UVSSA, UBP12, and RDO2/TFIIS Contribute to Arabidopsis UV Tolerance

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Plant DNA is damaged by exposure to solar radiation, which includes ultraviolet (UV) rays. UV damaged DNA is repaired either by photolyases, using visible light energy, or by nucleotide excision repair (NER), also known as dark repair. NER consists of two subpathways: global genomic repair (GGR), which repairs untranscribed DNA throughout the genome, and transcription-coupled repair (TCR), which repairs transcribed DNA. In mammals, CSA, CSB, UVSSA, USP7, and TFIIS have been implicated in TCR. Arabidopsis homologs of CSA (AtCSA-1/2) and CSB (CHR8) have previously been shown to contribute to UV tolerance. Here we examine the role of Arabidopsis homologs of UVSSA, USP7 (UBP12/13), and TFIIS (RDO2) in UV tolerance. We find that loss of function alleles of UVSSA, UBP12, and RDO2 exhibit increased UV sensitivity in both seedlings and adults. UV sensitivity in atcsa-1, uvssa, and ubp12 mutants is specific to dark conditions, consistent with a role in NER. Interestingly, chr8 mutants exhibit UV sensitivity in both light and dark conditions, suggesting that the Arabidopsis CSB homolog may play a role in both NER and light repair. Overall our results indicate a conserved role for UVSSA, USP7 (UBP12), and TFIIS (RDO2) in TCR.

Keywords: Arabidopsis, transcription coupled repair, UV, CSA, CSB, UVSSA, UBP7, TFIIS

INTRODUCTION

Unable to move, plants must adapt to their surroundings. An important and unavoidable component of a plant’s environment is solar radiation, which includes both beneficial visible light and damaging ultraviolet (UV) rays. UV radiation harms a variety of cellular components including DNA. UV damaged DNA, primarily pyrimidine photodimers, is repaired by photolyases, using the energy from visible light (light repair), and by nucleotide excision repair (NER) (dark repair) (Pang and Hays, 1991; Molinier, 2017).

Nucleotide excision repair is a conserved multistep pathway involving damage recognition, strand unwinding, excision, repair synthesis, and ligation. Damage recognition is via one of two NER sub-pathways. Global genomic repair (GGR) identifies UV damage in DNA throughout the genome, while transcription coupled repair (TCR) initiates repair of transcribed strands.

Abbreviations: CHR8, chromatin remodeling 8; CSA/B, Cockayne syndrome A/B; GGR, global genomic repair; NER, nucleotide excision repair; RDO2, reduced dormancy 2; RNAP, RNA polymerase II; TCR, transcription coupled repair; TFIIS, transcription elongation factor IIS; UBP and USP, ubiquitin specific proteases; UV, ultraviolet irradiation; UVSSA, UV stimulated scaffold protein A.
Gymnosperm site Gymnosperm UVSSA homologs were accessed via the PLAZA Phylogenic Tree Construction MATERIALS AND METHODS UBP12/13, and RDO2 in UV tolerance. Arabidopsis UVSSA homolog and examine the roles of UVSSA, 2017; Godoy Herz et al., 2019). In this study we identify the including in response to light (Dolata et al., 2015; Antosz et al., 2011; Cui et al., 2013; Derkacheva et al., 2016; Jeong et al., 2017; An et al., 2018). The Arabidopsis TFIIIS homolog is Reduced Dormancy 2 (RDO2, At2g38560), which is required for regulation of seed dormancy by Delay of Germination 1 (DOG1) (Léon-Kloofterzield et al., 1996; Grasser et al., 2009; Liu et al., 2011; Mortensen and Grasser, 2014). RDO2/TFIIIS has also been implicated in mRNA processing in plants, including in response to light (Dolata et al., 2015; Antosz et al., 2017; Godoy Herz et al., 2019). In this study we identify the Arabidopsis UVSSA homolog and examine the roles of UVSSA, UBP12/13, and RDO2 in UV tolerance.

