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The UVR8 UV-B Photoreceptor: Perception, Signaling and Response

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Ultraviolet-B radiation (UV-B) is an intrinsic part of sunlight that is accompanied by significant biological effects. Plants are able to perceive UV-B using the UV-B photoreceptor UVR8 which is linked to a specific molecular signaling pathway and leads to UV-B acclimation. Herein we review the biological process in plants from initial UV-B perception and signal transduction through to the known UV-B responses that promote survival in sunlight. The UVR8 UV-B photoreceptor exists as a homodimer that instantly monomerises upon UV-B absorption via specific intrinsic tryptophans which act as UV-B chromophores. The UVR8 monomer interacts with COP1, an E3 ubiquitin ligase, initiating a molecular signaling pathway that leads to gene expression changes. This signaling output leads to UVR8-dependent responses including UV-B-induced photomorphogenesis and the accumulation of UV-B-absorbing flavonols. Negative feedback regulation of the pathway is provided by the WD40-repeat proteins RUP1 and RUP2, which facilitate UVR8 redimerization, disrupting the UVR8-COP1 interaction. Despite rapid advancements in the field of recent years, further components of UVR8 UV-B signaling are constantly emerging, and the precise interplay of these and the established players UVR8, COP1, RUP1, RUP2 and HY5 needs to be defined. UVR8 UV-B signaling represents our further understanding of how plants are able to sense their light environment and adjust their growth accordingly.

INTRODUCTION

Plant Photoreceptors and Photomorphogenesis

Spanning from times of ancient Greek philosophy to the present day, it has long been observed that plants are plastic and are able to change their growth and development appropriately in response to light (Schäfer and Nagy 2006). As sessile organisms, plants have had to evolve many mechanisms to adapt to the changing environment. Moreover, since plants are photoautotrophic organisms, they ultimately need to adjust their growth to suit the surrounding light conditions. One simply has to compare a plant growing in near or complete darkness to the same species exposed to full sunlight to appreciate the regulation that light can exert on plant growth and development. An important part of this process is how light is used as an informational source though specific perception. These mechanisms are independent of photosynthesis and are collectively known as photomorphogenesis. Published works on plant photomorphogenesis reach as far back as the 17th and 18th century (Briggs 2006, Schäfer and Nagy 2006). Among the early reports, keen observations of Charles and Francis Darwin in 1880 on the bending of grass coleoptiles towards unilateral light described the process of phototropism (Darwin 1880, Briggs 2006). Thus, we have known for many years that light serves as an informational cue that plants use to adjust growth and development (Kami et al. 2010).

With the advent of molecular genetics, it was discovered that plants use a multitude of sensory proteins to create a link between environmental stimuli and physiological responses. In the case of light, plants use a wide variety of highly sensitive and sophisticated photoreceptors to perceive even minor changes in light quality (from UV-B to far-red light), quantity, direction and duration. Arabidopsis (*Arabidopsis thaliana*) makes use of no less than 13 photoreceptors, which include five red/far-red perceiving phytochromes (phyA-E), two phototropins (phot1 and phot2), two cryptochromes (cry1 and cry2) and three members of the Zeitlupe family (ZTL, FKF1 and LKP2) to perceive blue light, and the more recently characterized UV-B photoreceptor UVR8 (Kami et al. 2010, Heijde and Ulm 2012) (Figure 1). These receptors allow the plant to deploy wavelength-specific responses. Specific light perception helps the plant optimize photon capture and photosynthesis in sunlight by regulating processes like de-etiolation, phototropism, shade-avoidance, stomatal opening and the intracellular distribution of chloroplasts in response to weak or strong light intensity. More indirectly, light optimizes plant growth and reproductive success by regulating germination, flowering and entrainment of the circadian clock (Sullivan and Deng 2003, Kami et al. 2010, Arsovski et al. 2012). However, plants maintain a love/hate relationship with sunlight, as illustrated by high light stress (Li et al. 2009, Takahashi and Badger 2011) and potentially harmful UV-B radiation (herein referred to as UV-B).

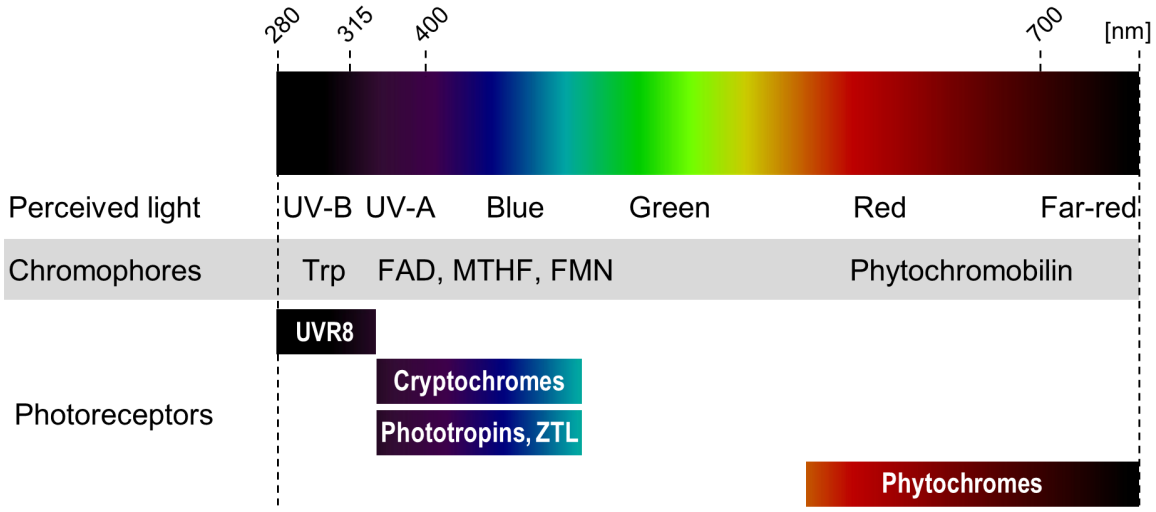


Figure 1. Photoreceptor-mediated light perception in higher plants.

Information from a large part of the solar spectrum is perceived by the currently known 13 plant photoreceptors in Arabidopsis and used to deploy wavelength-specific responses. UVR8 is the only UV-B photoreceptor identified to date and uses specific intrinsic tryptophans (Trp) as an UV-B-activated chromophore. To absorb light in the UV-A/blue part of the spectrum, cryptochromes use flavin adenine dinucleotide (FAD) and methenyltetrahydrofolate (MTHF), and phototropins and the Zeitlupe family (ZTL) proteins use flavin mononucleotide (FMN) as their chromophores. Phytochromes are red/far-red photoreceptors that use a plant-specific linear tetrapyrrol (phytochromobilin) for light capture. Image reprinted from Heijde and Ulm (2012) with permission, from Trends in Plant Science, Volume 17 © 2012 by Elsevier (www.elsevier.com).

UV-B

UV-B (280-315 nm) comprises one of the three classes of ultraviolet radiation and is positioned between UV-A (315-400 nm) and UV-C (100-280 nm) in the electromagnetic spectrum (Figure 1). The permeability of the atmospheric ozone layer to UV radiation begins within the UV-B range of wavelengths. Hence, natural sunlight contains UV-A and a part of UV-B but undetectable levels of UV-C and UV-B below 290nm. The level of UV-B reaching the earth's surface is highly dynamic and depends on large-scale factors such as stratospheric ozone, solar angle (latitude, season, time of day), altitude, tropospheric pollution and cloud cover, and small-scale variables such as surface reflectance and shading, e.g. in plant canopies (McKenzie et al. 2003, Paul and Gwynn-Jones 2003). However, UV-B makes up less than 0.5% of solar energy at the earth's surface (Blumthaler 1993). Regardless, the biological effects of UV-B are significant due to the energy that short-wavelength UV-B photons contain. An array of biologically active molecules, including nucleic acids, can absorb UV-B which leads to damage (e.g. DNA damage). Thus, UV-B is a potential abiotic stress factor for any organism exposed to sunlight, and particularly for photosynthetic organisms such as plants. Nevertheless, as can be appreciated in nature when wandering through exposed fields, plants are able to tolerate UV-B even under levels that accompany a long summer day with damage only seldom observed. Plants are indeed able to acclimate to UV-B, and a unique molecular signaling pathway exists to facilitate this (Figure 2). UV-B perception is via the UV-B photoreceptor UV RESISTANCE LOCUS 8 (UVR8; At5g63860) which is linked to a signaling pathway that leads to a complex series of plant responses to UV-B (Heijde and Ulm 2012).

In this chapter we will discuss the UVR8 signaling pathway in *Arabidopsis thaliana*. We will present the current state of the field concerning UV-B perception, the molecular mechanisms of the signalling pathway and the major physiological responses. As will be outlined, the UVR8-mediated pathway is of crucial importance for UV acclimation and thus finally UV-B tolerance. We will not however cover in any detail ecological and agronomical aspects of the impact of UV-B on plants, as well as UV-B stress signaling (i.e. where UV-B-mediated damage is perceived), for which the reader is referred to the recent literature (Britt 2004, Ballare et al. 2011, Ballare et al. 2012, Mannuss et al. 2012, Gonzalez Besteiro and Ulm 2013, Wargent and Jordan 2013).

PERCEPTION OF UV-B

Plants are able to specifically perceive UV-B photons. To do so, a perception mechanism is required to distinguish UV-B from other light qualities. Distinct responses to UV-B irradiation have been reported for some time in different plant species (e.g. Wellmann 1976, Ballare et al. 1991, Beggs and Wellmann 1994, Ballare et al. 1995, Frohnmeyer et al. 1999), with more recent reports focussed on Arabidopsis (e.g. Christie and Jenkins 1996, Kim et al. 1998, Boccalandro et al. 2001, Brosche et al. 2002, Ulm et al. 2004, Brown et al. 2005, Favory et al. 2009). However, prior to the molecular identification of UVR8 as the UV-B photoreceptor in

