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REVIEW PAPER

Illuminating light, cytokinin, and ethylene signalling crosstalk in plant development

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Abstract

Integrating important environmental signals with intrinsic developmental programmes is a crucial adaptive requirement for plant growth, survival, and reproduction. Key environmental cues include changes in several light variables, while important intrinsic (and highly interactive) regulators of many developmental processes include the phytohormones cytokinins (CKs) and ethylene. Here, we discuss the latest discoveries regarding the molecular mechanisms mediating CK/ethylene crosstalk at diverse levels of biosynthetic and metabolic pathways and their complex interactions with light. Furthermore, we summarize evidence indicating that multiple hormonal and light signals are integrated in the multistep phosphorelay (MSP) pathway, a backbone signalling pathway in plants. *Inter alia*, there are strong overlaps in subcellular localizations and functional similarities in components of these pathways, including receptors and various downstream agents. We highlight recent research demonstrating the importance of CK/ethylene/light crosstalk in selected aspects of plant development, particularly seed germination and early seedling development. The findings clearly demonstrate the crucial integration of plant responses to phytohormones and adaptive responses to environmental cues. Finally, we tentatively identify key future challenges to refine our understanding of the molecular mechanisms mediating crosstalk between light and hormonal signals, and their integration during plant life cycles.

Key words: Crosstalk, light, cytokinin, ethylene, multistep phosphorelay, development.

Introduction

As sessile organisms, plants require the abilities to sense environmental signals regarding current and probable future conditions, and to respond in adaptive manners that permit their growth, development, and reproduction. Therefore, the integration of various external signals with endogenous developmental programmes is essential for their survival. Key environmental cues including changes in several light variables, while major intrinsic regulators of many developmental processes include the plant hormones.

Plants need to respond to light originating from different directions, with varying frequencies, qualities, and quantities. Thus, they can recognize wide bands of the light spectrum, ranging from UV-B through UV-A/blue and red (R) to far-red (FR) light, via several classes of photoreceptors,

Abbreviations: bHLH, basic helix–loop–helix; CK, cytokinin; cZ, *cis*-zeatin; ER, endoplasmic reticulum; FR, far red; HK, histidine kinase; HPt, His-containing phosphotransfer; iP, isopentenyladenine; MSP, multistep phosphorelay; R, red; RAM, root apical meristem; RD, receiver domain; RR, response regulator; TF, transcription factor; tZ, *trans*-zeatin; WT, wild type.

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including phytochromes, cryptochromes, and phototropins. Phytochrome receptors are responsible for most of their light perception (Quail *et al.*, 1995; Rockwell *et al.*, 2006). All members of the phytochrome family (phyA–E) can sense R light, while FR light is only recognized by phyA. UV-A and blue light are believed to be perceived mainly by phototropins and cryptochromes (Chen *et al.*, 2004), although some other UV-A and UV-B light receptors, e.g. UVR8, have also been identified recently (Christie *et al.*, 2012).

Phytochromes are synthesized as apoproteins, and dimerize and bind to the light-absorbing chromophore to form a light-responsive holoprotein. Inactive (Pr) forms, localized in the cytoplasm, become biologically active (Pfr) forms upon light perception, resulting in changes in their conformation, autophosphorylation, and migration to the nucleus (Yeh and Lagarias, 1998; Yamaguchi *et al.*, 1999; Fankhauser, 2000; Nagy and Schafer, 2000; Kircher *et al.*, 2002). Phys display Ser/Thr kinase activity, allowing them to phosphorylate several substrates (Yeh and Lagarias, 1998; Fankhauser *et al.*, 1999; Schaller *et al.*, 2008). Similarly, they can be dephosphorylated by several protein phosphatases (Kim *et al.*, 2002; Ryu *et al.*, 2005; Phee *et al.*, 2008). Current evidence indicates that the main downstream regulators of phytochromes are the PHYTOCHROME-INTERACTING FACTORs (PIFs) (reviewed by Duek and Fankhauser, 2005; Castillon *et al.*, 2007; Kami *et al.*, 2010; Leivar and Quail, 2010). PIFs represent a subfamily of 15 basic helix–loop–helix (bHLH) light-associated transcription factors (TFs), which act mostly as repressors of light-activated genes but also as positive regulators of dark-induced genes. Light-activated phytochromes induce the phosphorylation and rapid degradation of PIFs (Al-Sady *et al.*, 2006; Shen *et al.*, 2007, 2008). This requires direct interaction between phytochromes and PIFs, but the role of phytochrome kinase activity in light-regulated gene expression is still unclear (reviewed by Kami *et al.*, 2010; Li *et al.*, 2011).

