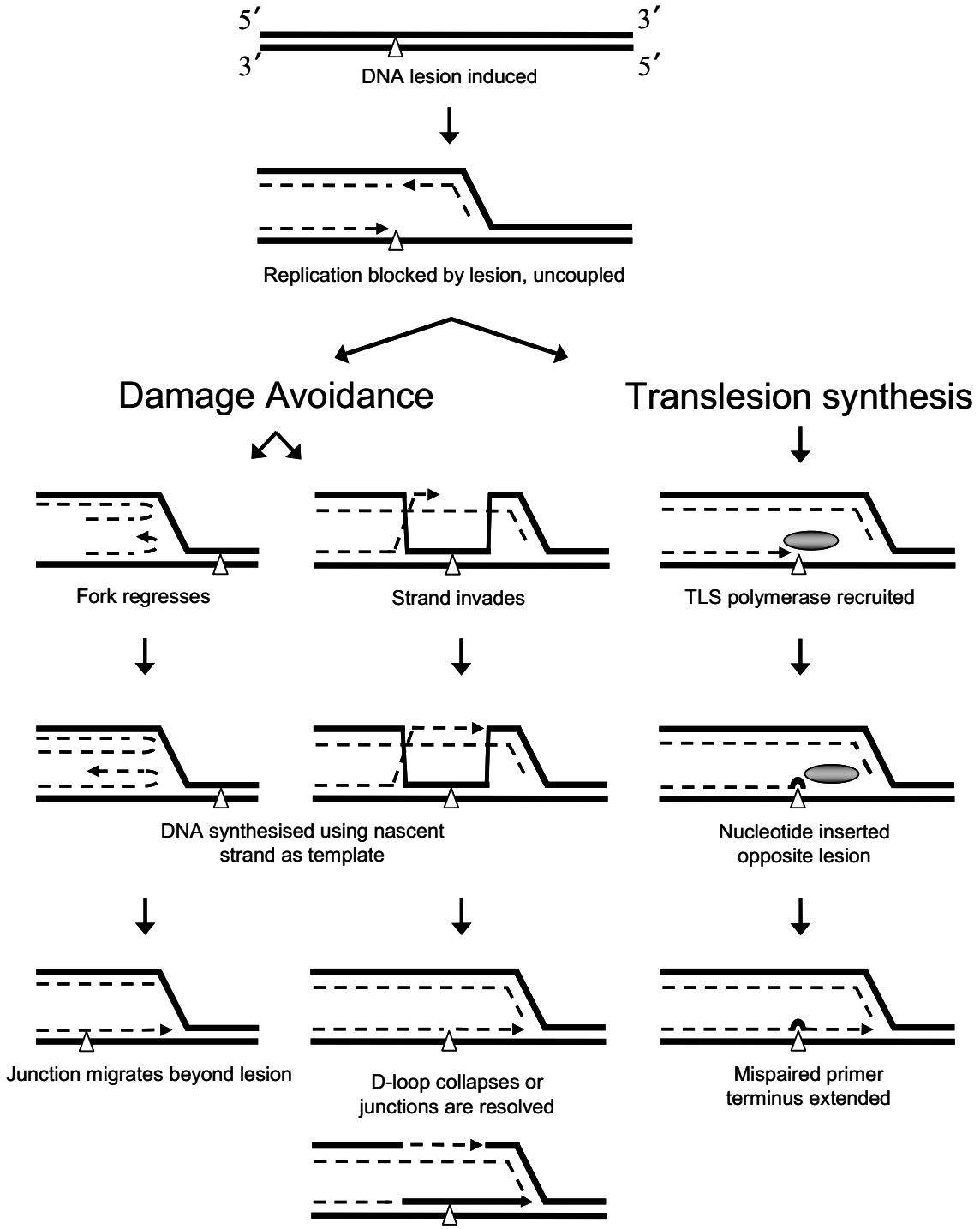

Fig. 1 Models for DNA damage avoidance and translesion synthesis. A lesion might block leading strand synthesis (in this figure) and uncouple lagging strand synthesis which might proceed past the damage site. The damage could be avoided if replication fork regression or strand invasion provided an alternative template (the nascent lagging strand) for continuation of leading strand synthesis. Depending on the physical parameters involved, junction migration, displacement (D)-loop collapse or junction resolution might enable synthesis of both strands to resume beyond the lesion. Replacement of the blocked replicative polymerase by a TLS polymerase would allow limited synthesis past the lesion. The replication machinery could then recommence leading and lagging strand synthesis.

mechanisms responsible involve copying the damaged template by translesion synthesis (TLS), or avoiding the damage via template switching (Friedberg *et al*. 2006; **Fig. 1**). The resulting tolerance of DNA lesions allows growing cells to evade replicative arrest, but may generate mutations through diminished replication accuracy during TLS.

In this article, we discuss tolerance of UV photoproducts with emphasis on TLS and reference to the mechanisms involved in the yeast *Saccharomyces cerevisiae* and mammalian cells. Using this framework we review experimental findings, including homology comparisons and characterisation of gene products or mutants for *Arabidopsis thaliana*, consistent with roles for plant genes in the bypass of UV-induced DNA damage. Collectively, the data are beginning to paint a picture of damage tolerance similar to that in other eukaryotes, but with some features that may be unique to plants.

TLS BY SPECIALISED POLYMERASES

TLS past UV photoproducts in eukaryotes is catalysed by non-essential, low fidelity DNA polymerases (Pols) that may accommodate lesions in more open active sites (Prakash *et al*. 2005). These include Pol zeta (Polζ), a B family

polymerase first linked to TLS in yeast and later in human cells (Morrison *et al*. 1989; Gibbs *et al*. 1998), as well as several Y family polymerases discovered over the past decade, Pol eta (Polη), Pol iota (Polι), Pol kappa (Polκ) and Rev1 (Prakash *et al*. 2005; Yagi *et al*. 2005; Dumstorf *et al*. 2006).

