Translesion Synthesis in Plants: Ultraviolet Resistance and Beyond

Ayako N. Sakamoto *

Department of Radiation-Applied Biology Research, National Institutes for Quantum and Radiological Science and Technology, Takasaki, Japan

Plant genomes sustain various forms of DNA damage that stall replication forks. Translesion synthesis (TLS) is one of the pathways to overcome stalled replication in which specific polymerases (TLS polymerase) perform bypass synthesis across DNA damage. This article gives a brief overview of plant TLS polymerases. In Arabidopsis, DNA polymerase (Pol) ζ, η, κ, θ, and λ and Reversionless1 (Rev1) are shown to be involved in the TLS. For example, AtPol η bypasses ultraviolet (UV)-induced cyclobutane pyrimidine dimers in vitro. Disruption of AtPol ζ or AtPol η increases root stem cell death after UV irradiation. These results suggest that AtPol ζ and ATPol η bypass UV-induced damage, prevent replication arrest, and allow damaged cells to survive and grow. In general, TLS polymerases have low fidelity and often induce mutations. Accordingly, disruption of AtPol ζ or AtRev1 reduces somatic mutation frequency, whereas disruption of AtPol η elevates it, suggesting that plants have both mutagenic and less mutagenic TLS activities.

The stalled replication fork can be resolved by a strand switch pathway involving a DNA helicase Rad5. Disruption of both AtPol ζ and AtRAD5a shows synergistic or additive effects in the sensitivity to DNA-damaging agents. Moreover, AtPol ζ or AtRev1 disruption elevates homologous recombination frequencies in somatic tissues. These results suggest that the Rad5-dependent pathway and TLS are parallel. Plants grown in the presence of heat shock protein 90 (HSP90) inhibitor showed lower mutation frequencies, suggesting that HSP90 regulates mutagenic TLS in plants. Hypersensitivities of TLS-deficient plants to γ-ray and/or crosslink damage suggest that plant TLS polymerases have multiple roles, as reported in other organisms.

Keywords: translesion synthesis, UV, mutation, DNA damage, genome stability

INTRODUCTION

Accurate replication of genomic DNA is vital for maintaining genome integrity. However, genomic DNA sustains various forms of damage caused by internal and external agents. Ultraviolet (UV) light is a major cause of DNA damage for land plants. It induces the formation of covalent bonds between the two adjacent pyrimidines. The two major products of UV damage, cyclobutane pyrimidine dimers (CPDs) and pyrimidine (6-4) pyrimidone photoproducts [(6-4)PPs], are quickly repaired by the action of CPD and 6-4 photolyases in plant cells (Britt, 1999; Li et al., 2010; Hitomi et al., 2012). In addition, nucleotide excision repair (NER) plays an important role in removing UV damage (Kimura et al., 2004; Kunz et al., 2005; Canturk et al., 2016). Nevertheless, the remaining damage is toxic for cells because it distorts the template structure and prevents replication. This stalled replication creates a fragile single-strand region that easily leads to double-strand breaks.
(DSBs), so organisms have multiple pathways to solve the stalled replication fork. Translesion synthesis (TLS) is one such pathway in which specific polymerases (TLS polymerase) are recruited to the replication machinery and perform the bypass synthesis across the DNA damage (Vaisman and Woodgate, 2017). Figure 1A illustrates the concept of TLS activity. When encountering DNA damage, the replicative polymerase (replicase) stalls because of distorted helix geometry. TLS polymerase, carrying a flexible active site, replaces the replicase and inserts one or more nucleotide(s) opposite the damage. Because of the relaxed constraints of these active sites, the TLS polymerase has a low fidelity and often incorporates one or more incorrect nucleotide(s) that can be removed by the exonuclease activity of replicases or the mismatch repair mechanism. However, unremoved errors result in base substitutions, frameshifts, or other types of mutation. This mutagenic nature of TLS has been linked to the senescence, carcinogenesis, and evolution of organisms.

It is more than a decade since the first report of TLS in plants. The accumulation of reports from multiple groups has clarified the roles and importance of TLS not only in UV resistance but also in the maintenance of genome stability in plants. This mini-review aims to summarize 1) TLS activity in plants in comparison with that in other organisms, 2) the contribution of TLS activity to plant responses to DNA-damaging stresses, and 3) possible other functions of TLS polymerases, which may unveil novel damage-resistant mechanisms in plants.