A further important downstream regulation of the phytochrome-mediated pathway occurs via the repression of CONSTITUTIVE PHOTOMORPHOGENIC 1 (COP1) E3 ubiquitin ligase activity (Seo *et al.*, 2004; Jang *et al.*, 2010). Inactivated COP1 cannot target the photomorphogenic (positive) TFs (e.g. HY5, HYH or LAF1, or HFR1; Osterlund *et al.*, 2000; Holm *et al.*, 2002; Seo *et al.*, 2003; Duek *et al.*, 2004; Jang *et al.*, 2005; Yang *et al.*, 2005) for ubiquitination, thereby permitting the rapid light-induced response to proceed. The PIF- and COP1-mediated light signalling is interconnected. COP1 positively regulates the PIF level (Bauer *et al.*, 2004; Leivar *et al.*, 2008). The level of phytochromes is also regulated via COP1-targeted degradation (Seo *et al.*, 2004; Jang *et al.*, 2010). In addition, PIFs contribute to the degradation of phyB by promoting phyB/COP1 interaction (Jang *et al.*, 2010). For more details about phytochromes and their protein–protein interactions and signalling, we refer readers to several excellent recent reviews (Bae and Choi, 2008; Kami *et al.*, 2010; Li *et al.*, 2011; Quail, 2011).

Plant adaptive light-mediated responses are controlled and modulated by diverse plant hormones, particularly (but certainly not only) cytokinins (CKs) and ethylene. Signals from light and hormonal signalling pathways are integrated at various levels of complex regulatory cascades, including signal recognition, transcription, translation, and diverse mechanisms that influence protein stability and hormone dynamics. The main goal of this review is to provide an overview of current knowledge of the molecular mechanisms mediating crosstalk between light (as one of the most important environmental signals), CKs, and ethylene. These stimuli are recognized by receptors that have similarity to sensor histidine kinases, implying that they may mediate interactions among signals transmitted by the pathways. Accordingly, several studies suggest that crosstalk among light, CKs, and ethylene can occur at the signalling level. However, current molecular data also indicate the existence of extensive crosstalk between light and metabolic pathways of both growth regulators. Here, we focus first on the latter, describing the cross-connections between light and both phytohormones at the biosynthesis and metabolism levels. Then, we overview recent research on CK and ethylene signal transduction pathways, highlighting similarities and differences in their perception and signal transduction, aiming to identify common targets that may be involved in the integration of light, CKs, and ethylene signals in a single signalling pathway. Finally, we address selected illustrative developmental processes that are strongly modulated by light/hormonal crosstalk.

Light crosstalk with CKs and ethylene at the biosynthesis and metabolism levels

CK biosynthesis

CKs are N6-substituted adenine derivatives with an isoprenoid or aromatic side chain. The isoprenoid side chain of isopentenyladenine (iP) can be hydroxylated in *cis* or *trans* positions, forming *cis*-zeatin (cZ) and *trans*-zeatin (tZ), respectively. The side chain of these species may also be reduced, forming dihydrozeatin. The conformation and structure of the side chain strongly influence the biological activities and functions of CKs. Notably, cZ generally displays significantly lower biological activity than tZ (Schmitz and Skoog, 1972; Kaminek *et al.*, 1987). However, cZ is the dominant CK in some species, such as potatoes, maize, rice, and legumes (Mauk and Langille, 1978; Takagi *et al.*, 1985; Veach *et al.*, 2003; Quesnelle and Emery, 2007; Vyroubalova *et al.*, 2009). Furthermore, it is the dominant CK in roots of hop (*Humulus lupulus*; Watanabe *et al.*, 1982), maize (*Zea mays*; Veach *et al.*, 2003; Saleem *et al.*, 2010), and *Arabidopsis* (Zdarska *et al.*, 2013). Some of the hydroxylated CKs are also resistant to degradation (see below), and the presence of a hydroxyl group allows further side-chain modification by *O*-glucosylation, which converts CKs into their storage forms, as described below and reviewed by Sakakibara (2006) and Frebort *et al.* (2011).