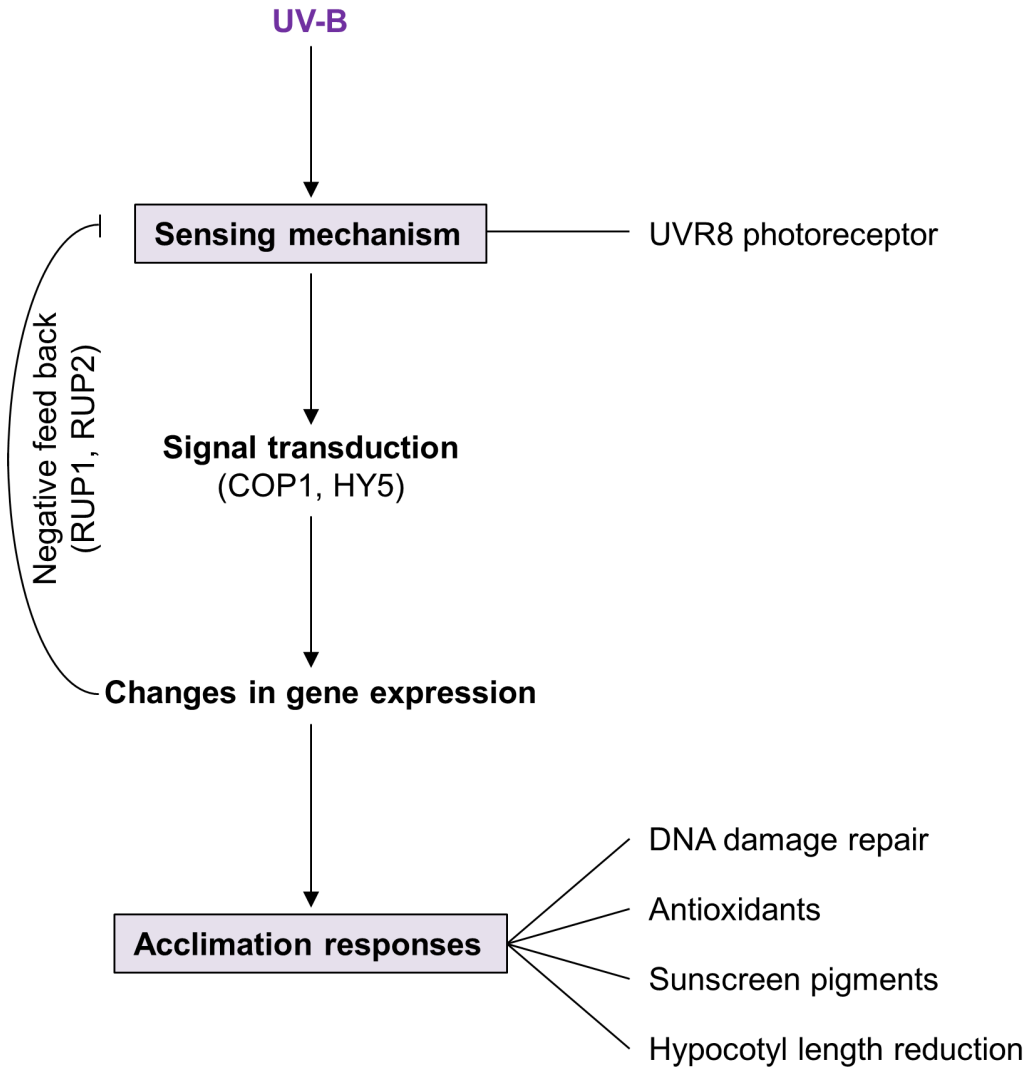


Figure 2. Schematic illustration of UV-B perception, signaling and responses in Arabidopsis (scheme adapted for UV-B from Li et al. 2009).

Plants sense UV-B with the UVR8 photoreceptor. Activation of UVR8 leads to interaction with the E3 ubiquitin ligase COP1 and stabilization of the bZIP transcription factor HY5 that relays the UV-B signal resulting in changes in gene expression. Among the suite of UV-B-responsive genes are those that encode proteins that function in UV-B-induced photomorphogenesis and acclimation. These include proteins involved in UV protection (e.g. phenylpropanoid biosynthesis pathway contributing UV-B-absorbing sunscreen pigments), scavenging of reactive oxygen species (antioxidants), DNA damage repair (e.g. photolyases) and hypocotyl growth inhibition. Also, the WD40-repeat proteins RUP1 and RUP2 are induced upon UV-B, which facilitate negative feedback of the UV-B signalling pathway by directly inactivating UVR8.

2011 (Rizzini et al. 2011), the nature of UV-B perception in plants was unclear. Speculations ranged from the existence of distinct UV-B perception linked to a regulatory molecular signaling pathway to that no UV-B-dedicated photosensory mechanism existed at all and UV-B-induced changes in secondary metabolism lead to the observed UV-B photomorphogenesis (Björn 1999, Jansen 2002, Frohnmeyer and Staiger 2003, Ulm and Nagy 2005, Ulm 2006, Jenkins and Brown 2007). With identification of UVR8 as the UV-B photoreceptor, a new era has begun regarding our understanding of plant UV-B responses, and the relationship of UV-B to plant photomorphogenesis in general.

The UV-B Photoreceptor UVR8

Arabidopsis UVR8 was originally identified through a genetic screen for mutants hypersensitive to UV-B (Kliebenstein et al. 2002). A physiological role for UVR8 in UV-B tolerance was further illustrated by the sensitivity of *uvr8* mutants compared to wild type under simulated sunlight (Favory et al. 2009). UVR8 is a seven-bladed β-propeller protein of 440 amino acids (Christie et al. 2012, Wu et al. 2012). Molecular and biochemical studies have demonstrated that in light conditions devoid of UV-B, the UVR8 photoreceptor exists as homodimer which undergoes instant

monomerization following UV-B exposure, a process dependent on an intrinsic tryptophan residue that serves as an UV-B chromophore (Rizzini et al. 2011) (Figures 3A and 4). More recently, two independent studies have resolved the crystal structure of the β-propeller core of UVR8, detailing the mechanism behind UVR8-mediated UV-B perception (Christie et al. 2012, Wu et al. 2012). Following UV-B perception and UVR8 monomerisation, the UVR8 dimer is able to regenerate from the extant UVR8 monomer pool, which effectively switches off UV-B molecular signaling (Heijde and Ulm 2013, Heilmann and Jenkins 2013) (Figure 4).

UVR8 structure and perception mechanism

Chromophore

A light-reactive chromophore is needed for photoreceptor function. Many photoreceptors make use of bound cofactors as chromophores, for example phytochromobilin for phytochromes, flavin mononucleotide (FMN) for phototropins, and flavin adenine nucleotide (FAD) and possibly a pterin for cryptochromes (Kami et al. 2010, Liu et al. 2010) (Figure 1). In the case of UVR8, a set of biochemical and genetic data strongly indicated that an intrinsic

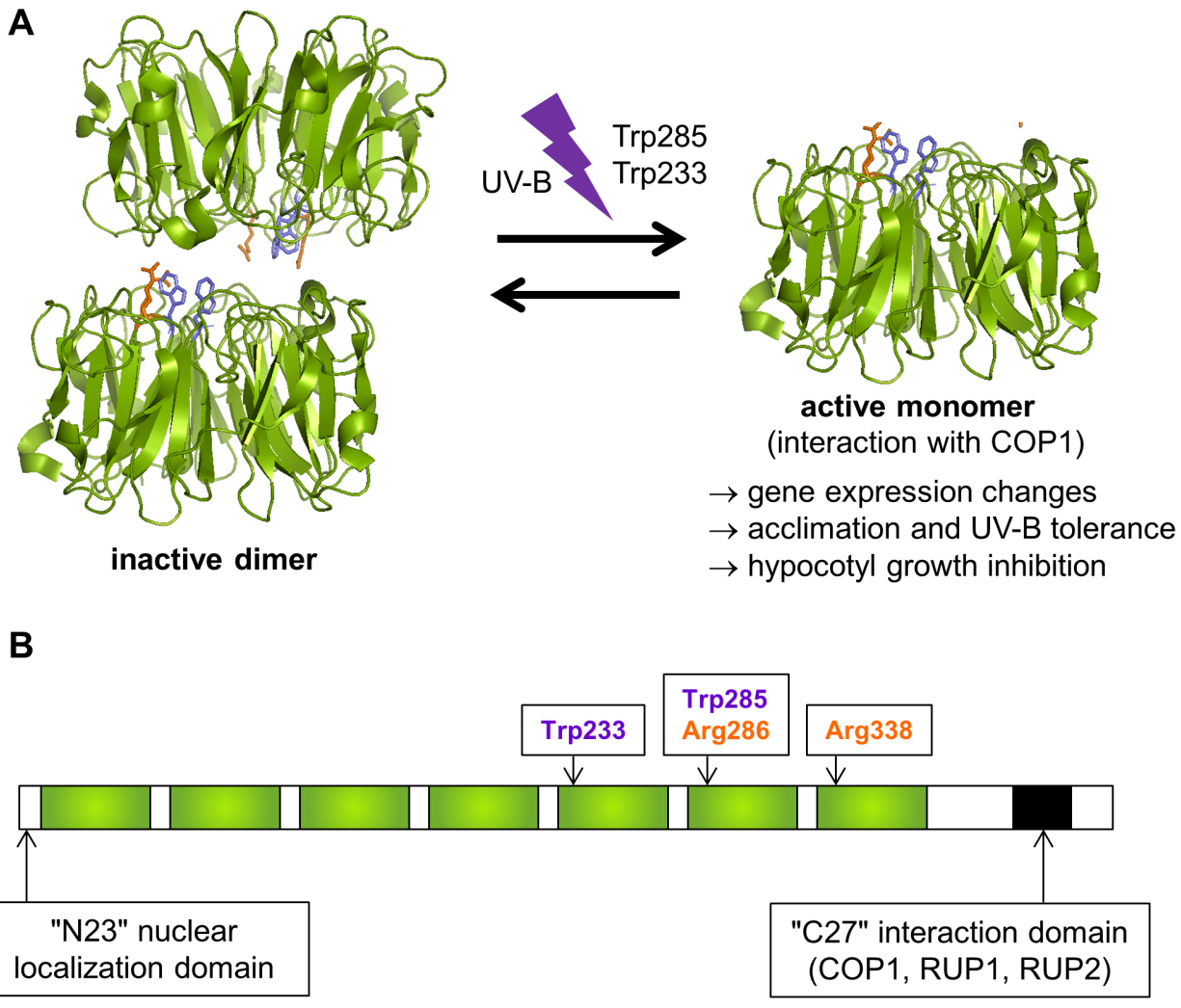


Figure 3. UVR8 homodimer/monomer and structure-function.

(A) UVR8 protein model generated from the solved core structure (UVR8$^{12-381}$) (Wu et al. 2012), indicating UV-B-dependent monomerisation of the UVR8 homodimer. Arginin (Arg) residues at position 286 and 338 (highlighted in orange) facilitate hydrogen bonds that hold the homodimer together whilst tryptophan (Trp) residues at position 285 and 233 (highlighted in blue) serve as chromophores for the perception of UV-B leading to monomerisation (see text for more detailed information). (B) Schematic representation of the UVR8 structure. Positioning of key Arg and Trp residues and functional domains are indicated.

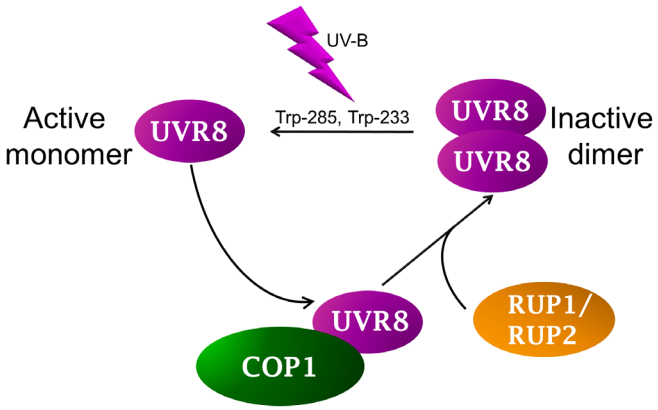


Figure 4. The UVR8 photocycle.

The UVR8 homodimer is monomerised by UV-B, with UV-B absorption proceeding via a tryptophan-based chromophore. The UVR8 monomer interacts directly with COP1 to initiate UV-B signaling. UVR8 monomer is redimerized through the action of RUP1 and RUP2, which disrupts the UVR8-COP1 interaction, inactivates the signaling pathway and regenerates the UVR8 homodimer again ready for UV-B perception.

tryptophan, namely tryptophan-285 (Trp-285 or W285), functions as a chromophore for UV-B perception (Rizzini et al. 2011). In agreement, purified UVR8 dimer devoid of any form of prosthetic chromophore is able to perceive UV-B and monomerize in vitro (Christie et al. 2012, Wu et al. 2012).