DNA POLYMERASE FAMILY MEMBERS IN PLANTS

DNA polymerases are classified into seven families based on their amino acid sequence similarity (Ishino and Ishino, 2014). Eukaryotes have Family A, B, X, and Y polymerases, whereas Family C polymerases are only seen in bacteria and Family D and E polymerases only in archaea. Arabidopsis has at least 11 polymerases classified into five families based on comparisons with human and yeast homologs (Table 1). The representative member of Family A polymerases is Escherichia coli polymerase I, which was the first DNA polymerase to be identified (Kornberg et al., 1956). Eukaryotic members of this group are polymerase γ (Polγ) and DNA polymerase θ (Polθ). Arabidopsis also has homologs of two prokaryotic-type DNA polymerases, Pol-like A and B (Parent et al., 2011), as well as Atpolθ, which was originally isolated as the causative gene of the short-root mutant tebichi (Inagaki et al., 2006). Family B polymerases include E. coli Pol II and eukaryotic polymerases α (Polα), β (Polδ), and ε (Polε), which are involved in the replication of nuclear DNA. Polα, δ, and ε are conserved in Arabidopsis (Ronceret et al., 2005; Shultz et al., 2007; Liu et al., 2010; Iglesias et al., 2015; Pedrozo-Garcia et al., 2016). This family includes DNA polymerase ζ, the first identified TLS polymerase that is also conserved in Arabidopsis (Sakamoto et al., 2003). Family X is only conserved in eukaryotes: its representative polymerase is Polymerase β, which is involved in base excision repair. Humans have four members in Family X (Polβ, Polζ, Polσ, and terminal deoxygenase), whereas plants only have Polζ, which is phylogenetically distant from the Polα of other organisms (Filée et al., 2002; Pavlov et al., 2006). Family Y carries the largest number of TLS polymerases, including E. coli Pol IV and V; eukaryotic Polη, Polκ, Poli; and Rev1 (Ohmori et al., 2001). Rev1 was originally isolated as a responsible gene for yeast reversionless1 mutant, which carries a deoxyctydyl transferase activity (Nelson et al., 1996). Homologs of Polη, Polκ, and Rev1 are found in Arabidopsis (Takahashi et al., 2007).

Most recently, it has been shown that some members of the Archea-Eucaryotic Primase superfamily, such as human PrimPol, perform bypass synthesis across DNA damage (Iyer et al., 2005; Bianchi et al., 2013; Guilliam et al., 2015). Arabidopsis has a herpes-pox type primase (Iyer et al., 2005), although its function has not yet been investigated.

ISOLATION OF TRANSLESION SYNTHESIS POLYMERASES BASED ON ULTRAVIOLET RESISTANCE

A UVB-sensitive mutant rev3 was isolated in Arabidopsis by screening ion-beam mutagenized seedlings under non-photoreactivating conditions (Sakamoto et al., 2003). The responsible gene, AtREV3, encodes a homolog of the catalytic subunit of DNA polymerase ζ (Polζ). DNA replication in the rev3 root meristem was reduced after UVB irradiation (Sakamoto et al., 2003). AtREV7 and AtREV1 encode a regulatory subunit of Polζ and a Family Y polymerase, respectively (Takahashi et al., 2005). The rev7 and rev1 plants showed reduced growth compared with wild-type plants under chronic UVB irradiation (Takahashi et al., 2005). AtPOLH encodes a homolog of DNA polymerase η (Polη) that complements the yeast rad30 mutant (Santiago et al., 2006). Disruption of Polκ and Polη had an additive effect on Arabidopsis root growth after UVB treatment (Anderson et al., 2008). Moreover, cell death was induced at root stem cells, and the number of mitotic cells was reduced severely in the UV-irradiated Polκ- and Polη-deficient plants (Curtis and Hays, 2007). This series of studies showed that these polymerases are important in plant UV resistance. The polymerases allow DNA replication to continue, saving the stem cell from cell death and maintaining growth in the presence of harmful UV irradiation.