MATERIALS AND METHODS Phylogenic Tree Construction Gymnosperm UVSSA homologs were accessed via the PLAZA gymnosperm site1 (Proost et al., 2015) while all other homologs were identified via KEGG (Kyoto Encyclopedia of Genes and Genomes2). UVSSA amino acid sequences were aligned in CLUSTAL Omega (Sievers et al., 2011) using the default settings and saved in NEXUS format for phylogenetic analysis. The aligned amino acid sequences were then analyzed by maximum parsimony as implemented in PAUP∗ version 4.0b8/4.0d78 using the default settings unless otherwise specified (Swofford, 2002). One million maximum parsimony heuristic search replicates were performed with random sequence addition, tree bisection and reconnection branch swapping on only the best trees, multiple trees saved at each step, and retention of all best trees. In addition, 1 million random sequence addition fast addition bootstrap search replicates were performed with retention of all groups consistent with 50% bootstrap consensus.

Plant Material and Growth Conditions The following T-DNA alleles were used in this study: SALK_030558 (AtCSA-1) (Lee et al., 2010), SALK_000799 and SAIL_273_G11 (CHR8), SAIL_58_C12 and SALK_061538 (UVSSA), GABI_742C10 (UBP12) (Cui et al., 2013), and SALK_027259 (RDO2) (Grasser et al., 2009; Liu et al., 2011). Col-0 was used as the wild type control for the SALK and GABI lines (Alonso et al., 2003; Kleinboelting et al., 2012), while Col-3 was used as the control for the SAIL lines (Sessions et al., 2002). All plant material was obtained from the Arabidopsis Biological Resource Center (ABRC) (Columbus, OH, United States) or the Nottingham Arabidopsis Stock Centre (NASC) (Nottingham, Loughborough, United Kingdom). Alleles were genotyped with the primers listed in Supplementary Table S1 along with T-DNA specific primers LBb1.3: ATTTTGCATATTCCGAAC (SALK lines), LB3SAIL: TAGCATCTGAATTTCGAGCA (GABI lines), and GK_8409: ATATTGACCATCATACTCATTGC (GABI line). For plant growth, seeds were sterilized and plated on Linsmaier and Skoog (LS) media (Caisson, Smithfield, UT, United States) with 0.6% sucrose and 0.8% Phytoblend (Caisson). After 2–3 days of stratification at 4°C, plates were moved to an incubator with fluorescent bulbs (100 μM photons m-2 s-1) and grown under long day conditions (16 h light/8 h dark) at 20°C and 50% relative humidity. For adult growth, 14 day old plants were transplanted into soil (Sunshine mix no. 1, Sun Gro, Bellevue, WA, United States) and grown under the same conditions.

RNA Extraction and RT-PCR Ribonucleic acid was extracted from approximately fifty 7-day-old seedlings per genotype with the RNeasy plant mini kit (Qiagen, Hilden, Germany) according to the manufacturer’s instructions including a DNase treatment. RNA was quantified with a Nanodrop spectrophotometer (Thermo Scientific) and 1 μg used to synthesize cDNA, using the Maxima First Strand cDNA synthesis kit (Fermentas, Waltham, MA, United States). For semi-quantitative RT-PCR, CHR8, UVSSA, AtCSA-1, and UBP12 were amplified for 30 cycles and RDO2 for 26 cycles using the primers indicated (Supplementary Table S1) and the Actin loading control amplified for 22 cycles. For quantitative real time PCR, cDNA was diluted 40 fold and PCR performed using SsoFast EvaGreen Supermix (Bio-Rad, Hercules, CA, United States), a CFX Connect Real time PCR detection system 1https://bioinformatics.psb.ugent.be/plaza/versions/gymno-plaza/
2http://www.kegg.jp/
(Bio-Rad), and the primers listed in Supplementary Table S1. EF1a (At5g60390) (Jain et al., 2006; Hossain et al., 2012) was used to normalize sample loading and three technical replicates were analyzed per sample.

**Adult Growth Analysis**

The following data was collected from plants transplanted to soil: flowering time (day the first bud is detected), rosette diameter at 4 weeks, number of shoots and siliquae length at 6 weeks.

**UV Sensitivity Assays**

Seeds were plated, stratified, and grown vertically in the conditions above for 3 days, then seedlings irradiated with 1000 J m\(^{-2}\) UV-C (converting to 65 s exposure to shortwave UV lamp XX-15S, UVP/LLC, Upland, CA, United States). Plates were rotated 90° and incubated in either long day or dark conditions for the indicated number of days, then scanned. Image J was used to measure root and hypocotyl length.