Currently, isoprenoid CK biosynthesis has been described, but the origin of aromatic CKs remains unclear. The crucial step in the biosynthesis of isoprenoid CKs is catalysed by adenosine phosphate-isopentenyltransferases (IPTs) (Kakimoto, 2001; Takei *et al.*, 2001). Nine isoforms of IPTs

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(AtIPT1–AtIPT9) are known in *Arabidopsis* (Kakimoto, 2001), but only seven (AtIPT1 and AtIPT3–AtIPT8) catalyse the key *N*-prenylation of adenosine-5'-phosphates (ATP, ADM, and AMP) at the N6 end with dimethylallyl diphosphate that results in N^6-(Δ^2-isopentenyl)adenine ribotide formation. Further metabolic steps lead to the side-chain modifications and synthesis of iP riboside 5-diphosphate and iP riboside 5-monophosphate, which provide metabolic pools for the synthesis of zeatin, isopentenyl CKs and their ribosides. tZ ribotides are produced by hydroxylation of iP ribotide side-chains via CYP735A (Takei *et al.*, 2004).

An alternative CK production route is via the modification of tRNAs (Golovko *et al.*, 2002), probably catalysed by tRNA-specific IPTs (AtIPT2 and AtIPT9 in *Arabidopsis*; Miyawaki *et al.*, 2006), but this pathway seems to be rather minor. Another alternative provides a direct means of zeatin production without isopentenyl intermediates. Here, the IPT seems to mediate *N*-prenylation of ATP/ADP/AMP using a hydroxylated version of dimethylallyl diphosphate, hydroxymethylbutenyl diphosphate (Åstot *et al.*, 2000). A further important modification of the 'classical' sequential view of CK metabolism occurs via LONELY GUY (LOG), which converts biologically inactive CK nucleotides into active free bases in a single-step reaction. This allows rapid activation of inactive CK pools, with a strong developmental impact via the regulation of shoot and root meristem activities (Kurakawa *et al.*, 2007; Kuroha *et al.*, 2009; Chickarmane *et al.*, 2012; Tokunaga *et al.*, 2012), leaf senescence (Kuroha *et al.*, 2009), nodule primordium development, lateral root formation (Mortier *et al.*, 2014), and vascular tissue formation in early embryogenesis (De Rybel *et al.*, 2014).

The final content of endogenous CKs is dependent on the balance between *de novo* synthesis, transport, isoform conversion, inactivation by conjugation (mainly glucosylation), and degradation (Sakakibara *et al.*, 2006). Important metabolic transformations include N7 and N9 glucosylations of the adenine moiety, forming *N*-glucosides. Alternatively, the hydroxyl group of zeatin-type CKs can be glucosylated or xylosylated, thereby respectively generating zeatin-*O*-glucosides and *O*-xylosides, which are biologically inactive (Sakakibara *et al.*, 2006). However, while *N*-glucosidation leads to irreversible CK inactivation, *O*-glucosides are considered as storage CK forms that can be reactivated by β-glucosidases (Brzobohaty *et al.*, 1993). CYTOKININ OXIDASE/DEHYDROGENASE (CKX) irreversibly inactivates CK via degradation (Paces *et al.*, 1971; Werner *et al.*, 2003). However, several CK forms, e.g. zeatin-*O*-glycosyl derivatives and dihydrozeatin, are resistant to CKX-mediated degradation (Laloue and Pethe, 1982).