DAMAGE BYPASS ACTIVITIES OF TRANSLESION SYNTHESIS POLYMERASES

TLS activity has been investigated in vitro using purified or recombinant polymerases and synthetic damage-inducing templates, such as cyclobutane TT dimer (CTD) and (6-4)TT photoproducts [(6-4)TP]. These analyses revealed that the bypass efficiency is dependent on both the type of damage and the polymerases involved (Figure 1B). For example, yeast and human Polη bypasses CTD efficiently (Johnson et al., 1999; Masutani et al., 1999), but Polθ only inefficiently bypasses (6-4)TP (Johnson et al., 2001). In humans, DNA polymerase ι (Polι) inserts a nucleotide opposite 3′-T in the (6-4)TP (Vaisman et al., 2003). The 3′-end is thought to be elongated by the second polymerase (Polκ, Polθ, or...
Polθ), which has 3′-end elongation activity (Prakash et al., 2005; Seki and Wood, 2008). The subsequent *in vivo* analyses suggest that the UV damage at CC or CT sequence are also bypassed by a similar one- or two-step mechanism. Thus, TLS involves the multiple switching of polymerases at the replication site (Figure 1B; Prakash and Prakash, 2002; Bebenek and Kunkel, 2004).

The bypass activity of AtPolη for the major UV damage was examined by two groups who showed that AtPolη bypasses the CTD *in vitro* (Anderson et al., 2008; Hoffman et al., 2008). The activity of AtPolη is comparable to that of human Polη when examined at optimum salt concentration and temperature, and HsPolη, ScPolη, and AtPolη do not bypass (6-4)TP (Hoffman et al., 2008).
Research has also been done on other types of DNA damage: AtPolκ inserted an A/C opposite 8-oxoG, a common form of oxidative damage induced by reactive oxygen species (García-Ortiz et al., 2007). Deletion of the C-terminal domain elevates the processivity and fidelity of AtPolκ, suggesting that the C-terminal domain regulates the activities of this polymerase through interactions with other proteins (García-Ortiz et al., 2004; García-Ortiz et al., 2007). DNA polymerase λ bypassed 8-oxoG in both error-free (dC insertion) and error-prone (dA insertion) manners (Amoroso et al., 2011). AtRev1 inserted a C opposite an apurin/apyrimidine (AP) site (Takahashi et al., 2007), which is formed by spontaneous depurination or occurs as an intermediate in the base excision repair process (Boiteux and Guillet, 2004). AtPolIA and AtPolIB have also been shown to bypass the AP site in vitro (Baruch-Torres and Brieba, 2017).

**DETECTION OF MUTATIONS INDUCED BY TRANSLESION SYNTHESIS**

Mutations induced by TLS have been investigated in *in vivo* assay systems (Lawrence and Christensen, 1978; Lawrence and Christensen, 1979; Roche et al., 1994; Harfe and Jinks-Robertson, 2000; Yu et al., 2001; Bresson and Fuchs, 2002; Kozmin et al., 2003; Gibbs et al., 2005; Szüts et al., 2008; Yoon et al., 2009; Yoon et al., 2010). In yeast, the deletion of Polη or Rev1 reduces the UV-induced mutation frequency (Lawrence and Christensen, 1978, Lawrence and Christensen, 1979), whereas the deletion of Polη increases the frequency (Yu et al., 2001; Kozmin et al., 2003). These observations are not consistent with the *in vitro* characteristics of Polκ and Polη because Polη is less accurate than Polκ when replicating undamaged DNA (McCulloch et al., 2007; Zhong et al., 2006). Comprehensive analysis of *in vitro* and *in vivo* data suggested that Polη bypasses CTD with some errors, which are removed by the exonuclease activity of other polymerase(s) (McCulloch and Kunkel, 2008). Prakash et al. (2005) suggest that yeast Polη bypasses CPD at CC or CT sequence in an error-free manner. However, Polη seems to induce C to T transition by inserting dA opposite deaminated C or mC in CPD (Ikekata and Ono, 2011). Yeast and mammalian Polη bypass (6-4)TP in an error-prone manner (Bresson and Fuchs, 2002; Yoon et al., 2010). It is suggested that Polη contributes to the mutagenic bypass of (6-4)PP by extending the mismatched primer end caused by the action of Polη or other polymerases (Prakash et al., 2005; Hirota et al., 2010). Thus, the mutation frequency depends on the polymerases available, damage type, sequence context, and the assay system, and so on.
In plants, the reversion frequencies in *Arabidopsis* plants were measured using β-glucuronidase (GUS)-based markers (Kovalchuk et al., 2000; Nakagawa et al., 2011a; Nakagawa et al., 2011b).