For adult UV assays, 21 day old plants in soil were irradiated with 500 J m\(^{-2}\) UV-C, incubated in the dark for 3 days, then returned to long day conditions. Three days later, individual leaves were scored as either undamaged (green) or damaged (yellow or brown), and % damaged leaves (number of damaged leaves/total leaves) was calculated for all plants.

**Statistical Analysis**

All experiments were performed at least twice and representative experiments shown. Two-tailed student’s t-tests (\(p \leq 0.05\)) were used to assess statistical significance.

**RESULTS**

In this study we identify the Arabidopsis UVSSA homolog. Arabidopsis UVSSA (encoded by At3g61800) is 39% and 28% identical to rice and human UVSSA, respectively. Clear UVSSA homologs are found throughout the animal and plant kingdoms including angiosperms, gymnosperms, ferns, and moss. One million maximum parsimony phylogenetic sequence replicates for UVSSA homolog amino acid sequences recovered a single most parsimonious tree (score 2561) (Figure 1) that is topologically congruent with well supported hypotheses of plant evolutionary history (Morris et al., 2018). Conserved domains in UVSSA proteins include ENTH/VHS in the N terminus and DUF2043 in the C terminus (Figure 2). ENTH/VHS domains are multi-helical with an alpha-alpha 2-layered structural fold, while DUF2043 is an approximately 100 amino acid long UVSSA-specific domain, with an alpha-alpha 2-layered structural fold, while DUF2043 is expressed throughout the plant, consistent with the broad role of these genes in development (Grasser et al., 2009; Cui et al., 2013; Derkacheva et al., 2016), while AtCSA-1, CHR8, and UVSSA are expressed at lower levels (Schmid et al., 2005). With respect to relative levels of expression (Supplementary Figure S1B), CHR8 and UVSSA are enriched in mature pollen, while RDO2, AtCSA-1, CHR8, and UVSSA are up-regulated more than two-fold in dry seed, perhaps contributing to maintenance of seed genome integrity (Waterworth et al., 2015).

Public expression data was also examined to determine the effect of potentially mutagenic stress on expression of these genes. CHR8 was found to be upregulated by genotoxic stress induced by bleomycin and mitomycin C treatment, consistent with previous reports (Molinier et al., 2005), in both the shoot and root, but the other genes were not, while UV-B treatment did not result in major changes to the levels of any of the genes (Supplementary Figure S2; Kilian et al., 2007).

In order to examine the role of these genes in Arabidopsis UV tolerance, T-DNA insertion mutants were obtained. Previously described alleles of AtCSA-1 (SALK_030558) (Lee et al., 2010) and RDO2 (SALK_027259) (Grasser et al., 2009; Liu et al., 2011) were utilized. UBP12 allele GABI_742C10 (ubp12-2) has previously
been shown to result in reduced levels of both **UBP12** and **UBP13**, thus acts as a weak double mutant (Cui et al., 2013). In previous studies RNAi lines of **CHR8** were shown to exhibit UV sensitivity (Shaked et al., 2006). Here we examine two T-DNA alleles of **CHR8**, **chr8-1** (SALK_000799) and **chr8-2** (SAIL_273_G11) (**Figure 3A**). For **UVSSA**, two T-DNA alleles were examined, **uvssa-1** (SAIL_58_C12), located 38 bp upstream of the start codon, and **uvssa-2** (SALK_061538), located in the first intron past the start codon.

We examined the effect of these alleles on gene expression using semi-quantitative RT-PCR. Primers flanking the **chr8-1** and **chr8-2** insertion sites detected no **CHR8** transcript, indicating these are null alleles (**Figure 3B**). Semi-quantitative RT-PCR with T-DNA insertion flanking primers also confirmed loss of transcript in the **atcsa-1**, **ubp12**, and **rado2** lines (**Supplementary Figure S3**). For **UVSSA**, we utilized primers in the first and second coding exons, since the effect of T-DNA insertion on coding sequences was our primary concern. **uvssa-2** results in a null allele, but in **uvssa-1** both the predicted band and a larger band were detected (**Figure 3C**). The size of the larger band was consistent with that of the unspliced transcript, so we hypothesized that **uvssa-1** insertion affected intron splicing [note the **uvssa-1** samples did not result in larger gDNA-size bands of **CHR8**, thus were not gDNA contaminated (data not shown)]. Real-time qPCR with an intron-specific primer was used to quantify the effect of the **uvssa-1** allele on splicing, and large amounts of the unspliced product were detected (**Figure 3D**). Due to the presence of an in frame stop codon in the intron, this transcript results in a truncated 77 amino acid product. **uvssa-1** also resulted in increased levels of correctly spliced **UVSSA**. Thus **uvssa-1** would be predicted to result in increased levels of both full length and truncated **UVSSA**.