Tryptophan is a naturally UV-absorbing aromatic amino acid. Sequence analysis shows that UVR8 is particularly enriched in tryptophans, which can be found 14 times in UVR8 versus only 4 times in human RCC1 (Regulator of Chromosome Condensation), which is structurally related to UVR8 (Kliebenstein et al. 2002, Rizzini et al. 2011, Wu et al. 2011). Trp-285 was shown to be essential for UVR8 monomerization as mutation of Trp-285 to phenylalanine ($UVR8^{W285F}$) rendered UVR8 as a constitutive dimer whereas Trp-285 to alanine ($UVR8^{W285A}$) resulted in a constitutive UVR8 monomer (Rizzini et al. 2011). However, it should be noted here that the constitutive monomer form of $UVR8^{W285A}$ is apparent with gel electrophoresis of nonboiled protein extracts from yeast and plants (Rizzini et al. 2011, O'Hara and Jenkins 2012). In contrast with these gel-based assays, size exclusion chromatography showed that purified $UVR8^{W285A}$ is a dimer in vitro that does not monomerize in response to UV-B (Christie et al. 2012, Wu et al. 2012). However, the available data suggests that $UVR8^{W285A}$ is a weak dimer and that the mutant protein very likely exists as a monomer in vivo (Rizzini et al. 2011, O'Hara and Jenkins 2012). Notwithstanding this, further structural and biophysical studies have since confirmed and further detailed the importance of Trp-285 in UV-B perception (Christie et al. 2012, Wu et al. 2012).

Structural basis of UVR8 dimer formation and UV-B-dependent monomerization

Several recent works have revealed much about how UVR8 exists as a homodimer capable of monomerization upon UV-B exposure. These publications present UVR8 predictive models arising from biochemical and structural analysis followed up by systematic mutational analysis of key residues. Of the 14 UVR8 tryptophans mentioned above, six (plus 1 tyrosine) are located within the protein core contributing to maintain the β-propeller structure, one is situated in the C-terminal part that was not included in the core structure, and seven are found at the homodimeric interface (Christie et al. 2012, O'Hara and Jenkins 2012, Wu et al. 2012) (Figure 5). Amongst the tryptophans at the dimer interface, mutational analysis showed that Trp-233, Trp-285, Trp-337 and Trp-94 of the opposing UVR8 monomer contribute to exciton coupling within the structure (Christie et al. 2012). These four residues were thus proposed to form a cross-dimer "tryptophan pyramid" involved in UV-B sensing (i.e. two "pyramids" per UVR8 homodimer) (Christie et al. 2012). Indeed, previous work mentioned above highlighted the importance of Trp-285 in maintaining the UVR8 homodimer, as $UVR8^{W285A}$ rendered UVR8 as a monomer that constitutively interacted with CONSTITUTIVELY PHOTOMORPHOGENIC 1 (COP1; At2g32950) in yeast (Rizzini et al. 2011). However, whether each of the four "pyramid" tryptophans play a role in UV-B perception is unclear. Whereas $UVR8^{W285F}$ prevented UV-B-mediated monomerisation of the UVR8 homodimer, Trp-337 to phenylalanine ($UVR8^{W337F}$) did not (Rizzini et al. 2011, Christie et al. 2012). Furthermore, an independent study also showed that mutation of Trp-337, as well as Trp-94, to phenylalanine ($UVR8^{W337F}$, $UVR8^{W94F}$) did not affect UV-B perception (Wu et al. 2012). A follow up comprehensive analysis described transgenic plants where each of the 14 tryptophan residues within UVR8 were mutated (O'Hara and Jenkins 2012). This study confirmed that Trp-285 in particular as well as Trp-233 play important roles in UV-B perception, and that Trp-337 contributes to but is not essential for this same process. Concurrently, mutation of Trp-94 did not affect UVR8 monomerisation upon UV-B indicating that a tryptophan "pyramid" structure per se is not required for UV-B perception. Interestingly, $UVR8^{W285F}$ was found to be weakly responsive to UV-C in vitro which is not the case for wild type UVR8 (Christie et al. 2012). This is in accordance with the absorption properties of phenylalanine versus tryptophan.

Looking further afield in the UVR8 protein, the arginine residues Arg^{146}, Arg^{286} and Arg^{338} surrounding the four "pyramid" tryptophans were shown to participate in salt bridges and an extensive network of cation-π interactions with the surrounding tryptophans (Christie et al. 2012, Wu et al. 2012). These bonds are critical for maintaining the UVR8 homodimer and their disturbance underlies UV-B perception. Overall, it has been reported that the homodimeric interface of UVR8 is mediated by 32 intermolecular hydrogen bonds, notably with eight intermolecular hydrogen bonds (four from each molecule) arising from Arg-286 (Wu et al. 2012). In agreement, mutation of Arg-286 to alanine ($UVR8^{R286A}$) creates a constitutive UVR8 monomer (Christie et al. 2012, Wu et al. 2012).

In summary, the current consensus is that UV-B perception by UVR8 is mediated by a chromophore made up of at least Trp-285 and Trp-233, which directly absorb and are excited by UV-B. The excited states of Trp-285 and Trp-233 are then unable to maintain a number of intramolecular cation-π interactions with surrounding residues, in particular with Arg-286 and Arg-338. These disrupted cation-π interactions in turn destabilize the intermolecular hydrogen bonds of the UVR8 homodimeric interface leading to homodimer dissociation and initiation of UV-B signaling (Christie

et al. 2012, Wu et al. 2012). It is of note here that the UVR8 crystal structure was resolved and analysed for the core sequence of UVR8 and in fact a C-terminal fragment required for signaling (Cloix et al. 2012) and an N-terminal fragment required for nuclear translocation (Kaiserli and Jenkins 2007) have not yet been included in any structural analysis (Christie et al. 2012, Wu et al. 2012). Therefore, although the crystal structure of UVR8 provides insight into the photoperception mechanism, it does not yet show how UVR8 initiates signaling through interaction with the downstream factor COP1, which, as is detailed in following sections, seems as crucial for UV-B signaling as UVR8 monomerisation.

UVR8 inactivation and ground state reversion

As for any photoreceptor, inactivation and ground ("dark") state reversion of UVR8 is of great importance. UVR8 reverts back to its homodimeric ground state by redimerization, which simultaneously stops UV-B signaling and restores UV-B responsiveness (Heijde and Ulm 2013, Heilmann and Jenkins 2013) (Figure 4). Regeneration of the UVR8 dimer following UV-B exposure occurs much more rapidly in vivo (1-2 hours) than in vitro (24-48 hours) (Christie et al. 2012, Wu et al. 2012, Heijde and Ulm 2013, Heilmann and Jenkins 2013). This is largely due to activ-

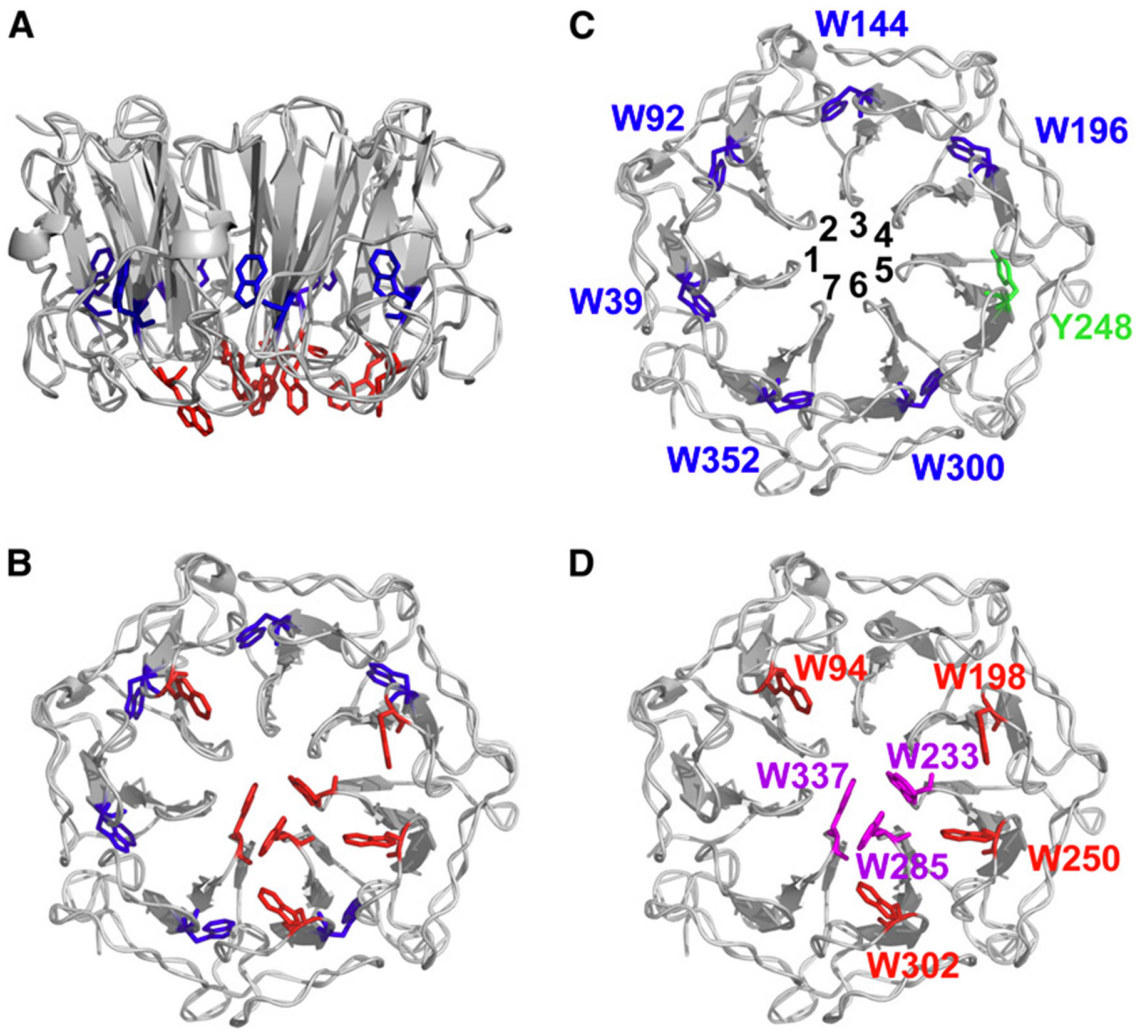


Figure 5. UVR8 structure and arrangement of key tryptophan and arginine residues.

(A) The arrangement of tryptophan (W) residues, excluding W400, in the UVR8 monomer as viewed from the side. The structure is shown for the solved core structure, amino acids 14 to 380 (Christie et al. 2012). Tryptophan residues located in the protein core are depicted in blue whereas those in red reside at the dimeric interaction surface. (B) As in (A), but viewed from the dimeric interaction surface. (C) Protein core tryptophan residues as viewed from the dimeric interaction surface. Each Trp is associated with a different propeller blade (numbered). Y248 from blade 5 completes the ring of aromatic residues. (D) Tryptophan residues at the dimeric interaction surface. Residues that constitute the tryptophan triad are depicted in magenta. Image reprinted from O'Hara and Jenkins (2012), with permission from The Plant Cell, Volume 24 © 2012 by the American Society of Plant Biologists (ASPB; www.aspb.org).

ity of the WD40-repeat proteins REPRESSOR OF UV-B PHOTOMORPHOGENESIS 1 and 2 (RUP1; At5g52250, and RUP2; At5g23730) that promotes the redimerization of UVR8 in vivo (Heijde and Ulm 2013) (Figure 4). Thus, whereas monomerization of UVR8 under UV-B is an intrinsic property of the protein, its natural means of reversion to a homodimer is dependent on interaction with regulatory proteins, as is described in further detail in following sections.