Polη

Polη efficiently replicates CPDs, in particular thymine-thymine (TT) dimers, in a relatively error-free manner (McCulloch *et al*. 2004; Gibbs *et al*. 2005; Prakash *et al*. 2005). It also may initiate synthesis from recombination intermediates during damage avoidance (Mcllwraith *et al*. 2005). For TLS *in vivo*, Polη interacts with ubiquitylated proliferating cell nuclear antigen (PCNA), the eukaryotic sliding clamp needed for processive DNA replication (Kannouche *et al*. 2004; Prakash *et al*. 2005; Plosky *et al*. 2006; Parker *et al*. 2007). The Polη-PCNA interaction is mediated by a PCNA interaction peptide (PIP) box and an ubiquitin-binding zinc finger (UBZ) (Bienko *et al*. 2005; Plosky *et al*. 2006; Parker *et al*. 2007). PCNA, the heteropentameric clamp loader replication factor C (RFC) and the heterotrimeric single-strand binding protein replication protein A (RPA) cooperatively stimulate DNA synthesis by Polη by increasing nucleotide insertion efficiency but not processivity (Prakash *et al*. 2005). However, the effect of these accessory replication factors on TLS polymerase activity is sequence-dependent and processivity can be increased in the right context (Vidal *et al*. 2004). The importance of Polη-mediated TLS in defence against UV photoproducts is clear. Inactivation of Polη sensitises yeast, mouse and human cells to the lethal and mutagenic effects of UV (Prakash *et al*. 2005; Dumstorf *et al*. 2006; Lin *et al*. 2006). These outcomes might reflect decreased error-free avoidance of UV photoproducts (Mcllwraith *et al*. 2005) and less efficient, more inaccurate replication of CPDs by other TLS polymerases (Prakash *et al*. 2005). The increase in UV mutagenesis could also explain why Polη deficiencies increase UV-induced skin cancer in mice (Dumstorf *et al*. 2006; Lin *et al*. 2006) and cause the variant form of the human skin cancer-prone disorder xeroderma pigmentosum (Johnson *et al*. 1999; Masutani *et al*. 1999).

Arabidopsis POLH encodes a Polη homologue (AtPolη) (Santiago *et al*. 2006; **Table 1**). The predicted AtPolη and its *Oryza sativa* (rice) counterpart (NP_916191) have the five Y family polymerase domains essential for DNA synthesis, and two conserved forms of the carboxyl-terminal PIP box present in human and yeast Polη (Prakash *et al*. 2005). However, both plant Polη homologues lack the carboxyl-terminal UBZ that human and yeast Polη requires for enhanced binding to monoubiquitylated PCNA (Bienko *et al*. 2005; Plosky *et al*. 2006; Parker *et al*. 2007). Human Polι also lacks a UBZ but binds ubiquitylated PCNA via its PIP box and at least one of two ubiquitin-binding motifs (UBM) not present in human or yeast Polη (Bienko *et al*. 2005; Plosky *et al*. 2006). Intriguingly, AtPolη and its rice counterpart have a single sequence homologous to the two Polι UBMs that partially overlaps the site of the UBZ in human Polη. These observations suggest that if plant Polη binds ubiquitylated PCNA, it may uniquely do so through a UBM rather than a UBZ.

Expression of the *AtPOLH* cDNA in a yeast *rad30* (*RAD30* encodes Polη) deletion mutant fully complemented the UV sensitivity of the mutant, and this complementation was abolished by mutating residues in one of the highly conserved polymerase domains in AtPolη (Santiago *et al*. 2006). These data must be interpreted cautiously because it is not clear if steps were taken to prevent photoreactivation during the complementation experiments, *AtPOLH* actually was expressed in yeast cells, or expression of *AtPOLH* reduced the rate of yeast DNA replication, which could indirectly decrease UV sensitivity. In studies to be reported elsewhere, however, we demonstrate that an *AtPOLH* mutation increases the sensitivity of *Arabidopsis* to UV-B radiation and AtPolη interacts with both yeast and *Arabidopsis* PCNA. The latter data are consistent with AtPolη being able to function in TLS in *Arabidopsis*, but are not conclusive.

Table 1 Summary of damage tolerance genes or candidate genes.

Homo sapiens	***Saccharomyces cerevisiae***	***Arabidopsis thaliana***	***A. thaliana* locus[b]**
Genes encoding translesion synthesis polymerases[a]			
POLH	*RAD30*	*AtPOLH*	At5g44740
POLI	Not present	Not present	
POLK	Not present	*AtPOLK*	At1g49980
REV1	*REV1*	*AtREV1*	At5g44750
REV3	*REV3*	*AtREV3*	At1g67500
REV7	*REV7*	*AtREV7*	At1g16590
Genes encoding replication/checkpoint clamps or loaders			
PCNA	*POL30*	*AtPCNA-1*	At1g07370
		AtPCNA-2	At2g29570
Not present	*RAD9*	Not present	
HUS1	*MEC3*	*AtHUS1*	At1g52530
RAD1	*DDC1*	*AtRAD1-like*	At4g17760
RAD9	*RAD17*	*AtRAD9*	At3g05480
RAD17	*RAD24*	*AtRAD17*	At5g66130
RFC1	*RFC1*	*AtRFC1*	At5g22010
RFC2	*RFC2*	*AtRFC2*	At1g63160
RFC3	*RFC3*	*AtRFC3*	At5g27740
RFC4	*RFC4*	*AtRFC4*	At1g21690
RFC5	*RFC5*	*AtRFC5*	At1g77470
Genes encoding PCNA modifying enzymes or related proteins			
	UBC9	*AtSCE1A*	At3g57870
	SIZ1	*AtSIZ1*	At5g60420
SENP1, 2, 3	*ULP1*	*AtULP1C*	At1g10570
		AtULPID	At1g60220
Not present	*ULP2*	*AtULP2A*	At4g04130
		AtULP2B	At4g19310
PLAA	*DOA1*	*AtDOA1*	At3g18860
HHR6A, B	*RAD6*	*AtUBC1*	At1g14400
		AtUBC2	At2g02760
		AtUBC3	At5g62540
RAD18	*RAD18*	Not present	
USP1	Not present	Not present	
	UBC13	*AtUBC13A*	At1g78870
		AtUBC13B	At1g16890
MMS2	*MMS2*	*AtUEV1A*	At1g23260
		AtUEV1B	At1g70660
		AtUEV1C	At2g36060
		AtUEV1D	At3g52560
Not present	*RAD5*	*AtRAD5A*	At5g43530
		AtRAD5B	At5g22750
SHPRH	Not present	Not present	
Not present	*SRS2*	Not present	

[a] The designation 'Not present' does not exclude the possibility of functional homologues.
[b] Candidate genes were identified from the *Arabidopsis* genome database at The *Arabidopsis* Information Resource (TAIR) (http://www.arabidopsis.org) by homology searches using human or yeast proteins as probes.

Polι and Polκ

Polι, a Polη paralogue, and Polκ, a homologue of *Escherichia coli* Pol IV, are absent from yeast but may participate in UV photoproduct bypass in multicellular organisms (Prakash *et al*. 2005; Yagi *et al*. 2005). Purified human Polι incorporated nucleotides opposite a TT or thymine-uracil CPD or TT (6-4) photoproduct and bypassed the lesions (Tissier *et al*. 2000; Vaisman *et al*. 2006). Other investigators detected insertion only opposite the 3′ base of a TT (6-4) photoproduct, and did not observe extension (Zhang *et al*. 2001; Prakash *et al*. 2005). Such discrepancies may reflect different assay conditions and sequence contexts which influence Polι activity *in vitro* (Vidal *et al*. 2004). Recently, inactivation of Polι was found to reduce UV mutagenesis in mouse fibroblasts, slightly sensitise them to UV-induced killing, and potentiate UV-induced skin cancer in mice also deficient in Polη (Dumstorf *et al*. 2006).