Mutant alleles of the TCR genes were grown in long day conditions with their respective controls and their developmental phenotypes examined. **ubp12-2** mutants exhibited decreased rosette size, early flowering (days), and decreased apical dominance (increased number of shoots) (**Supplementary Figure S4**), consistent with previously described phenotypes (Cui et al., 2013; Derkacheva et al., 2016). The other mutant alleles did not exhibit any developmental
As previously reported, we find atcsa-1, uvssa-2, and ubp12 mutants exhibit increased UV sensitivity in the dark (Figures 4D and Supplementary Figure S5C). ubp12 allele, uvssa-2, also exhibited increased UV sensitivity in the dark (Figure 4E). The uvssa-1 allele, which results in increased levels of both truncated and full length UVSSA, did not exhibit either increased or decreased UV tolerance following 2 or 3 days of dark incubation (Figure 4D and Supplementary Figure S5C). ubp12-2 allele, uvssa-2, and rdo2 exhibited increased dark UV sensitivity in hypocotyls (but not roots) after 2 days of incubation, but not after 3 days (Figure 4F and Supplementary Figure S5D). We also examined UV sensitivity in adult plants following dark incubation and found that, as in seedlings, atcsa-1, chr8, uvssa-2, ubp12, and rdo2 mutants exhibit UV sensitivity, while uvssa-1 does not (Figure 5).

To examine the specificity of the UV sensitivity of these alleles, they were also incubated in light (long day) following UV treatment. atcsa-1, uvssa-2, and ubp12 were not UV sensitive in the light (Figures 4A,E,F), consistent with the dark specific role of NER. Surprisingly, both chr8 alleles exhibited UV sensitivity following light incubation (Figures 4B,C), exhibiting the expected dose dependence, with the more severely truncated chr8-1 allele demonstrating a stronger root phenotype in both light and dark. This result suggests that CHR8 plays a role in light repair, distinct from the other components of the TCR pathway.

**DISCUSSION**

In this study, we examined the UV sensitivity of mutant alleles of Arabidopsis homologs of genes implicated in mammalian TCR. As previously reported, we find atcsa-1 mutants exhibit increased dark specific UV sensitivity (Biedermann and Hellmann, 2010). Our atcsa-1 dark root phenotype is not as strong as that of mutants in other TCR components such as CSB/CHR8 and UVSSA, this may be due to redundancy with AtCSA-2/CSAat1B.

The Arabidopsis homolog of mammalian CSB [also known as Excision Repair Cross-Complementing 6 (ERCC6)] and yeast Rad26 is CHR8 (Kunz et al., 2005; Singh et al., 2010). In this study, we utilized CHR8 T-DNA lines and observed increased UV sensitivity following dark incubation, consistent with previous studies using CHR8 RNAi lines (Shaked et al., 2006). Also, unique among the TCR mutants we examined, chr8 alleles exhibited increased UV sensitivity following light incubation. Mammalian CSB has been implicated in regulation of transcription and
FIGURE 4 | UV tolerance of mutants in TCR genes. Relative growth of roots and hypocotyls of (A) atcssa-1, (B) chr8-1, (C) chr8-2, (D) uvssa-1, (E) uvssa-2, (F) ubp12, and (G) rdo2 after 1000 J m$^{-2}$ UV treatment, followed by 2 days of long-day (light) or dark incubation. Data are expressed as length relative to unirradiated control of the same genotype. Values are means ± SE ($n = 20$), *$p \leq 0.05$ of mutants vs wild type.

base excision repair in addition to TCR (Stevnsner et al., 2008; Boetefuer et al., 2018), so one of these roles may contribute to the chr8 light UV sensitivity phenotype.