The markers carry a G-T mutation, which corresponds to the 3'-T of TT sequence, a possible target of UV dimer. A misincorporation of dC opposite 3'-T leads to detect a reversion (a T to G transversion). When irradiated with UVB, the Polθ- and Rev1-deficient plants made fewer reversions in somatic cells compared with wild-type plants. By contrast, the Polη-deficient plant showed higher reversion frequencies than wild-type plants, which were reduced in Polζ and Polη double-deficient plants. From these results, the authors proposed a model in which *Arabidopsis* has two TLS pathways for responding to UV damage: a more mutagenic pathway involving Polζ and Rev1 and a less mutagenic pathway involving Polη (Nakagawa et al., 2011a). Polη bypasses CTD in an error-free manner (Figure 1C). Polκ and Rev1 bypass both CTD and (6-4)TP in an error-prone manner. The Polη inserts a nucleotide opposite (6-4)TP, which is extended by Polκ, and causes the mutation. Since the bypass activity across (6-4)TP is low anyway, the minor dC insertions would be detected in this assay system. However, other explanations are possible, for example, when UV induces a double-strand break near the TT sequence, which is wrongly repaired and causes a mutation. Also, further analysis by employing a C-containing marker is necessary to profile UV-induced mutations in plants.

### REGULATION OF TRANSLATION SYNTHESIS

Maintenance of the replication fork is crucial because stalled replication forks easily lead to strand breaks. It has been suggested that a stalled replication fork signals the modification of proliferating cell nuclear antigen (PCNA), which triggers the switching of replicase to TLS polymerase (Stelter and Ulrich, 2003; Kanao and Masutani, 2017). That is, when the PCNA is monoubiquitinated, the replicase detaches from PCNA and TLS polymerases are recruited to the replication site to perform the bypass of damaged DNA, whereas polyubiquitinated PCNA leads to the strand switch pathway. The mammalian Polη, Polκ, and Rev1 have been shown to interact with monoubiquitinated PCNA through the UBZ or UBM motif located in the C-terminal (Bienko et al., 2005; Wood et al., 2007). Moreover, Rev1 has also been shown to interact with other TLS polymerases (Guo et al., 2003) and is suggested to function as a bridge through which the best polymerase for TLS is selected (Boehm et al., 2016).

*Arabidopsis* has two copies of PCNA, but only AtPCNA2 complements the yeast pol30 mutant (Anderson et al., 2008). The AtPolη has a UBM motif and two PIP repeats but does not have a UBZ motif conserved in animal and yeast Polη. The mutant AtPolη disrupted in PIP1, PIP2, or UBM still interacts with *Arabidopsis* PCNA2 but does not fully complement yeast rad30 cells (Anderson et al., 2008). Both *Arabidopsis* PCNAs interact with ubiquitin in *N. benthamiana* cells and are ubiquitinated in vitro.
(Strzalka et al., 2013). The AtREV1 interacts with PCNA2, AtPolη, and AtREV7, a regulatory subunit of AtPol in yeast (Sakamoto et al., 2018). The processivity of rice Polα is stimulated in the presence of PCNA (Uchiyama et al., 2004). Moreover, when Arabidopsis Polλ bypasses 8-oxoG, the ratio of error-free (dC insertion) to error-prone (dA insertion) bypass changed depending on its interaction with PCNA2 (Amoroso et al., 2011). These results suggest that the modification of PCNA leads to the switching from replicase to the appropriate TLS polymerase in plants.