These observations suggest that Polι contributes to the intracellular bypass of UV photoproducts. So far, Polι has been detected in vertebrates and insects but not plants.

Although Polκ does not replicate through UV lesions, it can extend from a nucleotide opposite the 3′ base of a TT CPD, but not a TT (6-4) photoproduct (Prakash *et al*. 2005; Yagi *et al*. 2005; Lone *et al*. 2007). These properties may reflect exclusion of part or all of these lesions from the Polκ catalytic centre due to encirclement of the DNA template by Polκ and its more spatially constrained active site which can accommodate only a single Watson-Crick base pair (Lone *et al*. 2007). Accordingly, and because *in vitro* human Polκ extends from paired primer termini 1% to 10% as often as from mispaired primer termini (Washington *et al*. 2002), it has been suggested that during TLS this enzyme specifically extends aberrant primer-terminal base pairs (Prakash *et al*. 2005; Carlson *et al*. 2006). The importance of such a role in the tolerance of UV-induced DNA damage is unknown. Polκ-deficient mouse and chicken cells exhibit increased UV sensitivity (Ogi *et al*. 2002; Okada *et al*. 2002), but this phenotype is probably due to the participation of Polκ in the repair synthesis step of nucleotide excision repair rather than to a defect in TLS (Ogi and Lehmann 2006).

Biochemical studies have shown that like Polη, Pols ι and κ interact with ubiquitylated PCNA through a PIP box and UBM or UBZ sequences, respectively (Bienko *et al*. 2005; Prakash *et al*. 2005; Bi *et al*. 2006; Plosky *et al*. 2006). Furthermore, PCNA, RFC and RPA cooperatively stimulate DNA synthesis by Pols ι and κ through increased efficiency of nucleotide incorporation and processivity of Polι (in the right sequence context), as well as promoting nucleotide insertion opposite the 3′ T of a TT (6-4) photoproduct by Polι (Vidal *et al*. 2004; Prakash *et al*. 2005).

Arabidopsis POLK encodes a predicted Polκ homologue (AtPolκ). Like its rice counterpart (ABF97636), AtPolκ has well-conserved forms of the five amino-terminal Y family polymerase domains and carboxyl-terminal PIP box present in human Polκ (García-Ortiz *et al*. 2004). Whereas other Polκ homologues have one or two carboxyl-terminal C_2HC UBZs (Bienko *et al*. 2005; Prakash *et al*. 2005), only a single C_2H_2 motif is found in *Arabidopsis* and rice Polκ, a difference that may be specific to plants. Purified AtPolκ has polymerase but not proofreading activity, exhibits low processivity on its own, and extends mismatched primer termini (García-Ortiz *et al*. 2004). However, its ability to insert nucleotides opposite DNA damage, or extend from a nucleotide incorporated opposite a UV photoproduct, remains to be assessed, as does the effect of its inactivation on plant UV resistance.

Polζ and Rev1

Human and yeast Polζ is a heterodimeric polymerase composed of the interacting Rev3 catalytic and Rev7 accessory subunits (Nelson *et al*. 1996b; Murakumo *et al*. 2000). Rev7 is critical for Polζ activity *in vivo*, but its precise function is uncertain, although yeast Rev7 enhances DNA polymerisation by Rev3 *in vitro* (Nelson *et al*. 1996b). Polζ is essential for UV mutagenesis in human cells and yeast (Lemontt 1971; Lawrence *et al*. 1985; Gibbs *et al*. 1998). It also is required for bypass of TT (6-4) photoproducts but not TT CPDs on vectors transformed into yeast cells that contain Polη, and probably for TLS past TT CPDs when not catalysed by Polη (Gibbs *et al*. 2005). Inactivation of *REV3* or *REV7* moderately sensitises yeast cells to UV, as does antisense reduction of human *REV3* expression (Lemontt 1971; Lawrence *et al*. 1985; Gibbs *et al*. 1998) suggesting a modest role for Polζ-mediated TLS in UV resistance.

UV resistance and mutagenesis in vertebrate cells and yeast also requires Rev1, the fourth eukaryotic member of the Y polymerase family (Gibbs *et al*. 2000; Nelson *et al*. 2000), but its role as a TLS polymerase is limited. Rev1 exhibits a highly specific dCMP transferase activity (Nelson *et al*. 1996a; Lin *et al*. 1999) templated by the protein itself rather than lesion-containing DNA (Nair *et al*. 2005). Although Rev1 is needed to bypass a TT (6-4) photoproduct, and probably a TT CPD in the absence of Polη, its dCMP transferase activity is not (Nelson *et al*. 2000), suggesting Rev1 serves a structural or regulatory role in TLS (Murakamo *et al*. 2001; Prakash *et al*. 2005). Consistent with this possibility, mammalian Rev1 interacts with Pols η, ι and κ, yeast and human Rev1 interacts with Rev7, and yeast Rev1 and Rev3 interact (Murakamo *et al*. 2001; Guo *et al*. 2003; Ohashi *et al*. 2004; Acharya *et al*. 2005, 2006). However, a stable Rev1-Rev3-Rev7 complex has been detected only in yeast when Rev1 binds to Rev3 as part of Polζ, but not when Rev1 binds to Rev7 separate from Rev3 (Murakamo *et al*. 2001; Acharya *et al*. 2006). Furthermore, interaction of Rev1 with Rev7 or Polκ does not influence the dCMP transferase activity of Rev1 nor does interaction of Rev1 with Polκ affect the DNA polymerase activity of Polκ (Guo *et al*. 2003; Masuda *et al*. 2003; Acharya *et al*. 2005). On the other hand, association of yeast Rev1 with Polζ does increase the efficiency with which Polζ extends from nucleotides opposite the 3′ T of a TT CPD or (6-4) photoproduct (Acharya *et al*. 2006).

Although Rev3 and Rev7 do not interact with PCNA (Garg *et al*. 2005; Haracska *et al*. 2006), PCNA, RFC and RPA together were reported to stimulate TLS by purified yeast Polζ on a UV photoproduct-bearing template (Garg *et al*. 2005). In contrast, other investigators detected no stimulation of the synthetic activity of Polζ by PCNA (Haracska *et al*. 2006). However, Rev1 increases the efficiency with which Polζ extends from UV photoproducts (Acharya *et al*. 2006), mouse Rev1 interacts with PCNA (Guo *et al*. 2006a, 2006b), and the Polζ preparation used by Garg *et al*. (2005) was impure. Thus, contamination of that preparation with Rev1 might have been responsible for the observed stimulatory effect of PCNA on TLS by yeast Polζ, if the stimulation also required interaction of Rev1 with PCNA. If so, Polζ might function *in vivo*, at least transiently, as a heterotetrameric complex of PCNA, Rev1, Rev3 and Rev7.