Expression and subcellular localization of UVR8

The expression and subcellular localisation of plant photoreceptors plays a large role in their biological function and how the signaling pathways they are linked to proceed. UVR8 is expressed throughout plant bodies, which technically gives any plant organ the ability to respond to UV-B (Rizzini et al. 2011). The majority of UVR8 protein is located in the cytoplasm but a small portion is also detectable in the nucleus, even in the absence of UV-B. Upon UV-B exposure, UVR8 is seen to accumulate within minutes in the nucleus, although not exclusively, as the majority of UVR8 remains cytoplasmic (Kaiserli and Jenkins 2007). The rapid UV-B-dependent nuclear accumulation of UVR8 artificially localised in the cytoplasm (i.e. fused with a nuclear export signal) suggests that a specific nuclear transport mechanism exists (Kaiserli and Jenkins 2007). This combined with the fact that UVR8 protein levels are unchanged by UV-B (Kaiserli and Jenkins 2007, Favory et al. 2009) rules out the possibility that nuclear UVR8 accumulation is the result of differential protein stabilization upon UV-B exposure. However, no clear nuclear localisation signal motif can be identified in the UVR8 sequence and the mechanism for UVR8 nuclear accumulation remains unknown. Nevertheless, removal of the N-terminal 23 amino acids (N23) of UVR8 prevents the protein from accumulating in the nucleus under UV-B, suggesting that this stretch of amino acids plays an important role in nuclear translocation (Kaiserli and Jenkins 2007) (Figure 3B). UVR8 nuclear localisation is necessary but not sufficient for UV-B signaling, as demonstrated by the requirement of UV-B for initiation of the pathway even when UVR8 is fused with a nuclear localisation signal and is constitutively nuclear (Kaiserli and Jenkins 2007). As mentioned above, the majority of UVR8 is retained in the cytoplasm under UV-B (Kaiserli and Jenkins 2007). This is interesting in light of the apparent necessity for UVR8 to be in the nucleus for UV-B signaling leading to changes in gene expression. Thus, a functional role for UVR8 in the cytoplasm cannot be ruled out at present, but most of the available evidence indicates its central function in UV-B signaling is in the nucleus.

Chromatin association of UVR8

UVR8 signaling is known to culminate in altered expression of a broad range of genes (Brown et al. 2005, Favory et al. 2009). The mechanism by which UVR8 regulates UV-B-dependent transcription is presently unknown. However, chromatin immunoprecipitation (ChIP) assays have suggested that UVR8 binds chromatin in vivo (Brown et al. 2005, Cloix and Jenkins 2008). Association of UVR8 with chromatin of UVR8 target genes is apparently constitutive and not UV-B-responsive, despite the fact that UVR8 accumulates in the nucleus upon UV-B (Brown et al. 2005, Kaiserli and Jenkins 2007, Cloix and Jenkins 2008). Within the tested promoter regions, UVR8 was found to interact with chromatin of some (e.g., At5g11260, *HY5*; At5g24850, *CRY3*; At2g47460, *PFG1*/*MYB12*) but not all (e.g., At3g17609, *HYH*; At5g13930, *CHS*) UVR8-regulated genes (Cloix and Jenkins 2008). More detailed analysis revealed that UVR8 associates in a UV-B-independent manner with a region more than 3kb in size around the *ELONGATED HYPOCOTYL 5* (*HY5*) genomic locus and thus UVR8 binding is not confined to the *HY5* promoter (Cloix and Jenkins 2008). Additionally, UVR8 chromatin association is via histones, preferentially histone H2B (Brown et al. 2005, Cloix and Jenkins 2008).

It is tempting to assume that UVR8 chromatin association is due to its structural similarity with human RCC1 which is a known chromatin-associated protein (Kliebenstein et al. 2002). Chromatin-bound RCC1 is essential for the accumulation of small GTPase Ran around the chromosomes, required for critical cellular processes such as mitosis, nucleocytoplasmic transport and formation of the nuclear envelope. Recent work illustrated how RCC1 interacts with histone and DNA components of the nucleosome (England et al. 2010, Makde et al. 2010). RCC1 is a β-propeller protein which employs a 'switchback loop' region and its N-terminal tail to interact with histones and nucleosomal DNA (England et al. 2010). Contacts between RCC1 and histones are made through the H2A-H2B histone dimer surface of the nucleosome core particle. Contacts between RCC1 and DNA are made through the DNA phosphate backbone, indicating that RCC1 interacts with chromatin by binding non-DNA-sequence specific areas (Makde et al. 2010). Consistently, the yeast RCC1 orthologue Srm1/Prp20 was found to bind most nucleosomes in the genome with no sequence specificity (Koerber et al. 2009). Similar unspecific binding is indicated for UVR8 by the fact that UVR8 seems to decorate a broad region of the *HY5* locus and that UVR8 chromatin association is via histones (Cloix and Jenkins 2008). The specificity of UVR8 chromatin binding of select target genes needs to be more firmly established and, if so, the mechanism conferring specificity must be revealed. Independent of the ambiguities concerning specificity, it also remains a valid question whether the primary function of UVR8 is with chromatin association, and, if yes, how UVR8 regulates gene expression mechanistically. It can be imagined that UVR8 is involved in the recruitment of transcriptional regulators and/or in chromatin remodelling (Cloix and Jenkins 2008, Jenkins 2009).

Evolutionary conservation

Considering the high levels of solar UV-B at the time of land-plant evolution (Rozema et al. 1997) and the potential of UV-B to damage genetic material as well as photosystem II (Britt 2004, Takahashi et al. 2010), early evolution of a UV-B-specific perception and signaling pathway would have been critical for the survival of any photosynthetic organism. For this reason, it is easy to imagine that the existence of a UV-B signaling pathway in plants is widespread, if not absolute. Indeed, genes encoding UVR8-like proteins can be broadly identified in the available sequenced plant genomes, including mosses and algae, with strong conservation of residues surrounding the tryptophan triad Trp-285, Trp-

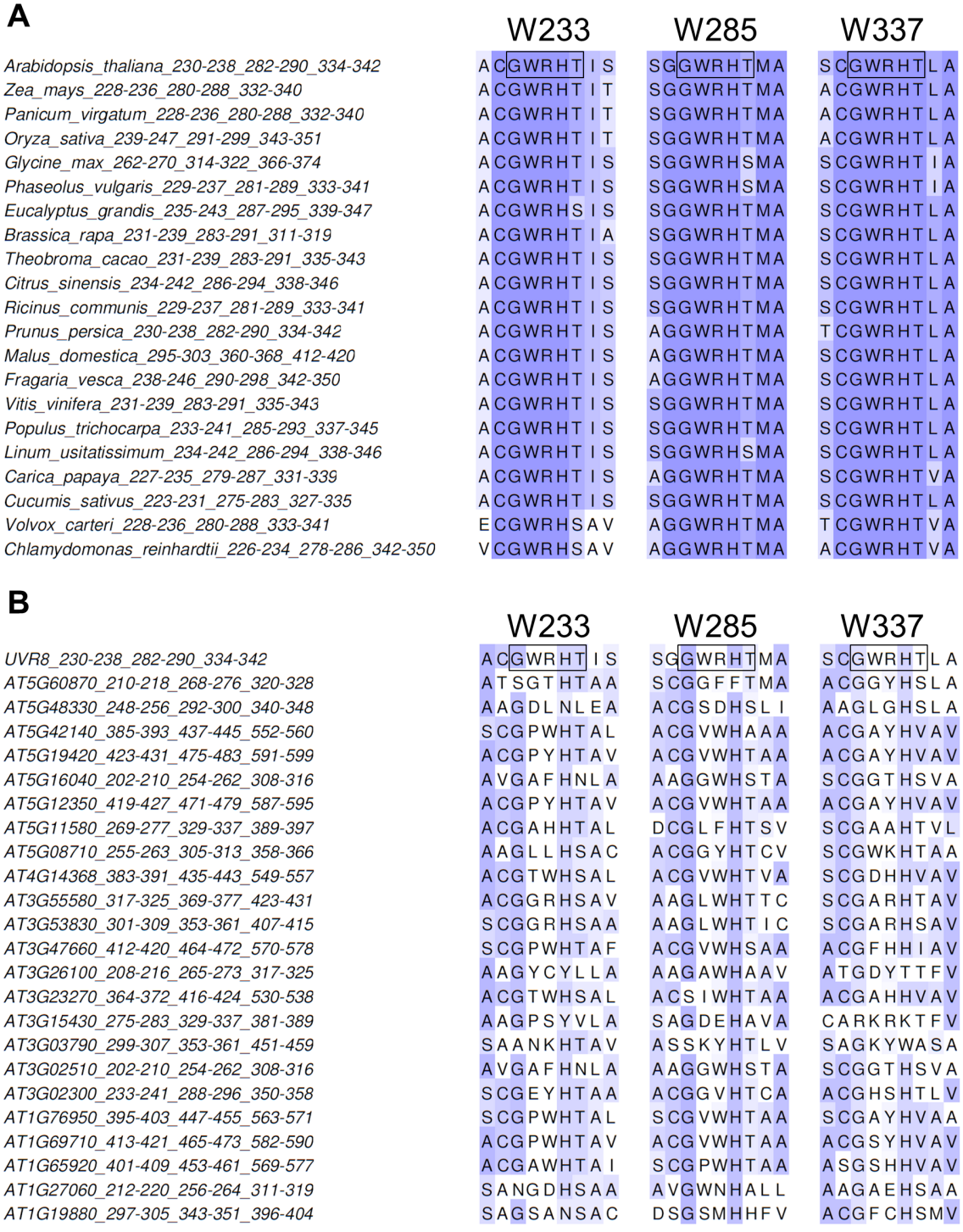


Figure 6. Sequence conservation surrounding key UVR8 tryptophan residues in UVR8-like proteins from other plants, but not in UVR8-related sequences of Arabidopsis.

Conservation of Trp-233, Trp-285 and Trp-337 and surrounding sequence (GWRHT) is obvious in UVR8 orthologous proteins from plants (A) but is not maintained in UVR8-like homologous Arabidopsis proteins (B). Candidate UVR8 homologs were derived from Kühn et al. (2011). This list of proteins included all Arabidopsis UVR8 homologues also identified using the Peptide Homologues function within the UVR8 Phytozome gene page (http://www.phytozome.net). UVR8 orthologs in select photosynthetic organisms were also identified using Phytozome. Peptide sequences were loaded into Jalview (Waterhouse et al. 2009) and residues were highlighted according to their degree of conservation. The Gly-Trp-Arg-His-Thr (GWRHT) repeats of UVR8 are indicated with boxes. (A, B) Number sequences describe amino acid positioning of the triplicate motifs in each respective protein.

233 and Trp-337 in Arabidopsis UVR8 (Wolf et al. 2010, Rizzini et al. 2011) (Figure 6A), described in a previous section as contributing to UV-B perception. UV-B signaling and the functionality of UV-B photoreceptors in these other organisms remains to be demonstrated, but such comparative studies may reveal further highly conserved areas of the UVR8 protein and provide more information regarding structure-function relationships.

Are There Additional Plant UV-B Photoreceptors?

Whereas it is clear that UVR8 functions as the major UV-B photoreceptor in Arabidopsis, it remains to be seen whether additional bona fide UV-B photoreceptors exist in plants. There are several examples in the literature that tempts one to speculate that plant UV-B signaling may proceed via several routes. These include peak induction of gene expression and production of UV-absorbing pigments in response to distinct wavelengths within the UV-B range and responses that still occur in *cop1* and *uvr8* seedlings where the UVR8-mediated UV-B signaling pathway is abolished (Ulm et al. 2004, Brown and Jenkins 2008, Kalbina et al. 2008, Safrany et al. 2008, Gardner et al. 2009, Shinkle et al. 2010, Leasure et al. 2011, Lang-Mladek et al. 2012). A recent report also indicated that pyrimidine dimers formed under UV-B in DNA may signal to stress-activated MAP kinase signaling (Gonzalez Besteiro and Ulm 2013). It is of note here that the UVR8 photoreceptor response can be clearly physiologically and molecularly separated from this stress/damage response (Gonzalez Besteiro et al. 2011).