It has been suggested that stalled replication in plants is also resolved by a Rad5-dependent strand switch pathway (Wang et al., 2011). The rev3 and rad5a mutations caused synergistic or additive effects on root growth in plants exposed to UV, MMS, or crosslink agents compared with plants containing each single mutation (Wang et al., 2011). The rad5a plant failed to induce homologous recombination events after bleomycin treatment (Chen et al., 2008). By contrast, rev3 and rev1 plants induced significantly more recombination events after UV irradiation (Sakamoto et al., 2018). If AtRAD5a and AtREV3 work via two alternative pathways, the elevation of recombination activities in rev3 and rev1 plant could be due to the activation of a RAD5-dependent pathway (Figure 1D).

TRANSLESION SYNTHESIS AND HEAT SHOCK PROTEIN 90

The 90-kDa heat shock protein (HSP90) is an evolutionarily conserved molecular chaperone that stabilizes and activates various proteins involved in homeostasis, transcriptional regulation, chromatin remodeling, and DNA repair (Pennisi et al., 2015). The Arabidopsis genome has four copies of cytosolic HSP90 and three copies of organellar HSP90 (Krisha and Gloor, 2001). Queitsch et al. (2012) reported that the application of geldanamycin, a specific inhibitor of HSP90, to Arabidopsis plants elevated homologous recombination (HR) frequencies, suggesting that the HSP90s are involved in genome maintenance in plants.

Human HSP90 interacts with HsPolη and HsRev1 and regulates the TLS activities (Sekimoto et al., 2010; Pozo et al., 2011). The frequency of UV-induced supF mutation in hPolη-proficient cells is elevated by applying 17-AAG, an HSP90 inhibitor, due to the inhibition of error-free bypass of UV damage (Sekimoto et al., 2010). Conversely, in HsPolη-deficient cells, 17-AAG treatment reduces mutation due to the inhibition of the REV1-dependent error-prone bypass (Pozo et al., 2011). In contrast with the results in mammals, treatment with geldanamycin reduces mutation frequencies in wild-type plants, which are AtPolη-proficient (Sakamoto et al., 2018). This suggests that HSP90 mainly regulates the error-prone TLS pathway, involving AtRev1, in Arabidopsis.

TRANSLESION SYNTHESIS AND CELL CYCLE CHECKPOINT

In Arabidopsis, UVB or gamma irradiation induces programmed cell death of stem and progenitor (StPr) cells in the root meristem that depends on ataxia-telangiectasia mutated (ATM), ataxia-telangiectasia and Rad3-related (ATR), and SUPPRESSOR OF GAMMA RESPONSE1 (Curtis and Hays, 2011; Furukawa et al., 2010). Curtis and Hays (2011) investigated the time course of cell death in UV-irradiated Polη-deficient (rev3) and Polη-deficient (polh) roots as well as the roots of damage checkpoint kinase atm and atr mutants. They found that the cells in polh plants started dying at around 16 h after UV treatment, but the cells in rev3 plant started to die at around 20 h. The time courses of cell death in atr and rev3 atr plants were similar to that in rev3 plants, whereas the UV dose-dependency plots of atr, rev3 atr, and rev3 fitted similar slopes. Thus, they hypothesized that there are two types of TLS in Arabidopsis StPr cells: rapid TLS involving Polη and slow TLS involving Polη. No Polη or a failure of rapid TLS results in the accumulation of single-stranded DNA, which activates a damage checkpoint and Polη bypasses the damage (slow TLS). If both Polη and Polη are absent, or if Polη and ATR are absent, then the stalled replication fork collapses to produce DSB, and the ATM activates DSB repair pathways. A similar epistatic relationship between ATR and Polη was observed in yeast; the Polη-dependent mutation requires the yeast ATR homolog Mec1 (Pagès et al., 2009). Therefore, some, but not all, of the TLS activities appear to be controlled by checkpoint activation in both plants and microorganisms.