Arabidopsis AtREV3, *AtREV7* and *AtREV1* encode Rev3, Rev7 and Rev1 homologues, respectively. *AtREV3* was identified by mapping an *Arabidopsis* mutation that confers slight sensitivity to UV-B exposure (Sakamoto *et al*. 2003). Whether this sensitisation reflects defective TLS is unknown. The predicted AtRev3 has the six carboxyl-terminal B family DNA polymerase domains characteristic of Rev3 homologues, and domains I-III have perfectly conserved active site motifs pointing to a role in DNA replication. The conservation of these domains also is significant because this is the region through which yeast Rev3 binds to Rev1 (Acharya *et al*. 2006). Surprisingly, the Rev3 sequences required for interaction with Rev7 in yeast or human cells (Murakumo *et al*. 2001; Acharya *et al*. 2006) are poorly conserved in AtRev3. However, two C_4 zinc-binding domains at the carboxyl terminus of yeast and human Rev3 also are present in AtRev3. The UVB sensitivity of the *Atrev3* mutant plus the strong conservation of most functional domains suggests a role for AtRev3 in TLS.

Full-length cDNAs that can encode *Arabidopsis* Rev7 or Rev1 homologues have been isolated (Takahashi *et al*. 2005). Positions 21 to 155 of human Rev7 encompass the Rev3 and Rev1 interaction domain (Murakumo *et al*. 2001). The corresponding region of AtRev7 exhibits considerable similarity suggesting AtRev7 may interact with AtRev3 and AtRev1, but this has not been determined. However, expression of an *AtREV7* cDNA partially complemented the UV sensitivity conferred by deleting yeast *REV7*, but failed to restore any UV resistance in a *rev3 rev7* double mutant (LJ McCarthy, NA Mathe, BA Kunz, unpublished data). These observations are consistent with AtRev7 interacting with yeast Rev3, and link the function of AtRev7 in yeast to Polζ, but cannot be taken to indicate that AtRev7 must operate similarly in *Arabidopsis*. In contrast to the phenotype of the *Atrev3* mutant, a T-DNA insertion that prevents detectable *AtREV7* transcript production did not increase

plant sensitivity to acute UV-B doses (Takahashi *et al*. 2005). The difference between the two plant mutants was small but unexpected given that Rev3 and Rev7 constitute Polζ, and yeast and human *rev3* and *rev7* mutants exhibit common responses.

Rev1 homologues feature the five polymerase domains found in Y family polymerases, and several regions involved in protein interactions. An amino-terminal BRCA1 terminus domain is required for interaction with PCNA and TLS past T-T (6-4) photoproducts (Nelson *et al*. 2000; Guo *et al*. 2006a). Monoubiquitylation of PCNA enhances binding by Rev1 through two carboxyl-terminal UBMs necessary for TLS and damage-induced mutagenesis (Guo *et al*. 2006b). The polymerase-associated domain of yeast Rev1 binds to Rev7 (Acharya *et al*. 2005), whereas mouse and human Rev1 interacts with Rev7 as well as Pols η, ι and κ, via its final 100 amino acids (Murakamo *et al*. 2001; Guo *et al*. 2003; Ohashi *et al*. 2004). All of these domains are conserved in the predicted AtRev1, suggesting commonality of function. Consistent with a role in Polζ-mediated TLS, T-DNA insertions that prevent detectable *AtREV1* transcript production modestly increase plant sensitivity to UVB, and the effect is epistatic with inactivation of *AtREV3* (Takahashi *et al*. 2005). However, the genetic relationships of *AtREV7* to *AtREV1* or *AtREV3* have not been investigated, nor has the ability of AtRev1 to interact with AtRev3, AtRev7 or AtPolη.

RECRUITMENT OF TLS POLYMERASES TO BLOCKED REPLICATION FORKS

In order to catalyse lesion bypass, TLS polymerases must gain access to the replication machinery arrested at a damage site, and they may do so in several ways. Following UV treatment of human cells, Pols η and ι localise to replication foci thought to represent sites where replication forks are stalled at UV photoproducts (Kannouche *et al*. 2003, 2004; Watanabe *et al*. 2004). Polη may be directed to blocked forks via interaction with the Rad18 protein which accumulates at DNA damage sites (Watanabe *et al*. 2004; Chiu *et al*. 2006; Nakajima *et al*. 2006). However, since an *Arabidopsis* Rad18 homologue has not been detected, either AtPolη can interact directly with the replication complex at a blocked fork, or a functional homologue of Rad18 may guide plant Polη to sites of damage. Localisation of Polι to replication foci depends on the presence of Polη with which it interacts (Kannouche *et al*. 2003). Alternatively, since Rev1 has a high affinity for single-stranded DNA (Masuda and Kamiya 2006), interaction with Rev1 may target Pols η, ι, κ and ζ to replication gaps extending downstream from DNA lesions (Murakumo *et al*. 2001; Guo *et al*. 2003; Ohashi *et al*. 2004; Acharya *et al*. 2006; Waters and Walker 2006). Another way in which Pols η, ι, κ, and Rev1 might be directed to replication foci, and gain access to primer termini, is via interaction with PCNA, which would be expected to be present at stalled replication forks and is recruited to sites of UV-induced DNA damage (Kannouche *et al*. 2004; Vidal *et al*. 2004; Essers *et al*. 2005; Prakash *et al*. 2005; Guo *et al*. 2006a). Whether only one, or all of these mechanisms serve to direct TLS polymerases to replication foci remains to be determined. Several findings suggest, however, that similar interactions may occur in plants. AtPolη physically associates with AtPCNA (W Xiao, BA Kunz, unpublished data), *Atrev1* and *Atrev3* mutations interact epistatically with respect to UV sensitivity (Takahashi *et al*. 2005), and *AtREV7* complements the UV sensitivity conferred by a yeast *rev7* deletion in a *REV3*-dependent manner (LJ McCarthy, NA Mathe, BA Kunz, unpublished data).

CONTROL OF DAMAGE TOLERANCE

TLS permits cell survival in the face of unrepaired DNA damage but often may be accompanied by mutagenesis due to the poor fidelity of TLS polymerases. This reduction in genetic stability can pose a potential threat to the cell, and so the activity of TLS polymerases must be tightly controlled. This line of reasoning also suggests that the error-free damage avoidance pathway normally might be the preferred means of lesion tolerance. Details of the molecular mechanisms that control the choice of pathway used to tolerate UV photoproducts in yeast and human cells have begun to emerge over the past few years. Although many aspects remain unknown, it has become clear that modification of PCNA, the stability of Polη and DNA damage surveillance proteins are key factors.