Illuminating CK biosynthesis and metabolism

Few studies have addressed the role of light in CK metabolism as yet, despite indications that it can strongly influence CK activity and degradation, including the following observations. Kraepiel *et al.* (1995) detected 2-fold lower than wild-type (WT) zeatin levels in light signalling-defective *pew1* and *pew2* mutants of *Nicotiana plumbaginifolia*, although levels of iP and other CK ribosides were not affected by the mutations. The *pew1* chromophore biosynthetic mutation causes deficiency in all phytochrome types of photosensors, and *pew2* does not express phytochromes in the darkness (Kraepiel *et al.*, 1995), thus resembling *aurea* tomato mutants (Sharma *et al.*, 1993). In addition, stronger increases in levels of tZ and zeatin-type ribosides have been detected in detached, senescing barley leaves in the light than in the dark, clearly indicating a role of light in CK metabolism during senescence (Zubo *et al.*, 2008). However, apparently conflicting upregulation of *CKX* expression and CK degradative activity under periodic illumination (relative to dark incubation) has also been observed in detached, senescing barley leaves (Schluter *et al.*, 2011). Similarly, *Cucurbita pepo* cotyledons exhibit lower CKX activity in the dark than under periodic illumination (Ananieva *et al.*, 2008). In stark contrast, the opposite pattern has been observed in intact barley plants, i.e. the downregulation of CKX activity after illumination. Increases in *AtCKX2* and *AtCKX5* expression have also been demonstrated in *Arabidopsis* leaves of intact plants incubated in the dark (Buchanan-Wollaston *et al.*, 2005; van der Graaff *et al.*, 2006; Schluter *et al.*, 2011). Interestingly, the upregulation of *CKX* expression seems to be slower in intact plants than in detached leaves. Thus, the differences observed between intact and detached barley leaves might be related to the transport of substances in intact plants. Alternatively, other factors (e.g. responses to wounding or other stress factors) could influence final CK contents, possibly in a tissue- and species-specific manner.

The final observations to be mentioned in this section concern rapid, light-modulated changes in CK levels recorded during germination of Scots pine (*Pinus silvestris L.*) seeds by Qamaruddin and Tillberg (1989). They did not detect the tZ riboside (using high-performance liquid chromatography and immunoassays) in imbibed seeds, but iP levels (detected by gas chromatography/mass spectrometry) were low in the dark, increased by 15 min pulses of R light, and decreased by 10 min pulses of FR light (Qamaruddin and Tillberg, 1989).

In conclusion, current data suggest that light is an important factor in the control of CK biosynthesis and metabolism. Indications that zeatin contents are reduced in the *N. plumbaginifolia* phytochrome-deficient *pew* mutants, and the dependence of iP content upon R/FR light treatment in Scots pine seeds, suggest that phytochrome receptors could play important roles in the regulation of CK levels. However, the downstream signalling intermediates, and details of the signalling pathway regulating *CKX* expression in a light-dependent manner, remain unclear.

Ethylene biosynthesis

Ethylene is synthesized in all almost all tissues of all higher plants (Schaller and Kieber, 2002), via four key catalytic steps. The first, formation of methionine (Met) from homocysteine, is catalysed by methionine synthase. Met is further converted into *S*-adenosyl-methionine (AdoMet) by AdoMet synthetase. AdoMet acts as a precursor in many biosynthetic pathways including the production of polyamines.

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Its conversion to 1-aminocyclopropane-1-carboxylic acid (ACC), catalysed by ACC synthase (ACS), is considered a rate-limiting step of ethylene biosynthesis. In the *Arabidopsis* genome, there are 12 recognized *ACS* genes (*ACS1–ACS12*), but only *ACS2*, *ACS4–ACS9* and *ACS11* encode genuine ACC synthases (Yamagami *et al.*, 2003; Tsuchisaka and Theologis, 2004; Tsuchisaka *et al.*, 2009). The ACS enzymes also display specific expression patterns according to developmental context and responses to environmental stimuli. In the final step, ACC oxidase (ACO) catalyses ACC conversion into ethylene. For a detailed review of ethylene biosynthesis, see, for instance, Wang *et al.* (2002).