REV7, the regulatory subunit of Polζ, contains a HORMA (Hop1, Rev7, and MADD2) domain (Aravind and Koonin, 1998). Based on its homology to MADD2, the key component of the mitotic-spindle-assembly checkpoint, and Hop1, a meiotic-synaptonemal complex component, it has been speculated that REV7 acts as an adaptor for DNA repairs and the spindle assembly checkpoint (Aravind and Koonin, 1998). Human REV7 makes a homodimer, and REV7-MAD2 a heterodimer, in vitro (Murakumo et al., 2000). In the absence of REV7, human cells arrest in the G2/M-phase and display increased monoastal and abnormal spindles with misaligned chromosomes (Bhat et al., 2015). Crystal structure and NMR analyses showed that two copies of REV7 bind to the canonical REV7-binding motifs (RBMs) of REV3 (Rizzo et al., 2018). In plants, Arabidopsis REV7 makes a homodimer in both the nucleus and the cytosol (Sakamoto et al., 2018). However, there is only one repeat of RRM in AtREV3 sequences, which is similar to yeast REV3 (Tomida et al., 2015). Therefore, the conformation of active Polη in plants could be different from that in mammals.

TRANSLESION SYNTHESIS DNA POLYMERASE IN THE REPAIR OF DOUBLE-STRAND BREAKS OR CROSSLINK DAMAGE

Substantial evidence points to the involvement of TLS polymerases in the DSB repair pathway. For example, chicken REV3(−/−) cells and Arabidopsis rev3 plants are sensitive to ionizing radiation (Sakamoto et al., 2003; Sonoda et al., 2003). Arabidopsis Polη-disruption plants are hypersensitive to ionizing radiation and bleomycin (Furukawa et al., 2016). In yeast, Polη and Rev1 are associated with the homing endonuclease
(HO)-induced DSB end (Hirano and Sugimoto, 2006). Moreover, ScREV3 is responsible for mutations near the HO-induced cleavage site (Holbeck and Strathern, 1997; Rattray et al., 2002). These results show that some TLS polymerases, at least, have a role in DSB-repair processes in both animals and plants. Recently, DNA polymerase θ was shown to be involved in the alternative end-joining (Alt-EJ) pathway in animals (Chan et al., 2010; Wood and Doublé, 2016; Schimmel et al., 2017) and in moss (Mara et al., 2019). Polθ-deficient Arabidopsis cannot integrate T-DNA, suggesting that the Polθ stabilizes two minimally paired 3′ overhanging DNA ends during the T-DNA integration process (van Kregten et al., 2016). It is possible that TLS polymerases work in DSB repair pathway in some context.

Polθ is the best understood polymerase involved in the repair of interstrand crosslink (ICL) damage (Harris et al., 1999; Shima et al., 2003; Beagan et al., 2017). Other TLS polymerases have also been suggested to work in the process of ICL damage repair. For example, REV3−/− cells or organisms are sensitive to ICL-inducing treatments in mammals, chickens, yeast, and plants (Grossmann et al., 2000; Sakamoto et al., 2003; Nojima et al., 2005; Takahashi et al., 2005; Sarkar et al., 2006; Sharma et al., 2012). Disruption of Rev1 and Polη makes the cell or organism hypersensitive to ICL treatment (Takahashi et al., 2005; Sharma et al., 2012), and hPolq can bypass the ICL adduct in vitro (Vaisman et al., 2000). It has been suggested that ICL damage is processed by the Fanconi anemia complementation group A (FANCA)-dependent pathway, which includes nucleolytic incision, TLS, and HR (Kim and D'Andrea, 2012). Several TLS polymerases have been shown to bypass ICL damage if the DNA around the ICL is appropriately trimmed (Ho et al., 2011; Roy et al., 2016). These data suggest that TLS activities are important in overcoming ICL damage. In conclusion, TLS polymerases have multiple roles, which are critical for the genome stability of animals, plants, and microorganisms.

CONCLUSION AND FUTURE PERSPECTIVES

The deletion of TLS polymerase often causes lethal or severe phenotypes in animals (Esposito et al., 2000; O-Wang et al., 2002; Wittsieben et al., 2006; Dumstorf et al., 2006; Stallons and McGregor, 2010). By contrast, almost all TLS polymerase activities can be disrupted in plants without severe reduction of fertility. Therefore, the plant system is ideal for analyzing the function, regulation, and interaction of TLS polymerases. Information on the structure and catalytic fidelity of TLS polymerases can assist us to build a novel genome-editing enzyme with elaborate specificities. Plant cells can provide a good platform for developing these upcoming technologies.

AUTHOR CONTRIBUTIONS

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Conflict of Interest: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The handling editor is currently co-organizing a Research Topic with the author, and confirms the absence of any other collaboration.

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