In a family of over 20 UVR8-related RCC1-motif-containing Arabidopsis proteins (RUG proteins, for RCC1/UVR8/GEF-like) (Kühn et al. 2011), there is no clear conservation of the tryptophan triad Trp-285, Trp-233 and Trp-337 in UVR8 and the Gly-Trp-Arg-His-Thr consensus sequence in these positions (Figure 6B). This combined with the apparent null response to regulatory levels of UV-B in *uvr8* knock-out mutants (Favory et al. 2009) suggests that there are no UVR8-related proteins in Arabidopsis that also participate in UV-B perception. Thus, UV-B contrasts with other light qualities which are perceived by the phytochrome (phyA-E), cryptochrome (cry1 and cry2), phototropin (phot1 and phot2) and Zeitlupe (ZTL, FKF1 and LKP2) photoreceptor families (Kami et al. 2010). Aside from UVR8 homologous proteins, it is still a valid question whether structurally distinct proteins or even non-protein mechanisms are capable of specific UV-B perception. UV-B perception can arguably also proceed via UV-B-induced changes in any number of biomolecules. For example, it was suggested that UV-B responses in mammalian cells are initiated by generation of tryptophan photoproducts which then bind to the arylhydrocarbon receptor (Fritsche et al. 2007).

UVR8 PHOTORECEPTOR-MEDIATED SIGNALING PATHWAY

Once UV-B is perceived and the UVR8 dimer is monomerized, a molecular signaling pathway is initiated that transduces this initial event into appropriate changes in gene expression (Figure 2). For this to occur, action needs to take place within the nucleus. In agreement, and as mentioned in a previous section, UVR8 partially shifts from the cytoplasm to the nucleus upon UV-B exposure (Kaiserli and Jenkins 2007). However, one cannot assume by any means that UVR8 acts alone in UV-B signaling. This section describes the currently known UVR8-interacting proteins, such as the E3 ubiquitin ligase COP1, and the WD40-repeat β-propeller proteins RUP1 and RUP2 (Table 1). Also described are proteins further removed from UVR8 yet which are still essential for UV-B signaling responses, such as the bZIP transcription factor HY5 (Table 1).

Positive Regulators

The E3 ubiquitin ligase COP1

COP1 plays a pivotal role in signaling for visible light qualities. Via interaction with SPA family members, COP1 acts as an E3 ubiquitin ligase and facilitates select protein ubiquitination and degradation (Lau and Deng 2012). In darkness, this process modulates the abundance of light signaling proteins, including the transcription factor HY5, to suppress seedling photomorphogenesis. It is for this reason that *cop1* seedlings are referred to as constitutively photomorphogenic and display a light-grown phenotype even when grown in darkness (Deng et al. 1991).

cop1 seedlings present an exaggerated photomorphogenic and severely dwarf phenotype when grown in light but interestingly do not seem to deploy typical photomorphogenic or molecular responses to UV-B (Oravecz et al. 2006). Although it is difficult to compare with wild type directly since *cop1* seedlings already exhibit constitutively short hypocotyls, *cop1* seedlings do not display the typical reduced hypocotyl elongation under UV-B compared to white-light-grown seedlings (Kim et al. 1998, Oravecz et al. 2006, Huang et al. 2012) (Figure 7A). This lack of UV-B-induced photomorphogenesis in *cop1* seedlings, alongside the absence of UV-B-induced flavonoid accumulation, gene expression changes, and accumulation of HY5 supports the notion that COP1 plays a promotive role in UV-B responses (Oravecz et al. 2006). This contrasts with the repressive role COP1 is known to play in visible light signaling where HY5 is degraded through COP1 ubiquitination in darkness, but is able to accumulate in *cop1* seedlings leading to the constitutive photomorphogenic mutant phenotype (Osterlund et al. 2000). COP1 in UV-B signaling displays further contrasting properties in that, alongside UVR8 and HY5, COP1 accumulates in the nucleus following UV-B exposure and UV-B responses are independent of SPA proteins (Oravecz et al. 2006). Further investigation into the role of COP1 in UV-B signaling revealed a direct, UV-B-dependent interaction between UVR8 and COP1 (Favory et al. 2009). This UVR8-COP1 interaction is required for UV-B signaling but not for UV-B-induced UVR8 monomerization and accumulation in the nucleus (Rizzini et al. 2011, Cloix et al. 2012).

Since UVR8-COP1 interaction is seen only upon UV-B exposure (Favory et al. 2009, Rizzini et al. 2011, Cloix et al. 2012), it can be safely assumed that COP1 interacts only with the UVR8 monomer. This is further supported by analysis of UVR8-COP1 interaction with UVR8 proteins mutated in Trp-285 that apparently exist either as a constitutive monomer ($UVR8^{W285A}$) or constitutive dimer ($UVR8^{W285F}$) (Rizzini et al. 2011, O'Hara and Jenkins 2012). COP1 was seen to interact with the $UVR8^{W285A}$ constitutive monomer regardless of UV-B exposure, both in yeast and co-immunoprecipitations from plant tissues. Conversely, the UVR8-COP1 interaction was abolished with the $UVR8^{W285F}$ constitutive dimer

Table 1. List of proteins involved in the UVR8 UV-B signaling pathway in Arabidopsis

AGI[1]	Name	Structure	Interactions[2]	Role in UV-B signaling
At5g63860	UVR8 (UV RESISTANCE LOCUS 8) (Kliebenstein et al. 2002)	β-propeller protein (Christie et al. 2012, Wu et al. 2012)	UVR8 (Favory et al. 2009, Rizzini et al. 2011) COP1 (only +UVB) (Favory et al. 2009) RUP1, RUP2 (Gruber et al. 2010)	Photoreceptor (Rizzini et al. 2011)
At2g32950	COP1 (CONSTITUTIVELY PHOTOMORPHOGENIC 1) (Deng et al. 1991)	RING-cc-WD40 (Deng et al. 1992)	UVR8 (Favory et al. 2009) COP1 (Torii et al. 1998) HY5 (Ang et al. 1998) BBX24 (Holm et al. 2001)	Positive regulator (Oravecz et al. 2006)
At5g11260	HY5 (ELONGATED HYPOCOTYL 5) (Koornneef et al. 1980)	bZIP transcription factor (Oyama et al. 1997)	COP1 (Ang et al. 1998) BBX24 (Jiang et al. 2012) FHY3 (Huang et al. 2012) HYH (Holm et al. 2002)	Positive regulator (Ulm et al. 2004)
At3g17609	HYH (HY5-HOMOLOG) (Holm et al. 2002)	bZIP transcription factor (Holm et al. 2002)	COP1 (Holm et al. 2002) HY5 (Holm et al. 2002)	Positive regulator (minor role, partially redundant with HY5) (Brown and Jenkins 2008)
At3g22170	FHY3 (FAR-RED ELONGATED HYPOCOTYL 3)	C2H2 zinc finger-transposase domain-SWIM zinc finger (Wang and Deng 2002)	HY5 (Huang et al. 2012)	Promotes expression of *COP1* in response to UV-B (Huang et al. 2012)
At5g52250	RUP1 (REPRESSOR OF UV-B PHOTOMORPHOGENESIS 1) (Gruber et al. 2010) [Also identified as EFO1 (EARLY FLOWERING BY OVEREXPRESSION 1) (Wang et al. 2011)]	WD40 repeat protein (Gruber et al. 2010)	UVR8 (Gruber et al. 2010)	Negative feed-back regulator facilitating UVR8 redimerization (Heijde and Ulm 2013)
At5g23730	RUP2 (REPRESSOR OF UV-B PHOTOMORPHOGENESIS 1) (Gruber et al. 2010) [Also identified as EFO2 (EARLY FLOWERING BY OVEREXPRESSION 2) (Wang et al. 2011)]	WD40 repeat protein (Gruber et al. 2010)	UVR8 (Gruber et al. 2010)	Negative feed-back regulator facilitating UVR8 redimerization (Heijde and Ulm 2013)
At1g06040	BBX24 (B-BOX DOMAIN PROTEIN 24) / STO (SALT TOLERANCE) (Lippuner et al. 1996, Khanna et al. 2009)	B-box zinc finger protein (Lippuner et al. 1996)	COP1 (Holm et al. 2001) HY5 (Jiang et al. 2012)	Negative regulator of HY5 function (Jiang et al. 2012)

[1]With the AGI (Arabidopsis Genome Initiative) identifier, updated further information can be retrieved from The Arabidopsis Information Resource (TAIR) (http://www.arabidopsis.org/).
[2]Only interactions involved in UV-B signaling or with other proteins in the list are shown. Additional interacting proteins can be found in the literature for COP1 and HY5.

(Rizzini et al. 2011, O'Hara and Jenkins 2012). It should be noted here that constitutive interaction between UVR8-COP1, such as that seen with GFP-UVR8^{W285A}, does not seem to result in constitutive UV-B responses in transgenic plants (O'Hara and Jenkins 2012). This raises an interesting question concerning the exact mechanistic role of the UVR8-COP1 interaction in UV-B signaling. The necessity of the UVR8-COP1 interaction for UV-B signaling is supported by the fact that *uvr8* and *cop1* alleles which abolish UV-B responses consistently produce mutant proteins that do not interact with their respective wild-type partner (Favory et al. 2009, Cloix et al. 2012). These various *cop1* and *uvr8* alleles provide us some insight into the mechanism of UVR8-COP1 interaction.

UVR8 is a 440-amino-acid protein whose β-propeller structure is described above. Proven mutant alleles that abolish COP1 interaction include *uvr8-15* (UVR8^{G145S}), *uvr8-9* (UVR8^{G202R}) (Favory et al. 2009, Rizzini et al. 2011), UVR8^{G197A} and UVR8^{G199A} (O'Hara and Jenkins 2012) as well as *uvr8-2* (UVR8$^{\Delta C40}$) (Cloix et al. 2012). Moreover, the recent deliberate deletion of a conserved UVR8 C-terminal 27 amino acid fragment (C27; amino acids 397-423) (Figure 3B), which coincidentally was also found lacking in the *uvr8-2* allele, highlighted the importance of this region for UV-B signaling (Cloix et al. 2012). Whilst UVR8$^{\Delta C27}$ still forms a homodimer in the plant in the absence of UV-B, and monomerizes instantly and accumulates in the nucleus upon UV-B exposure, UV-B signaling is compromised (Cloix et al. 2012). Further co-immunoprecipitation and yeast two-hybrid experiments revealed that UVR8$^{\Delta C27}$ does not interact with COP1. Likewise, UVR8$^{\Delta C27}$ does not interact with RUP1 or RUP2 (Cloix et al. 2012). Interestingly, C27 interaction with COP1, RUP1 and RUP2 was found to be constitutive and independent of UV-B exposure. Such an interaction pattern suggests that, under UV-B, UVR8 C27 is 'revealed' and then facilitates the UVR8-COP1 interaction required for initiation of the signaling pathway. Thus, the current model suggests that the N-terminal core fragment of UVR8 is responsible for UV-B perception whilst the UVR8 C-terminus is responsible for interaction with other proteins in the UV-B signaling pathway, notably COP1, for relay of UV-B signal (Figure 3B).

Structurally, COP1 is composed of three major domains: a zinc-binding RING-finger, a coiled-coil domain and a WD40 repeat domain (Deng et al. 1992). Mutant alleles proven to prevent interaction with UVR8 include *cop1-19*, carrying a point mutation in the WD40 domain (COP1^{G608R}) (Favory et al. 2009, Rizzini et al. 2011) and *cop1-4*, which lacks the WD40 domain entirely (COP1^{N282}) (Favory et al. 2009, Rizzini et al. 2011, Cloix et al. 2012). Other *cop1* alleles non-functional in UV-B signaling, such as *cop1-1* (COP1$^{\Delta 355-376}$) (Oravecz et al. 2006), most likely also do not facilitate UVR8-COP1 interaction, but this remains to be demonstrated. Thus, the most important part of COP1 required for UV-B signaling seems to be the WD40 domain, which is required for UV-B-dependent interaction with UVR8 (Favory et al. 2009, Rizzini et al. 2011).