Light and ethylene biosynthesis

Research into the light dependence of ethylene biosynthesis has uncovered many important regulatory mechanisms. R light downregulates ethylene production in etiolated pea, rice, garden balsam, wheat, and bean seedlings, and in some cases, this negative effect of R light can be reversed by FR light (Imaseki *et al.*, 1971; Kang and Burg, 1972; Jiao *et al.*, 1987; Vangronsveld *et al.*, 1988; Michalczuk and Rudnicki, 1993; Steed *et al.*, 2004). Interestingly, light intensity analyses show that FR-enriched light and/or low-intensity light induce increases in ethylene levels in sorghum and tobacco plants (Finlayson *et al.*, 1998; Pierik *et al.*, 2004). Correspondingly, *Arabidopsis* plants grown under low light show enhanced levels of *ACS6*, *ACS8*, *ACS9*, and *ACS11* transcripts and upregulated ethylene production, while *ACS6*, *ACS8*, and *ACS11* transcript levels are higher than WT levels in the *phyB-9* mutant, even if grown in high-intensity light (Vandenbussche *et al.*, 2003). In contrast, ethylene production reportedly reaches around 10-fold higher levels in light-grown than in etiolated *Arabidopsis* seedlings (Vogel *et al.*, 1998), suggesting a more complex relationship between light and ethylene biosynthesis. Accordingly, ethylene biosynthesis has strong, proven dependence on the species, tissues, developmental phase, and both the quality and quantity of incident light (Corbineau *et al.*, 1995).

The mentioned (mostly negative) effects of both R and FR light on ethylene production imply possible roles for both phyA and phyB in light-modulated ethylene production, since these are the most important phytochromes mediating responses to both FR and R light. Accordingly, studies focused on *phy*-deficient *Arabidopsis* and tobacco plants have highlighted a role for phyB in mediating reductions in ethylene content and sensitivity (Finlayson *et al.*, 1998; Vandenbussche *et al.*, 2003; Pierik *et al.*, 2004; Bours *et al.*, 2013). The role of phyA was demonstrated in a comparison of single *phyA* and *phyB* and double *phyA phyB* mutants, which indicated that the phyA photoreceptor plays a prominent role in the downregulation of ethylene accumulation in pea. The *phyA* mutant, but not the *phyB* mutant, had a similar phenotype to plants with elevated ethylene contents (Foo *et al.*, 2006), prompting these authors to suggest that the important *phy*-dependent traits and responses (e.g. *phy*-dependent inhibition of stem and internode elongation) are mediated by changes in ethylene levels.

Although the importance of photoreceptors and phytochrome-mediated signalling has been broadly studied and confirmed, there is limited evidence regarding the downstream molecular mechanisms involved in the light-mediated control of ethylene production/accumulation (Finlayson *et al.*, 1998; Vandenbussche *et al.*, 2003; Foo *et al.*, 2006; Bours *et al.*, 2013). Khanna *et al.* (2007) showed that seedlings overexpressing a negative regulator of light signalling, *PHYTOCHROME-INTERACTING FACTOR 5* (*PIF5*), had enhanced levels of the ethylene biosynthetic enzymes ACS4 and ACS8, and produce 4-fold higher levels of ethylene than etiolated WT seedlings. However, this effect of *PIF5* overexpression on ethylene levels can be reversed by continuous red light treatment. Interestingly, no differences were observed in either continuous red- or dark-grown seedlings of the *pif5* mutant relative to WT seedlings. This unexpected lack of *pif5* impact on ethylene production led Khanna *et al.* (2007) to propose a spatially specific effect of PIF5 on ethylene levels that is not detectable by quantitative reverse transcription PCR analysis and ethylene measurements of material isolated from entire seedlings, and/or redundancy with other PIFs or ACS proteins. However, it should be noted that *PIF5* overexpression seems to have rather specific effects on ethylene regulation, as lines overexpressing closely related *PIF*s—*PIF1* (Shen *et al.*, 2005), *PIF3* (Al-Sady *et al.*, 2006), and *PIF4* (Huq and Quail, 2002) do not show enhanced ethylene production. Khanna *et al.* (2007) also demonstrated that, in continuous red light, phyB levels are reduced in *PIF5*-overexpressing seedlings but elevated in *pif5* mutants, indicating that PIF5 plays an important role in the regulation of phytochrome abundance.