Enzymatic Cascade For PCNA Modification

UV-induced modification of PCNA is an important regulatory switch that rescues lesion-blocked replication forks by directing them into damage tolerance pathways (Hoege *et al*. 2002). The modifiers are small globular proteins that alter the properties of protein targets by attaching covalently to them. For PCNA, the modifiers are ubiquitin and small ubiquitin-related modifier (SUMO) protein. Attachment occurs via an enzymatic cascade involving an ATP-dependent activating enzyme (E1) that catalyses formation of a thioester bond between the carboxyl-terminal carboxyl group of the modifier and an internal cysteine residue of the E1 (Bachmair *et al*. 2001; Hay 2005; Kraft *et al*. 2005). The modifier is then transesterified from the E1 to the active site cysteine of a conjugating enzyme (E2). Although there are a number of E2s for ubiquitin, there seems to be one universal E2, Ubc9, for SUMO. The final step links the carboxyl-terminal residue of the modifier to a surface ε-amino group of a lysine residue on the substrate protein. For ubiquitin, substrate recognition is usually mediated by a protein ligase (E3) that belongs to one of two functional groups. One group contains an "homology to the E6-AP C terminus" (HECT) domain and transfers ubiquitin to the substrate via an internal thioester bond. E3s in the second group contain a "really interesting new gene" (RING) domain and function as scaffolds to juxtapose the substrate and E2 with thioester-linked ubiquitin. The RING domain may be part of a single large protein with substrate recognition capability or be in a small protein that is part of a multi-protein E3 complex, often a Skp1-Cul1-F-box type ubiquitin ligase. Ubc9 is able to transfer SUMO directly to substrate proteins, but SUMO E3 ligases increase the efficiency of SUMO conjugation in a substrate-specific manner.

SUMOylation of PCNA

In yeast, a complex of Ubc9, the E2 that conjugates SUMO protein, and Siz1, a SUMO ligase, SUMOylates PCNA at lysine (K) 164 (**Fig. 2**) in S phase and in response to severe DNA damage (Hoege *et al*. 2002). Interaction of SUMOylated PCNA with the Srs2 helicase recruits Srs2 to stalled replication forks in yeast (Papouli *et al*. 2005; Pfander *et al*. 2005). Since Srs2 suppresses inter- and intra-chromosomal recombination, SUMOylation of PCNA has been suggested to help control the choice of the pathway used to rescue a blocked replication fork (Papouli *et al*. 2005; Pfander *et al*. 2005). Deconjugation of SUMOylated PCNA by the SUMO-specific proteases Ulp1 and Ulp2 also may be involved in pathway selection as inactivation of Ulp1 and Ulp2 sensitises yeast cells to DNA damaging agents including UV (Li and Hochstrasser 2000; Soustelle *et al*. 2004). Importantly, SUMOylation of proteins often seems to be temporary and to provoke an alteration in the target protein that persists after removal of SUMO (Hay 2005). Thus, one can envisage a scenario in which PCNA SUMOylation might reduce recombination-mediated damage avoidance in favour of TLS whereas rapid SUMO deconjugation might leave PCNA altered in a manner that favours damage avoidance over TLS. However, because only a small fraction of the available PCNA appears to be SUMOylated at any one time (Papouli *et al*. 2005), the same pathway choice may not be made at all blocked replication forks.