In contrast to the role of COP1 as an E3 ubiquitin ligase, UVR8-COP1 interaction does not lead to degradation of UVR8 (Favory et al. 2009). Interestingly, UV-B exposure is known to increase COP1 protein levels at the post-transcriptional level in a UVR8-dependent fashion, perhaps due to a decrease in COP1 autoubiquitination (Favory et al. 2009). Moreover, a recent study showed two transcription factors, FAR-RED ELONGATED HYPOCOTYL3 (FHY3; At3g22170) and HY5, contribute by increasing *COP1* transcript under UV-B (Huang et al. 2012). The maintenance and accumulation of COP1 in the nucleus following UV-B exposure suggests that COP1's function in UV-B signaling takes place in the nucleus (Oravecz et al. 2006, Favory et al. 2009). The COP1-UVR8 interaction most likely underlies the specific activity of COP1 in UV-B signaling (Favory et al. 2009) but how this interaction determines the exact role of COP1 in response to UV-B and how COP1 interacts with other proteins remains to be elucidated.

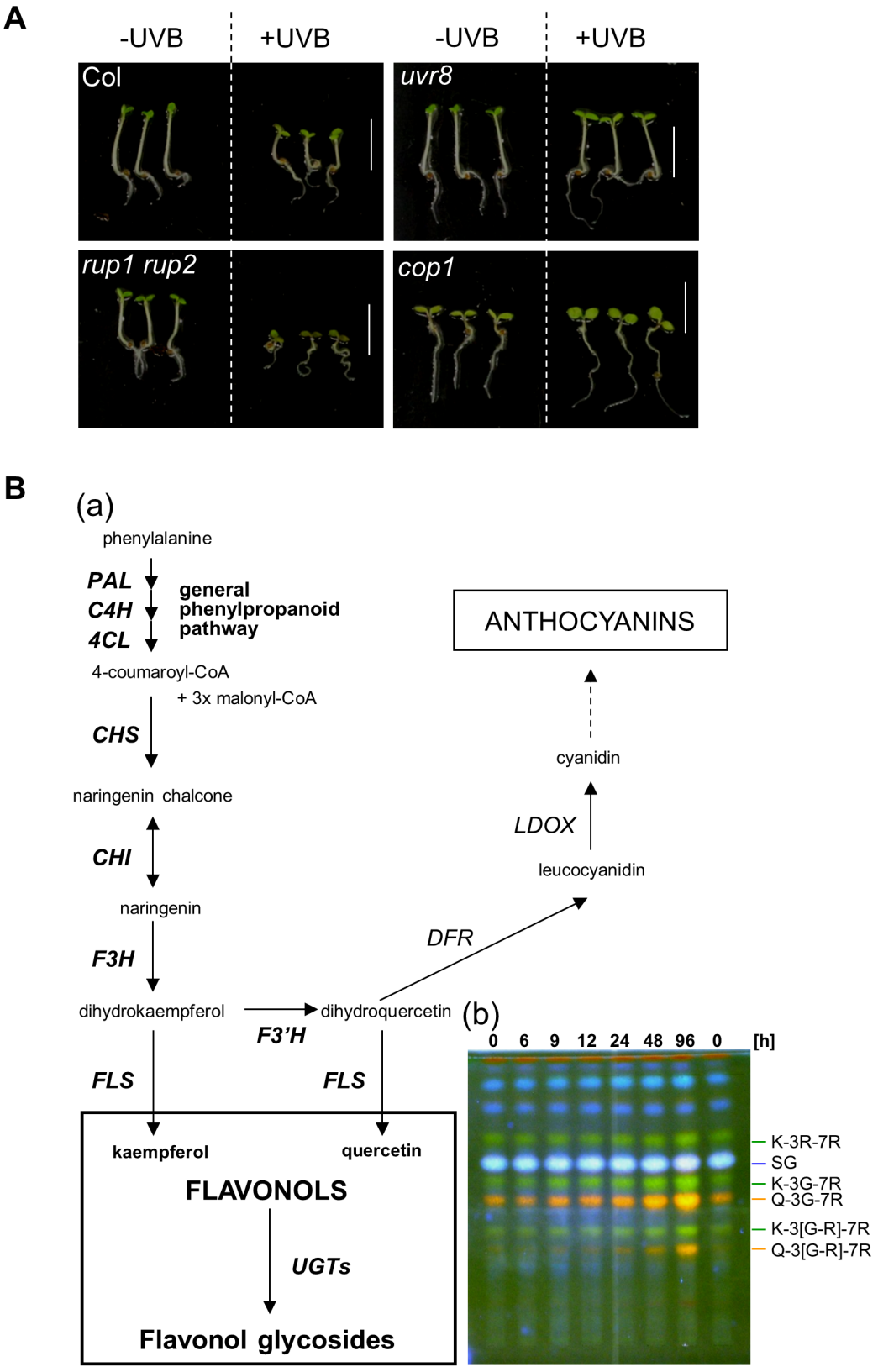
The bZIP transcription factor HY5 and its homologue HYH

The basic leucine zipper (bZIP) transcription factor HY5 also plays a significant role in UV-B signaling (Ulm et al. 2004, Brown et al. 2005, Brown and Jenkins 2008, Stracke et al. 2010, Huang et al. 2012) (Figure 2). As for COP1, the involvement of HY5 immediately places UV-B into the larger network of plant light signaling, for which HY5 plays a well-characterised and central role (Jiao et al. 2007). HY5 responds to a broad spectrum of light to modulate light-responsive gene expression. In a genome-wide analysis of in vivo HY5 binding sites, more than 9000 Arabidopsis genes, many of which were light-responsive, were shown to be targets of HY5 (Zhang et al. 2011).

Initially, a role for HY5 in UV-B signaling was proposed once *HY5* was identified as one of many genes subject to expression induction upon UV-B exposure (Ulm et al. 2004). UVR8- and COP1-dependent UV-B induction of *HY5* transcript and protein level has since been demonstrated numerous times (Brown et al. 2005, Oravecz et al. 2006, Kaiserli and Jenkins 2007, Brown et al. 2009, Favory et al. 2009). Interestingly, UVR8 itself is proposed to associate with chromatin in the vicinity of the *HY5* genomic locus (Brown et al. 2005, Cloix and Jenkins 2008). Transcription factors are amongst the most interesting genes to be induced by UV-B, as they potentially control a wide transcriptional network which can amplify the UV-B response. Indeed, subsequent experiments showed that in *hy5* seedlings, a subset of known UV-B-responsive genes were not transcriptionally activated upon UV-B exposure (Ulm et al. 2004, Brown et al. 2005, Oravecz et al. 2006, Brown and Jenkins 2008, Stracke et al. 2010). The central role of HY5 in the UV-B acclimation response is further highlighted by the UV-B stress hypersensitivity of *hy5* seedlings (Brown et al. 2005, Oravecz et al. 2006, Huang et al. 2012).

Independently of UV-B studies, HY5 was found to interact with its functional homologue HY5 HOMOLOG (HYH), also a positive regulator of photomorphogenesis (Holm et al. 2002). A functional role for HYH in UVR8-mediated UV-B signaling was then suggested, although with much less involvement, acting in conjunction with HY5 and with significant redundancy (Brown and Jenkins 2008, Stracke et al. 2010). HY5 and HYH are often cited as governing the majority, if not all, of the UV-B transcriptional response (Brown and Jenkins 2008). However, there remain some UV-B-induced transcriptional changes that are HY5-/HYH-independent (Feher et al. 2011).

The function of HY5 in UVR8-mediated UV-B signaling is accompanied by some unique features. In darkness, HY5 is a target of COP1 and proteasome-mediated degradation (Osterlund et al. 2000). Under UV-B however, COP1 is required for *HY5* expression induction (Oravecz et al. 2006). Also, once expression is induced, HY5 is involved in a positive feedback loop promoting *COP1* expression, specifically by binding to one of three ACGT



containing elements (ACEs) within the *COP1* promoter (Huang et al. 2012). In agreement, *COP1* expression induction and protein accumulation under UV-B is affected in a *hy5* mutant background (Huang et al. 2012). HY5 is known to play a prominent role in light responses of the young seedling and the significance of this role is diminished during later developmental stages and in adult plants (Hardtke et al. 2000). This functional transition is in accordance with higher abundance of HY5 in the seedling compared to the mature plant. Thus, a further unique feature of HY5 in UVR8-mediated UV-B signaling is that HY5 is reengaged, maintaining a functional significance even in older seedlings and mature plants (Ulm et al. 2004, Oravecz et al. 2006).

The transcription factor FHY3

As mentioned above, induction of *COP1* expression under UV-B involves FHY3, a transposon-derived transcription factor. Whereas *FHY3* expression is repressed by far-red light (Lin et al. 2007), it is induced by UV-B (Huang et al. 2012). FHY3 was seen to directly and positively regulate *COP1* expression, with this process dependent on the presence of UVR8. As a consequence, UV-B-induced gene expression and physiological responses are reduced in *fhy3* mutants (Huang et al. 2012). Mechanistically, specific binding between FHY3 and a distinct FHY3 binding site (FBS) in the *COP1* promoter region was demonstrated both in vitro and in vivo, and is adjacent to an ACE element bound by HY5 (Huang et al. 2012). However, the functional interaction between FHY3 and HY5 seems diminished by UV-B (Huang et al. 2012). Both FHY3 and HY5 also have documented roles in phyA signaling and circadian regulation (Lin et al. 2007, Li et al. 2010, Lau and Deng 2012), but apparently operate in a different manner to their function in UVR8 UV-B signaling (Huang et al. 2012). How UVR8 links to and impinges on FHY3 protein activity remains to be determined.

Negative Regulators

The WD40 proteins RUP1 and RUP2

Signaling pathways usually encompass negative feedback loops. Negative feedback loops serve to control the signaling response, such as by limiting the maximum signaling output to preserve responsiveness to changing levels of input signal (Brandman and Meyer 2008). The importance of a negative feedback loop in UV-B signaling is highlighted by the dwarf and overly-photomorphogenic phenotype of Arabidopsis UVR8 overexpression plants when they are grown under sun-simulating conditions (Favory et al. 2009).

The two highly homologous, UV-B-induced proteins RUP1 and RUP2 are negative feedback regulators of UVR8-mediated UV-B signaling (Gruber et al. 2010). RUP1 and RUP2 are WD40-repeat proteins that are phylogenetically related to other key light signaling components COP1 and the SPA proteins (Gruber et al. 2010) and are included in a protein subfamily containing DWD (for DDB1 binding WD40) motifs which facilitate interaction with DDB1. Proteins that harbour DWD motifs serve as the substrate receptors for DDB1-CUL4-ROC1-based E3 ubiquitin ligases (Lee et al. 2008), albeit this has not yet been demonstrated for RUP1 and RUP2. Expression of both *RUP1* and *RUP2* is induced by UV-B in a UVR8-, COP1-, and HY5-dependent manner (Gruber et al. 2010). Interestingly, in an independent study that described RUP1 and RUP2 as EFO1 and EFO2 (EARLY FLOWERING BY OVEREXPRESSION 1 and 2), *RUP1/EFO1 and RUP2/EFO2* expression was seen to be gated by the circadian clock, with expression levels peaking at daybreak and gradually subsiding to their lowest level at the onset of the night period (Wang et al. 2011).