In humans, mutation of UVSSA results in defective TCR and UV sensitive syndrome (Cleaver, 2012). Loss of the C. elegans UVSSA homolog also results in increased UV sensitivity (Babu and Schumacher, 2016). While UVSSA is conserved throughout the animal kingdom (Nakazawa et al., 2012), it is absent from Drosophila. However, Drosophila also lack CSA and CSB homologs, and do not appear to perform TCR (Sekelsky, 2017). Yeast also lack UVSSA, although both S. cerevisiae and S. pombe have CSB homologs and perform TCR (Li and Li, 2017; Xu et al., 2017). Here we show that UVSSA is found throughout the plant kingdom, with conserved ENTH/VHS and DUF2043 domains. Recently, the region corresponding to amino acid 400–415 of human UVSSA was found to be well conserved in animals and required for TFIIH interaction (Okuda et al., 2017). Although this region is still acidic in plants, it is not well conserved with human UVSSA and plants lack F408 and V411, which are required for TFIIH interaction and TCR in humans (Okuda et al., 2017), as well as K414, which is mono-ubiquitinated (Higa et al., 2018). In addition, residues 251–254 of human UVSSA have been shown to be required for USP7 interaction, CSB stability, and TCR (Higa et al., 2016), yet this sequence is also not conserved in plants. Nonetheless our data show that lack of UVSSA results in dark specific UV sensitivity in Arabidopsis, consistent with a role in NER.

Arabidopsis USP7 homologs UBP12 and UBP13, like other ubiquitin specific proteases, play important roles in plant development and environmental response (Zhou et al., 2017). UBP12/13 interact with LHP1 and deubiquitinate RGFR1 and
FIGURE 5 | UV tolerance in adult plants. Percentage damaged leaves after 500 J m⁻² UV treatment, followed by 3 days of dark incubation. Values are means ± SE (n = 6), *p ≤ 0.05 of mutants vs respective wild type.

MYC2 (Derkacheva et al., 2016; Jeong et al., 2017; An et al., 2018). Our results here indicate that UBPI2 (and UBPI3) are involved in UV tolerance, suggesting they may also deubiquitinate UVSSA and CSB, as has been proposed for mammalian USP7 (Geijer and Marteijn, 2018). UBPI2 and UBPI3 act redundantly, and double null alleles are inviable due to pollen defects (Ewan et al., 2011; Derkacheva et al., 2016). Here we use an allele of UBPI2, ubp12-2, which also results in a partial decrease in UBPI3 level, and resulting in a weak double mutant (Cui et al., 2013). However, because this is a weak (non-null) double mutant, we may be underestimating the role of UBPI2/13 in UV tolerance.

In mammals, in addition to acting during transcript elongation, TFIIS has been shown to facilitate transcription re-initiation following RNAP arrest, and is recruited to the stalled polymerase in a CSB and CSA dependent manner (Donahue et al., 1994; Kalogeraki et al., 2005; Fousteri et al., 2006; Dutta et al., 2015). In yeast, loss of TFIIS only results in increased UV sensitivity in a GGR-deficient background, however, the same is true of CSB homolog Rad26 (Wong and Ingles, 2001). In mammals, reduction of TFIIS resulted in reduced RNA synthesis recovery, but had no effect on UV sensitivity (Jensen and Mullenders, 2010). In this study we detected a UV sensitive phenotype in TFIIS deficient Arabidopsis (rdo2), however, it was milder than observed for the other TCR mutants and not detectable 3 days after seedling UV treatment. Interestingly, the UV sensitive phenotype of both rdo2 and atcsa-1 was stronger in hypocotyls than in roots, at 2 days than at 3 days, and in adults than in seedlings, suggesting the role of these genes in UV tolerance may vary with tissue, time, and phenotype assessed (growth versus tissue death).

CONCLUSION

In this study, we have identified the Arabidopsis UVSSA homolog and shown that Arabidopsis UVSSA, USP7 (UBP12/13), and TFIIS (RDO2) homologs contribute to UV tolerance, along with CSA and CSB (CHR8) homologs, suggesting conservation in the mechanisms of TCR.

DATA AVAILABILITY

All datasets for this study are included in the manuscript and the Supplementary Files.

AUTHOR CONTRIBUTIONS

WAK, AS, and DS performed the experiments. JM conducted the phylogenetic analysis. DS wrote the first draft of the manuscript. All authors contributed to revised manuscript and approved the final version, designed the experiments and analyzed the data.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpls.2019.00516/full#supplementary-material
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