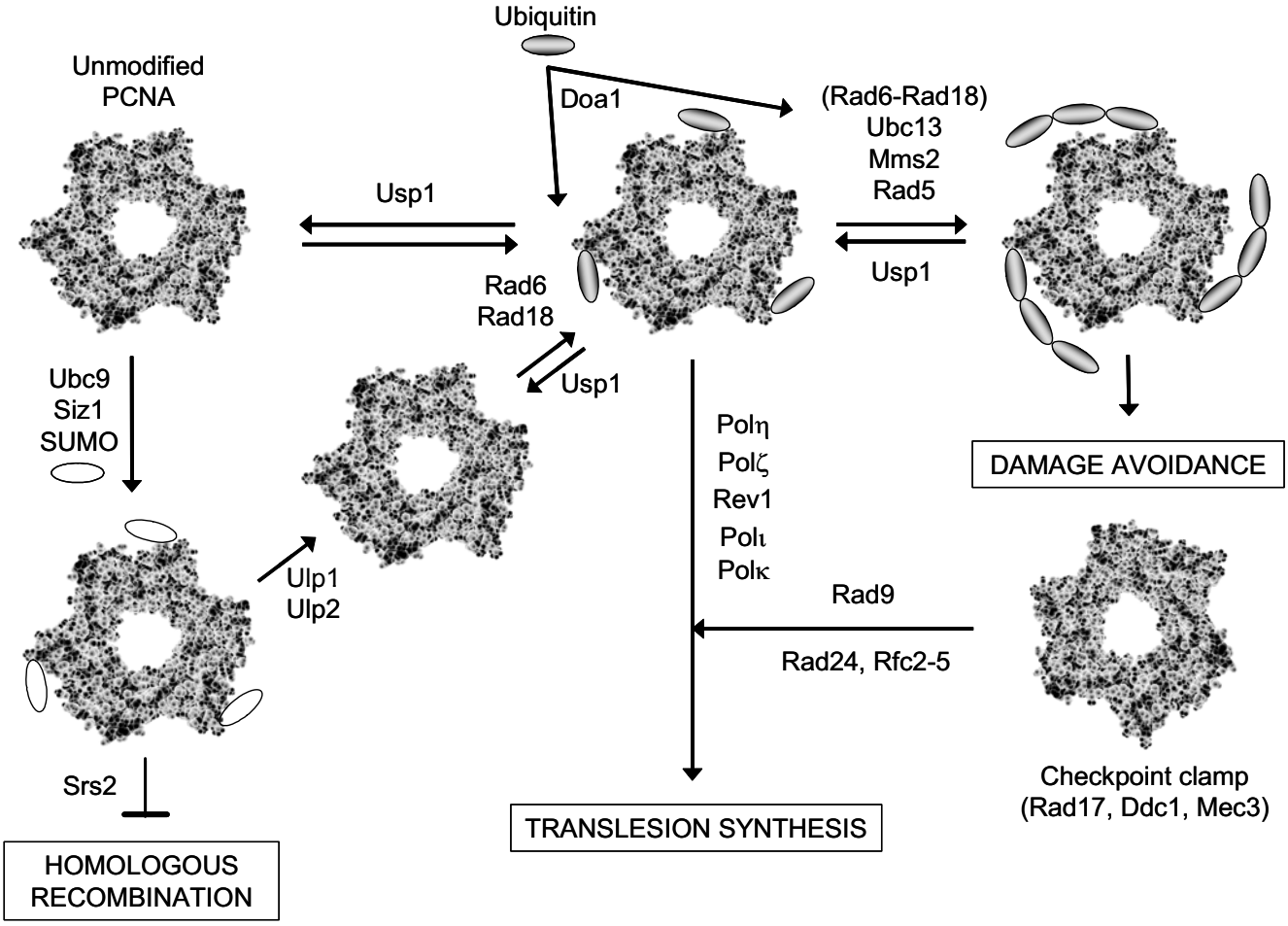

Fig. 2 Model for promotion of damage tolerance by modification of PCNA. SUMOylation of PCNA at K164 by the Ubc9-Siz1 E2-E3 complex recruits the Srs2 helicase to prevent unwanted recombination at stalled replication forks. DeSUMOylation by the Ulp1 or Ulp2 protease may produce an "altered" form of PCNA that is diverted to the Rad6-dependent pathway. Monoubiquitylation of unmodified or "altered" PCNA at K164 by the Rad6-Rad18 E2-E3 complex promotes TLS. Rad6-Rad18 may cooperate with the Ubc13-Mms2-Rad5 E2-E3 complex to polyubiquitylate the "altered" or unaltered form of PCNA at K164, promoting damage avoidance. Doa1 diverts ubiquitin to the latter two complexes. Usp1 protease deubiquitylates PCNA. Selection of a TLS polymerase may be influenced by the Rad17-Ddc1-Mec3 checkpoint clamp, the Rad24-Rfc2-5 clamp loader, and the Rad9 checkpoint protein. The model is based on yeast and human cell data, but not all processes or proteins may operate in both cell types and some aspects of the model are speculative. Yeast protein designations are used, except for Polι and Polκ. See the text for additional details.

Arabidopsis SCE1A and *SIZ1* encode Ubc9 and Siz1 homologues (Kurepa *et al*. 2003; Lois *et al*. 2003; Miura *et al*. 2005). The catalytic domain and all residues identified as important for transesterification of SUMO to human Ubc9 are conserved in AtUbc9 which interacts with the SUMO isoforms AtSUMO1 and AtSUMO2, and has SUMO-conjugating activity *in vitro* (Kurepa *et al*. 2003; Lois *et al*. 2003). Domains in yeast Siz1 that are necessary for SUMO binding and ligase activity are conserved in AtSiz1 which functions as a SUMO ligase *in vitro* and *in vivo* but unlike yeast Siz1 does not allow SUMOylation of yeast PCNA at K164 *in vitro* (Miura *et al*. 2005; Colby *et al*. 2006). *Arabidopsis* also encodes two Ulp1 homologues (AtUlp1c, AtUlp1d) that are able to deconjugate SUMOylated yeast PCNA *in vitro* (Colby *et al*. 2006), and two potential Ulp2 homologues have been identified but their ability to deconjugate SUMOylated proteins has not been tested (Kurepa *et al*. 2003).

Whether plant PCNA is a target for SUMOlyation by AtUbc9 and AtSiz1 *in vitro* or *in vivo* is unknown. Furthermore, SUMOylated PCNA has not been detected in mammalian cells (Kannouche *et al*. 2004; Watanabe *et al*. 2004) which, like *Arabidopsis*, do not appear to encode a Srs2 homologue. Thus, higher eukaryotes may use an alternate mechanism(s) for minimising unwanted recombination at stalled replication forks or may have a functional homologue of Srs2.

Monoubiquitylation of PCNA and TLS

In response to DNA damage, PCNA is monoubiquitylated at K164 by a complex of the Rad6 E2 ubiquitin-conjugating enzyme and Rad18, an E3 DNA-binding ubiquitin ligase belonging to the RING group (Bailly *et al*. 1997; Hoege *et al*. 2002; Kannouche *et al*. 2004). An increase in monoubiquitylated PCNA is required for UV mutagenesis in yeast and likely involves the UV-inducibility of *RAD6* and *RAD18* (Stelter and Ulrich 2003; Friedberg *et al*. 2006). In human cells, accumulation of monoubiquitylated PCNA and UV mutagenesis also depend on the state of Usp1, a cysteine protease that deubiquitylates PCNA. Usp1 counterbalances the ubiquitylation machinery to maintain low levels of monoubiquitylated PCNA, presumably to limit replication-associated mutagenesis by TLS polymerases in non-damaged cells. DNA damage induces autocatalytic cleavage of Usp1 thereby precipitating the build-up of monoubiquitylated PCNA (Huang *et al*. 2006). Monoubiquitylation can occur on each monomer in the PCNA clamp (Haracska *et al*. 2006) and may restore fork progression via the TLS pathway (Hoege *et al*. 2002). Selection of the TLS pathway might involve enhanced binding of TLS polymerases to PCNA, their activation by interaction with modified PCNA, or dissociation from monoubiquitylated PCNA of a protein that prevents interaction of PCNA with TLS polymerases (Kannouche *et al*. 2004; Bienko *et al*. 2005; Garg and Burgers 2005; Bi *et al*. 2006; Guo *et al*. 2006b; Harac-

ska *et al*. 2006).

Arabidopsis AtUbc1, AtUbc2 and AtUbc3 are Rad6 homologues and have the conserved cysteine at position 88 that is essential for ubiquitin-conjugating activity (Bachmair *et al*. 2001; Kraft *et al*. 2005). Indeed AtUbc1-AtUbc3 are able to conjugate ubiquitin to target proteins *in vitro*, but it is not known whether they ubiquitylate PCNA or contribute to UV resistance *in planta* (Kraft *et al*. 2005). However, expression of *AtUBC2* in yeast partially complemented the UV sensitivity conferred by deletion of *RAD6*, although the participation of AtUbc2 in UV mutagenesis was not assessed (Zwirn *et al*. 1997). Nonetheless, given that there is no evidence for interaction of AtUbc2 with yeast Rad18 or resumption of PCNA ubiqutylation, restoration of UV resistance cannot be attributed to AtUbc2 functioning in damage tolerance in yeast. Interestingly, *Arabidopsis* lacks a Rad18 homologue, but an *Arabidopsis* Rad6 homologue may operate with a multi-protein E3 complex rather than a single Rad18-like ubiquitin ligase. Indeed, a rice Rad6 homologue interacts with Sgt1, a subunit of a Skp1-Cul1-F-box ubiquitin ligase (Azevodo *et al*. 2002; Yamamoto *et al*. 2004). Thus, in plants a multi-protein ubiquitin ligase might substitute for Rad18 in damage tolerance. Alternatively, because AtUbc1-AtUbc3 have E3-independent ubiquitin-conjugating activity *in vitro*, PCNA monoubiquitylation in *Arabidopsis* might not require a separate ubiquitin ligase. If so, the presence of multiple Rad6 homologues in *Arabidopsis* might reflect the need for different substrate specificities among the homologues. Although *Arabidopsis* contains at least 27 genes specifying ubiquitin-specific proteases, none has overall homology to human Usp1 (Yan *et al*. 2000). Therefore, if PCNA is monoubiquitylated in plants, it is likely to be deubiquitylated by a protein other than a Usp1 homologue.