Under light conditions devoid of UV-B, *RUP1*- and *RUP2*-overexpression prevents the inhibition of hypocotyl growth and promotes early flowering, regardless of if plants are grown under long- or short-day photoperiods (Wang et al. 2011). *RUP2*-overexpression also reduces UV-B-induced photomorphogenesis and prevents UV-B acclimation (Gruber et al. 2010), which agrees with the role of RUP1 and RUP2 as negative regulators of UV-B signaling. In contrast to *RUP2*-overexpression, hypocotyl elongation in *rup1 rup2* seedlings is hyper-attenuated and mature *rup1 rup2* plants display a severe dwarf phenotype when grown under UV-B (Figure 7A). Moreover, *rup1 rup2* seedlings have higher UV-B induction of known UV-B-responsive marker genes, such as *HY5* and *CHS*, and show enhanced tolerance to UV-B stress. This implies a UV-B-over-responsiveness in *rup1 rup2* plants and highlights the important role RUP1 and RUP2 play in achieving a balance between UV-B responses and plant growth (Gruber et al. 2010). Coincidentally, RNAi knockdown

Figure 7. UV-B-induced photomorphogenesis in 4-day-old Arabidopsis seedlings.

(A) UV-B inhibition of hypocotyl elongation is apparent in wild type (Col) but not *uvr8-6* or *cop1-4* mutant seedlings. UV-B-induced photomorphogenesis is enhanced in *rup1 rup2* seedlings. Wild-type and mutant seedlings were grown under white light with or without supplementary narrowband UV-B (according to Favory et al. 2009). Scale = 5 mm.

(B) The flavonoid biosynthetic pathway and its regulation by UV-B in Arabidopsis. (a) Schematic representation of the flavonoid biosynthetic pathway. The UV-B-induced genes are highlighted (bolt) (for more information see Stracke et al. 2010). Abbreviations: 4CL, 4-coumarate:CoA ligase; C4H, cinnamate-4-hydroxylase; CHS, chalcone synthase; CHI, chalcone isomerase; F3H, flavanone 3-hydroxylase; F3'H, flavonoid 3'-hydroxylase; FLS, flavonol synthase; PAL, phenylalanine ammonium lyase; UGT, UDP-dependent glycosyltransferase; DFR, dihydroflavonol 4-reductase; LDOX, leucoanthocyanidin dioxygenase. (b) Diphenylboric acid 2-aminoethylester (DPBA)-stained high performance thin layer chromatography (HPTLC) separation of methanolic extracts from Arabidopsis seedlings showing flavonol glycoside accumulation and composition in response to supplementary UV-B irradiation for the indicated time. Color key: green, kaempferol derivative; orange, quercetin derivative; faint blue, sinapate derivative. Names of identified structures: K-3R-7R, kaempferol-3-O-rhamnoside-7-O-rhamnoside; SG, sinapoyl glucose; K-3G-7R, kaempferol-3-O-glucoside-7-O-rhamnoside; Q-3G-7R, quercetin-3-O-glucoside-7-O-rhamnoside; K-3[G-R]-7R, kaempferol 3-O-[rhamnosyl-glucoside]-7-O-rhamnoside; Q-3[G-R]-7R, quercetin 3-O-[rhamnosyl-glucoside]-7-O-rhamnoside. Image adapted from Stracke et al. (2010) with permission, from Plant, Cell and Environment, Volume 33 © 2009 by Blackwell Publishing Ltd (www.wiley.com).

of a *RUP1* homolog in tomato (named *LeCOP1LIKE*) confers exaggerated photomorphogenesis, dark-green leaves and enhanced fruit carotenoid levels to field-grown plants (Liu et al. 2004), which is potentially due to *LeCOP1LIKE* activity as a repressor of UV-B signaling.

Both RUP1 and RUP2 interact directly with UVR8 (Gruber et al. 2010). UVR8-RUP1/RUP2 interaction increases under UV-B due to *RUP1* and *RUP2* expression induction and subsequent protein accumulation (Gruber et al. 2010). The significance of this interaction is now further appreciated with recent elucidation of the RUP1/RUP2 mechanism of action (Heijde and Ulm 2013). UVR8 is known to revert to a dimer form post UV-B exposure, with this process proceeding faster in vivo than in vitro (Heijde and Ulm 2013, Heilmann and Jenkins 2013). An important role for RUP1/RUP2 in UVR8 redimerization was recently described that is mechanistically independent of COP1 (Heijde and Ulm 2013) (Figure 4). This explains the faster in vivo UVR8 redimerization and possibly why redimerization can be affected, specifically under prolonged irradiation conditions, by the presence or absence of COP1 and whether protein synthesis takes place (Heilmann and Jenkins 2013), as these factors influence accumulation of RUP1 and RUP2 (Gruber et al. 2010, Heijde and Ulm 2012). In accordance, UVR8 redimerization requires UVR8 C27 which, as well as facilitating UVR8-COP1 interaction, is necessary for UVR8-RUP1/RUP2 interaction (Cloix et al. 2012). Due to a block in UVR8 redimerization, the UVR8-COP1 interaction persists for longer post UV-B exposure in *rup1 rup2* double mutants (Heijde and Ulm 2013). Thus, RUP1 and RUP2 serve as negative regulators of UV-B signaling by facilitating UVR8 redimerization post UV-B exposure, which consequently disrupts the key interaction of UVR8 with COP1 (Heijde and Ulm 2013).

The B-Box protein STO/BBX24

A recent addition to molecular UV-B signaling is SALT TOLERANCE/BBX24 (STO/BBX24, herein referred to as BBX24; At1g06040), which is proposed to act as a negative regulator of the pathway (Jiang et al. 2012). BBX24 was initially characterised as conferring salt tolerance when expressed in yeast (Lippuner et al. 1996), as well as in plants (Nagaoka and Takano 2003). However, further characterisation revealed the involvement of BBX24 in plant light signaling, specifically as a negative regulator of red/far-red- and blue-light signaling (Indorf et al. 2007). Recent work has shown that *BBX24* is induced by UV-B and that the *bbx24* mutation confers a hypersensitive UV-B response, exhibited by an overall dwarf phenotype, short hypocotyls and enhanced anthocyanin accumulation under UV-B (Jiang et al. 2012). Thus, the function of BBX24 has been extended to a negative regulator of UV-B signaling. However, unlike RUP1 and RUP2, BBX24 does not interact with UVR8. Rather, BBX24 interacts with HY5 and COP1 in vivo (Jiang et al. 2012).

The BBX24-HY5 interaction was found to reduce HY5 accumulation and repress its role as a transcriptional activator under UV-B (Jiang et al. 2012), providing a means of how BBX24 may negatively regulate the UV-B signaling pathway. The consequence of BBX24-COP1 interaction was shown to differ depending on the presence or absence of UV-B. In darkness, COP1 represses *BBX24* transcription and leads to proteasome-mediated BBX24 degradation in the nucleus (Indorf et al. 2007, Yan et al. 2011, Jiang et al. 2012). However, under UV-B, BBX24 accumulates despite an increased presence of COP1 in the nucleus (Jiang et al. 2012). Moreover, reduced BBX24 levels under UV-B in *cop1* suggest that the UV-B-mediated accumulation of BBX24 is dependent on the presence of COP1 (Jiang et al. 2012). Interestingly, BBX24 also interacts with RADICAL-INDUCED CELL DEATH1 (RCD1; At1g32230) and *rcd1* mutants show enhanced induction of COP1-regulated genes under UV-B (Jiang et al. 2009, Jiang et al. 2012). This suggests that BBX24 and RCD1 may work in conjunction in the negative regulation of UV-B signaling.

UVR8-MEDIATED PHYSIOLOGICAL RESPONSES

The main advantage of UVR8-mediated UV-B perception and a specific molecular signaling pathway in plants is that UV-B-specific responses can be deployed as needed. UV-B induces a multitude of physiological responses influencing growth and development at various stages of the plant life cycle, which can be seen in both the natural environment and under controlled laboratory conditions (Jenkins 2009, Ballare et al. 2012, Heijde and Ulm 2012, Wargent and Jordan 2013). Generally speaking, our current understanding is that UVR8-associated responses help the plant acclimate to UV-B and therefore serve to prevent UV-B damage and stress.

In a laboratory setting, the most comprehensively studied UVR8-mediated physiological responses to UV-B are inhibition of hypocotyl growth and the accumulation of UV-B-absorbing compounds (e.g. flavonol glycosides) (Kliebenstein et al. 2002, Favory et al. 2009, Stracke et al. 2010, Morales et al. 2013) (Figure 7). Such responses are brought about by UV-B-induced expression of a range of genes (Kliebenstein et al. 2002, Ulm et al. 2004, Brown et al. 2005, Favory et al. 2009). Furthermore, UVR8 controls endoreduplication and leaf morphogenesis, as well as stomatal differentiation (Wargent et al. 2009), and promotes photosynthetic efficiency at elevated levels of UV-B (Davey et al. 2012). Recently, a role was suggested for UV-B in entrainment of the circadian clock in a UVR8-dependent manner (Feher et al. 2011). Moreover, the effect of UV-B on pathogen resistance was found to be mediated by UVR8 (Demkura and Ballare 2012). A role for UVR8 remains to be established in a number of other UV-B responses in Arabidopsis, including stomata regulation (Eisinger et al. 2003), phototropism (Eisinger et al. 2003, Shinkle et al. 2004), dynamics of phytohormones under UV-B (Savenstrand et al. 2004, Hectors et al. 2012), vitamin B6 biosynthesis (Brosche et al. 2002, Ristilä et al. 2011, Morales et al. 2013) and alterations in secondary metabolism (Jansen et al. 2008, Kusano et al. 2011). A number of further UVR8-mediated responses can be deduced from UV-B-induced and UVR8-dependent gene expression changes (Brosche et al. 2002, Ulm et al. 2004, Brown et al. 2005, Oravecz et al. 2006, Hectors et al. 2007, Zhou et al. 2007, Favory et al. 2009, Morales et al. 2013) but these remain to be validated. In summary, there are presently both definite and implied UVR8-mediated physiological responses. The UV-B responses that require further experimentation to be linked to UVR8 will not be detailed further here. Rather, this section details UV-B responses already associated with UVR8.

Hypocotyl Growth Inhibition

Hypocotyl growth inhibition is a well-described phenomenon in plant photobiology (Vandenbussche et al. 2005) and was the initial phenotype used to identify Arabidopsis mutants impaired in light perception and signaling (Koornneef et al. 1980). When a young seedling emerges from the soil and enters the light environment it undergoes a developmental transition known as photomorphogenesis. This process is characterized by a switch from etiolation fueled by mobilisation of seed triacylglycerols to photosynthetic growth. The dark-to-light transition is accompanied by hypocotyl growth inhibition, cotyledon opening and expansion, and chloroplast development which underlies the greening process (Arsovski et al. 2012). A complex network of different photoreceptor and phytohormone signaling pathways ensures the coordinated deploy of this consequential developmental transition (Kami et al. 2010, Lau and Deng 2010).

In general, the plant is exposed to a complex environment with various dynamic biotic and abiotic stress elements. Metabolic energy must be allocated to the right task at the right moment to optimize plant growth and ensure survival. For UV-B, protective measures have to be mounted appropriately to match the plant's developmental state and surrounding environment. UV-B physiological responses in Arabidopsis seedlings share common features with photomorphogenesis during the dark-to-light transition. UV-B-induced photomorphogenesis may represent a survival strategy whereby metabolic energy is diverted so that growth is reduced in favor of UV-B tolerance. UVR8-mediated UV-B perception regulates UV-B-induced hypocotyl growth inhibition, as, in contrast to wild type, the hypocotyl length of *uvr8* seedlings is similar under white light and white light supplemented with UV-B (Favory et al. 2009) (Figure 7A). Moreover, *hy5*, *cop1* and *fhy3* mutants show reduced hypocotyl growth inhibition in response to UV-B, whereas red and blue-light photoreceptor mutants are not affected (Kim et al. 1998, Oravecz et al. 2006, Favory et al. 2009, Huang et al. 2012). Further aspects of the photomorphogenic UV-B response are currently not elucidated. However, HY5 was recently implicated in UV-B-mediated cotyledon expansion (Conte et al. 2010), and thus it is likely that UVR8 also plays a role in this process.