Ubiquitin is likely redirected by yeast Doa1 from the proteosomal degradation pathway to the ubiquitin-conjugating assemblies that target PCNA (Lis and Romesberg 2006). Doa1, which is essential for damage-induced ubiquitylation of PCNA, and its human homologue Plaa are predicted to contain seven WD-40 repeats, amino-termini with homology to phospholipase A2-activating protein, and a Plaa family ubiquitin binding domain (Lis and Romesberg 2006; Mullally *et al*. 2006). *Arabidopsis* has a Doa1 homologue in which all of these features are conserved, but the activity and role of the protein remain to be determined.

Polyubiquitylation of PCNA and error-free damage avoidance

Damage avoidance is error-free and so may be favoured over TLS by mutation-prone polymerases. Selection of the damage avoidance pathway requires the assembly of K63-linked polyubiquitin chains onto monoubiquitin at K164 of PCNA in yeast and human cells. This modification is catalysed in UV-irradiated cells by a heterodimeric ubiquitin-conjugating enzyme composed of Ubc13 and the ubiquitin E2 variant (UEV) protein Mms2 (Hoffmann and Pickart 1999; Hoege *et al*. 2002; Chiu *et al*. 2006; Motegi *et al*. 2006; Unk *et al*. 2006). Ubc13-Mms2 interacts via Ubc13 with the DNA-binding ubiquitin ligase Rad5 (Shprh in human cells), a RING protein that targets PCNA (Ulrich and Jentsch 2000; Unk *et al*. 2006). Polyubiquitylation of PCNA may involve cooperation of the Rad6-Rad18 and Ubc13-Mms2-Rad5/Shprh complexes mediated by interaction between Rad5/Shprh and Rad18 (Ulrich and Jentsch 2000; Motegi *et al*. 2006; Unk *et al*. 2006). The greater UV sensitivity of a *rad5* deletion mutant compared to the UV sensitivities of *mms2* and *ubc13* deletions mutants, coupled with a requirement for Rad5, but not Mms2 or Ubc13 for UV-induced reversion at the *ARG4* locus, has led to the suggestion that Rad5 also may function independently of Ubc13-Mms2 to enhance TLS efficiency (Čejka *et al*. 2001; Gangavarapu *et al*. 2006). Despite its importance, how the choice is made between the TLS and damage avoidance pathways when a replication fork encounters a DNA lesion, and the factors that influence this choice, are not clear. However, since Rad18 and Rad5 also interact physically with Ubc9 (Hoege *et al*. 2002), SUMOylation and ubiquitylation of PCNA may be regulated in part by communication between the modifying complexes.

Arabidopsis AtUbc13A and *AtUbc13B* encode Ubc13 counterparts and appear to be due to a recent duplication event (Wen *et al*. 2006). The four *AtUev1A-D* loci encode Mms2 homologues, and likely resulted from two sequential duplications. Several observations are consistent with the AtUbc13 and AtUev1 proteins forming at least one AtUbc13-AtUev1 polyubiquitylating complex that participates in damage tolerance (Wen *et al*. 2006; R Wen, L. Newton, H Wang, W Xiao, unpublished data). First, specific residues in human or yeast Ubc13 or Mms2 have been shown to be essential for the interaction of the two proteins, binding of ubiquitin to the Ubc3-Mms2 ubiquitin acceptor site, unanchored polyubiquitin chain assembly by the Ubc13-Mms2 complex *in vitro* or cellular UV resistance conferred by *UBC13* or *MMS2* (Pastushok *et al*. 2005; Tsui *et al*. 2005; Eddins *et al*. 2006). The critical Ubc13 or Mms2 residues are conserved in AtUbc13A and AtUbc13B or AtUev1A-D, respectively. Second, AtUbc13A and AtUbc13B interact with each of AtUev1A-D, and each *Arabidopsis* Ubc13 or Mms2 homologue also interacts with yeast and human Mms2 or Ubc13, as appropriate. Third, AtUbc13A with AtUev1A or AtUev1C generates unanchored di-ubiquitin chains *in vitro*. Fourth, interference RNA suppression of *AtUBC13 in planta* moderately sensitises root growth to UV, and inactivation of *AtUEV1D* reduces seed germination and seedling growth in response to DNA damage. Finally, expression of *AtUBC13A* and *AtUBC13B* or *AtUEV1A-D* in yeast can fully complement yeast *ubc13* or *mms2* deletions, respectively. However, these results, especially those of the heterologous complementation assays, should not be interpreted to indicate that AtUbc13A, AtUbc13B and AtUev1A-D necessarily function in damage tolerance in *Arabidopsis*. The difficulty in doing so is illustrated by the observation that although human Uve1A, a homologue of yeast Mms2, functions in place of Mms2 in yeast, in human cells it is required for nuclear factor κB activation rather than damage tolerance (Anderson *et al*. 2005).

Yeast Rad5 and human Shprh contain a C_3HC_4 RING motif characteristic of ubiquitin ligases and located between the third and fourth of seven SWI/SNF helicase domains (Sood *et al*. 2003). These features are strongly conserved in two predicted *Arabidopsis* Rad5 homologues and a predicted protein with some similarities to human Shprh. However, human Shprh differs from yeast Rad5 in also having a "plant homeodomain" (PHD) domain and a "linker histone domain typical of the H1 and H5 families" (H1,5) domain (Sood *et al*. 2003). Neither domain is present in either *Arabidopsis* Rad5 homologue, but a disrupted form of the PHD domain is in the *Arabidopsis* Shprh-like protein which is missing the H1,5 domain. Thus, it seems unlikely that *Arabidopsis* has a *bona fide* Shprh sequence homologue. Whether either Rad5 homologue contributes to UV resistance, interacts with AtUbc13A or AtUbc13B, or can function in polyubiquitylation is unknown.

Polη expression and stability

Under normal conditions yeast Polη has a half-life of 20 minutes (Skoneczna *et al*. 2007), presumably to limit its activity in the absence of DNA damage. Defects in the β1 (*pup-T30A*), β2 (*pre3-T20A*), or β5 (*pre2-K108R*) components of the yeast proteasome, the Ump1 proteasome maturase or the Skp1-cullin-Ufo1 ubiquitin ligase confer a Polη-dependent increase in spontaneous and UV-induced mutations, increase the steady-state level and half-life of Polη, and lead to detection of ubiquitylated Polη species (Podlaska *et al*. 2003; Skoneczna *et al*. 2007). Thus, post-translational polyubiquitylation of the polymerase may reg-

ulate its stability by targeting it for controlled proteolysis. When yeast cells are UV-irradiated, however, transcription of *RAD30* is induced, and Polη is temporarily stabilised (half-life: two hours) so that it accumulates transiently (McDonald *et al*. 1997; Skoneczna *et al*. 2007). An increase in the concentration of Polη at the replication fork may facilitate its entry to the replication complex and so promote TLS past UV photoproducts. Expression of *POLH* is not UV-inducible in human fibroblasts (Liu and Chen 2006), and so far only monoubiquitylated Polη, Polι and Rev1 have been detected in mammalian cells (Bienko *et al*. 2005; Guo *et al*. 2006b). Furthermore, it is not known if putative TLS polymerases are ubquitylated in plants. Thus, whether regulation of the stability of TLS polymerases plays a role in the control of TLS in higher eukaryotes is uncertain.

Roles for damage response proteins

Coordination of DNA damage tolerance pathways in yeast also requires DNA damage checkpoint proteins, most of which have human homologues. In particular, Srs2, which interacts with SUMOlyated PCNA, also has a checkpoint role (Liberi *et al*. 2000; Vaze *et al*. 2002), and the Ddc1, Mec3, Rad9, Rad17 and Rad24 checkpoint proteins function in damage tolerance (Paulovich *et al*. 1998; Barbour *et al*. 2006). Although the part played by Rad9 is unclear, Rad17, Ddc1 and Mec3, and their human homologues Rad9, Rad1, and Hus1, form a PCNA-related heterotrimeric clamp (human 9-1-1 complex) loaded onto DNA *in vitro* by the Rad24-RFC (human Rad17-RFC) clamp loader (Bermudez *et al*. 2003; Majka and Burgers 2003). Several findings link this checkpoint clamp to Polζ-mediated TLS in yeast. Proteins that form the clamp or its loader are required for UV mutagenesis (Paulovich *et al*. 1998), clamp components interact with Rev7, and the clamp increases the efficiency of Rev7 binding to UV-irradiated chromosomes (Sabbioneda *et al*. 2005). However, the Rad17-Ddc1-Mec3 clamp does not stimulate TLS by Polζ (Garg *et al*. 2005) suggesting that the checkpoint clamp-loader system may contribute to regulation of tolerance pathways via recruitment of TLS polymerases rather than being directly involved in TLS. *Arabidopsis* appears to lack a counterpart of *S. cerevisiae* Rad9, but homologues of Rad17, Ddc1, Mec3 and Rad24 have been identified, and corresponding cDNAs isolated (Heitzeberg *et al*. 2004). *Arabidopsis* also has loci encoding counterparts of Rfc2, Rfc3, Rfc4 and Rfc5, the remaining clamp loader components. Mutations in the Rad17 and Rad24 homologues epistatically sensitise *Arabidopsis* to strand-breaking agents (Heitzeberg *et al*. 2004), but neither the influence of the clamp or clamp loader homologues on UV resistance has been assessed.

CONCLUDING REMARKS

Owing to their prolonged exposure to sunlight, plants have developed mechanisms for reducing tissue penetration by harmful solar UV wavelengths, and reversing or removing UV-induced DNA damage. Recent findings suggest that plants also have the requisite machinery for tolerating UV photoproducts, but there are reasons to think the mechanisms involved may not precisely mirror those in human cells or yeast. Certainly, there appear to be differences among the gene profiles of the three species. For example, *Arabidopsis* potentially has more TLS polymerases than yeast but fewer than human cells. In addition, multiple homologues of single copy human or yeast genes, including *MMS2*, *PCNA* and *UBC13* are present in the plant, which may reflect functional redundancy or a division of labour. Furthermore, *Arabidopsis* seems to be missing counterparts of Rad9, Rad18, Srs2 and Usp1, and this may point to differences in the regulation of damage tolerance in plants, or the presence of functional rather than sequence homologues of certain yeast or human damage tolerance proteins.

The way in which plants develop is an aspect of plant life that may influence tissue-specific needs for and regulation of damage tolerance. For example, cell proliferation occurs in meristematic tissues and not normally in mature tissues. Thus, damage tolerance genes might be expressed exclusively in actively growing tissues. Consistent with this possibility, rice PCNA was found to be expressed in tissues where cells would be actively proliferating, including young leaves, the shoot apical meristem and the root apical meristem, but not in mature leaves where cells do not proliferate (Kimura *et al*. 2004). However, this difference in tissue-specific expression could be related mainly to the role of PCNA in chromosomal DNA replication rather than damage tolerance. *AtREV3* or *AtPOLH* transcripts were detected in leaf, root, and flower tissues of two-week-old or four-week-old plants, respectively, and in stems and siliques for *AtPOLH* (Sakamoto *et al*. 2003; Santiago *et al*. 2006). Similarly, *AtUBC13* transcripts were identified in five-week-old leaf, stem or flower tissues (Wen *et al*. 2006) Furthermore, the *AtPOLK* promoter was active in a variety of tissues including non-proliferating organs such as mature leaves, sepals and stamen filaments (García-Ortez *et al*. 2004). Collectively, these observations indicate damage tolerance proteins are expressed in proliferating and non-proliferating tissues throughout the plant, although what purpose they might have in the latter tissues is unclear. It is interesting, however, that *AtREV3*, *AtPOLH* and *AtUBC13* transcripts, as well as *AtPOLK* promoter activity, were observed in one or more tissues (leaves, cotyledons, hypocotyl) (Sakamoto *et al*. 2003; García-Ortez *et al*. 2004; Santiago *et al*. 2006; Wen *et al*. 2006) whose development is associated with endoreduplication (one to several rounds of genome replication in the absence of mitosis) (Galbraith *et al*. 1991; Melaragno *et al*. 1993; Trass *et al*. 1998; Lomontey *et al*. 2000). Conceivably, damage tolerance proteins might also function during cycles of endoreduplication in growing plants.

Whether in plants damage tolerance makes an important contribution to UV resistance, protects against blockage of replication fork progression by endogenous damage, or adds to genetic instability through error-prone TLS is not known. The influence of defects in damage tolerance genes on mutagenesis or other indicators of genetic stability in plants has not been assessed. A better understanding of the biological roles of putative plant damage tolerance genes will require their continued genetic analysis as well as isolation and characterisation of the proteins they encode.

ACKNOWLEDGEMENTS

Work from the authors' laboratories was supported by the Australian Research Council (BAK) and the Canadian Institutes of Health Research (WX).

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