Flavonoids

Flavonoids encompass a diverse group of phenolic secondary metabolites and serve a broad range of biological functions (Winkel-Shirley 2002). The colorless flavonols are among the most abundant flavonoids in plants (Bohm 1998) and possess UV-B absorption properties which render them effective in vivo filters of UV-B. Flavonol glycosides accumulate in the vacuoles of epidermal and subepidermal cell layers, which then protect underlying tissue from UV-B irradiation (Caldwell et al. 1983, Jenkins 2008). Accordingly, Arabidopsis mutants devoid of flavonoids are highly UV-B sensitive (Li et al. 1993, Landry et al. 1995, Stracke et al. 2010).

Flavonol biosynthesis is largely regulated by control over the transcription of key genes encoding biosynthetic enzymes, including *CHALCONE SYNTHASE* (*CHS*) (Jenkins 2008). CHS is responsible for the primary metabolic reaction committing the general phenylpropanoid pathway to flavonoid biosynthesis (Figure 7B). Early studies have extensively described the UV-B induction of *CHS* expression (Frohnmeyer et al. 1992, Kubasek et al. 1992, Christie and Jenkins 1996). These works formed the basis for the use of *CHS* as an excellent UV-B signaling response marker. In Arabidopsis, UV-B-mediated induction of *CHS* expression is UVR8-, COP1- and HY5-dependent (Kliebenstein et al. 2002, Brown et al. 2005, Oravecz et al. 2006, Favory et al. 2009, Stracke et al. 2010). The exact mechanism how transcriptional control is exerted over *CHS* in response to UV-B is presently unclear. It is however known that HY5 can directly bind to the *CHS* promoter, but this alone is not sufficient for *CHS* transcriptional activation (Ang et al. 1998, Lee et al. 2007, Stracke et al. 2010). However, overexpression of HY5 fused with an activation domain is sufficient for *CHS* expression induction, indicating that a presently unknown UV-B-activated transcription factor must also be involved (Stracke et al. 2010).

Alongside a direct association with the *CHS* promoter, HY5 binds promoter elements of the UV-B-activated *MYB12* gene (Lee et al. 2007, Stracke et al. 2010). In Arabidopsis, MYB12 belongs to a subgroup of three R2R3-MYB transcription factors that are specifically involved in the regulation of flavonol biosynthesis, including *CHS* expression, and are thus named PRODUCTION OF FLAVONOL GLYCOSIDES (PFG) 1/MYB12, PFG2/MYB11 and PFG3/MYB111 (Stracke et al. 2007). UV-B activation of *MYB12* is UVR8-, COP1- and HY5-dependent (Oravecz et al. 2006, Favory et al. 2009, Stracke et al. 2010). Also, similarly to HY5, UVR8 was found to bind to chromatin in the *MYB12* promoter region (Cloix and Jenkins 2008). Altogether, this suggests that UVR8 and HY5 regulate *MYB12*, as well as the genes encoding the remaining two PFG MYB transcription factors MYB11 and MYB111. MYB12, MYB11 and MYB111 would then, together with HY5, regulate downstream target genes, including *CHS*, leading to flavonol synthesis. White light- and UV-B-dependent *CHS* gene expression is still however apparent in *myb11 myb12 myb111* triple mutant, but it is strongly reduced (Stracke et al. 2010). Hence, *myb11 myb12 myb111* triple mutant is hypersensitive to UV-B stress and seedlings with elevated levels of MYB12 protein show increased UV-B tolerance (Stracke et al. 2010). Thus, the PFG MYB transcription factors are required to mount proper metabolite "sunscreen" protection against UV-B, but additional factors aside from HY5 that are absolutely required for UV-B induction of *CHS* gene expression are not known at present.

It should be mentioned here that a further class of phenylpropanoids which serve as UV-B sunscreens are the sinapate esters. Interestingly, another MYB transcription factor, MYB4, functions as a transcriptional repressor of *CINNAMATE 4-HYDROXYLASE* (*C4H*) gene expression which leads to decreased levels of sinapate esters (Jin et al. 2000). UV-B exposure negatively regulates the transcription of *MYB4*, which relieves repression of *C4H* leading to synthesis of sinapate ester sunscreens. In agreement, the *myb4* mutant allele confers enhanced levels of sinapate esters and higher UV-B tolerance (Jin et al. 2000). Under UV-B, MYB4 translocates to the nucleus where it binds to its own promoter to repress its own expression. This creates a negative autoregulatory loop resulting in the accumulation of UV-absorbing pigments (Zhao et al. 2007). However, it remains to be determined if MYB4 is part of the UVR8-mediated UV-B response.

Light Entrainment of the Circadian Clock

The circadian clock is a biological timing mechanism that provides rhythmicity to many molecular and physiological processes, allowing them to be timed to the most appropriate time of the day. Environmental conditions also change rhythmically and so precise synchronization of internal biological processes is advantageous for plant fitness and survival (Dodd et al. 2005). Light-activated photoreceptors provide an effective input to synchronize the oscillator to environmental cycles (Somers et al. 1998, McClung et al. 2002).

UV-B perceived by UVR8 also acts as an entraining signal for the circadian clock (Feher et al. 2011). In addition to UVR8, COP1 is required for this process, but HY5 and HYH are dispensable. The expression of select clock genes is UV-B-responsive, indicating that UV-B entrains the plant clock via transcriptional activation. Moreover, UV-B induction of clock gene expression is gated by the clock. It should be noted however that the UV-B response in general is not under circadian control, as, for example, UV-B-dependent induction of *HY5* expression does not follow a circadian rhythm (Feher et al. 2011). Interestingly, in arrhythmic *elf3* (*early flowering 3*) mutants, UV-B-induced gene expression is enhanced and the circadian gating of such expression is lost, but *elf3* plants display no more tolerance to UV-B stress compared to wild type (Feher et al. 2011). It is thus considered that temporal restriction of UV-B-specific responses by the clock may limit metabolic energy costs without compromising UV-B protection. However, the exact role of clock-regulated UV-B gene expression induction remains to be determined.

Plant-Herbivore and Plant-Pathogen Interactions

Light, including UV-B, is emerging as an important regulator of plant immune responses against pathogens and herbivores. In particular, solar UV-B has emerged as a positive modulator of plant defense (Ballare et al. 2012). Most reports of this positive UV-B effect arise from studies of plant-herbivore interaction, where UV-B is often seen to reduce plant herbivory by insects (Kuhlmann and Müller 2011, Ballare et al. 2012). As yet, the UVR8 pathway has not been linked directly to reduced herbivory. However, the reported effects are induced by relatively low UV-B irradiances under field conditions, where plants are grown in the absence of visible UV-B stress symptoms. This indicates that the UVR8 UV-B photoreceptor is likely involved (Demkura et al. 2010, Ballare et al. 2012).

A recent study in *Arabidopsis* shows that UV-B confers cross-resistance to a fungal pathogen and addresses the role of UVR8 in this phenomenon (Demkura and Ballare 2012). As described above, UVR8-mediated UV-B perception leads to increased accumulation of flavonoids and sinapates in leaf tissues. An UV-B-induced defense response against the necrotrophic fungus *Botrytis cinerea* was seen to be maintained in mutant plants impaired in flavonoid biosynthesis, whereas this cross-resistance was abolished in sinapate biosynthesis mutants (Demkura and Ballare 2012). Thus, UVR8 apparently mediates UV-B-induced pathogen resistance by regulating sinapate, but not flavonoid, accumulation. Interestingly, the positive effect of UV-B on plant pathogen resistance is independent of jasmonate (JA) signaling and tryptophan-derived defense compounds, such as indolic glucosinolates or camalexin (Demkura and Ballare 2012). Thus, UV-B exposure and UVR8 signaling seems to provide pathogen cross-resistance at least partially through accumulation of common phenylpropanoids that function in response to both stress factors. However, how much this UV-B effect translates to enhanced pathogen resistance in the field requires further investigation.

Plant defence responses to pathogen attack were shown to take priority over UV-B protection in terms of metabolic resource allocation. Pathogen attack suppresses UV-B-induced accumulation of certain flavonols, a phenomenon observed in several plant species which indicates such a cross-talk mechanism has been evolutionary conserved (Dangl et al. 1987, Lozoya et al. 1991, Logemann and Hahlbrock 2002, Schenke et al. 2011, Serrano et al. 2012). However, a suppression of the UV-B response when pathogen defence is active seems to be specific for UV-B-responsive regulation of phenylpropanoids (Serrano et al. 2012). Since UV-B-induced HY5 accumulation is maintained in the presence of pathogen elicitors, it seems that UV-B acclimation is not impaired in general under pathogen attack (Serrano et al. 2012). Thus, under conditions that lead to UV-B response/plant defence crosstalk, reduced accumulation of certain UV-B-induced phenylpropanoids may result from the preferential allocation of common metabolite precursors towards production of pathogen-defence-associated molecules.

CONCLUSIONS AND PERSPECTIVES

The UVR8 UV-B photoreceptor is important for the acclimation of plants to potentially damaging UV-B radiation and thus contributes to plant survival in sunlight. Research combining genetic, biochemical, and molecular approaches in *Arabidopsis thaliana* was crucial for initial characterisation of the molecular UV-B signaling pathway. Using Arabidopsis, recent successes have led to identification and mechanistic characterisation of key players in UV-B perception and signaling. Specifically, UVR8-mediated UV-B perception and the subsequent UVR8-COP1 interaction have emerged as a central, primary mechanism for UV-B signaling. Through identification of the UVR8 UV-B photoreceptor and major downstream signaling components, we are now poised to address a number of open questions, including: How broadly are physiological UV-B responses mediated by UVR8? In this context, do additional UV-B photoreceptors exist and, if so, what are their roles and molecular identities? How does UVR8 regulate gene expression? How does the UVR8 pathway cross-talk and integrate with visible light photoreceptor pathways?

Such questions are designed to further our basic understanding of the intriguing UV-B perception and signaling mechanism in plants. Alongside this, numerous applications of our newfound knowledge can be envisaged. A very specific application is in the rapidly developing field of optogenetics where different photoreceptors are used to generate light-controlled modules that in turn control the function and localization of diverse proteins (Toettcher et al. 2011, Müller and Weber 2013). The specificity and sensitivity of UVR8 to UV-B indicate that it will be a promising addition to the optogenetic toolkit, allowing UV-B to exert regulation in a

visible light background. Indeed, first implementations of UVR8 in novel optogenetic systems were recently reported whereby UV-B was used to control nuclear retention, chromatin association, protein secretion and gene expression in mammalian cells (Chen et al. 2013, Crefcoeur et al. 2013, Müller et al. 2013). In agriculture, our increasing knowledge of UV-B protective mechanisms employed by the plant may potentially lead to industrial applications. UVR8-mediated UV-B signaling may be exploited to mitigate the undesirable effects or harness the desirable effects of UV-B exposure, to overall improve plant productivity and quality (Wargent and Jordan 2013). For example, changes in plant secondary metabolism in response to UV-B should be considered in terms of nutritional value (Jansen et al. 2008, Schreiner et al. 2012). Also, with a clearer understanding of the interplay between UV-B, phytohormones and responses to other environmental cues (including high light), UVR8 UV-B signaling may prove a means to manipulate plant growth and/or plant tolerance to abiotic and biotic stress.

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