As well as the light-mediated transcriptional controls of ethylene biosynthetic genes mentioned above, light-dependent regulation of ethylene biosynthesis involves various mechanisms that influence the stability or activities of key proteins, notably ACS stability. For example, analysis of *ACS5* dominant and recessive mutants has indicated that ACS5 is regulated post-transcriptionally by various stimuli. Seedlings of *Arabidopsis ethylene overproducer 2* (*eto2*) mutants, in which the C terminus of ACS5 is affected, exhibit at least 20-fold higher ethylene production than WT counterparts in darkness but only a slight increase in the light. These findings indicate that ACS5 makes a minor contribution to the ethylene production of light-grown *Arabidopsis* seedlings and that the C terminus of ACS5 represses ethylene production, particularly in the dark (Vogel *et al.*, 1998).

In addition, recent findings show that ACS5 is directly stabilized by the binding of 14-3-3 proteins (Yoon and Kieber, 2013). In parallel, 14-3-3 binds to the ETHYLENE OVERPRODUCER1 (ETO1) and its paralogues ETO1-LIKE1 and ETO1-LIKE2 proteins (EOLs), the negative regulators of ACS5. ETO1/EOLs are components of CULLIN E3 ligase and target a subset of ACS proteins for ubiquitination and 26S proteasome-mediated degradation. In contrast to the protective effect observed towards ACS5, binding of 14-3-3 proteins destabilizes ETO1/EOLs via an as yet unknown mechanism. Interestingly, Yoon and Kieber (2013) observed that light treatment of etiolated seedlings stabilizes ACS5 but destabilizes ETO1/EOLs, implying that

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light-mediated destabilization of ETO1/EOLs might contribute to the increase in ASC5 stability upon light irradiation. 14-3-3 proteins are also implicated in the regulation of other plant signalling systems, including systems involving other phytohormones, pathogen defence, stress, and light-mediated responses, e.g. flowering and stomatal opening (Mayfield *et al.*, 2007; Denison *et al.*, 2011; Tseng *et al.*, 2012). Thus, 14-3-3 proteins are promising candidates for mediators of some of the crosstalk between light and hormonal regulatory pathways. However, the upstream molecular mechanisms involved in light-affected changes in ACS5 and ETO1/EOL stability remain to be elucidated. The importance of non-transcriptional regulatory mechanisms in the light-dependent control of ethylene biosynthesis is supported by further experimental observations presented by Steed *et al.* (2004) of reductions in ethylene content in illuminated pea epicotyls that were not accompanied by changes in *PsACS1*, *PsACS2*, and *PsACO1* transcript levels. This suggests that light-dependent post-transcriptional regulation of ethylene biosynthetic pathway components may also play a role.

The indirect effect of light on ethylene biosynthesis mediated by light-regulated CO_2 content has also been investigated (de Laat *et al.*, 1981; Bassi and Spencer, 1982; Preger and Gepstein, 1984). CO_2 is an essential activator of ACO; in the presence of 4% CO_2, its activity is 10 times higher than in atmospheres with normal CO_2 content of 0.03% (Dong *et al.*, 1992; Smith and John, 1993). A rapid change from low-light to high-light intensity leads to an immediate reduction in ethylene production (Vandenbussche *et al.*, 2003). These authors hypothesized that, in low-light conditions, the amount of CO_2 is sufficient to mediate high ACO activity. However, in high-light conditions, photosynthesis activity and Rubisco content increase, competing for CO_2 with ACO and thus reducing its activity. This is consistent with the inhibitory effects of light on ethylene biosynthesis observed in green tissues (Yang and Hoffman, 1984).

Light also entrains a circadian clock via signals transduced through the phytochromes and cryptochromes to the central oscillator. Moreover, the circadian clock regulates the level of phytochrome expression, which might constitute a feedback loop involved in clock adjustment (Toth *et al.*, 2001). The expression of *ACS8* is also controlled by the circadian clock, and thus is probably responsible for the rhythmic changes in ethylene production (Thain *et al.*, 2004).

The diversity of the mechanisms and regulatory levels involved clearly indicates that tight co-ordination of light and ethylene (and other) signalling pathways is required for successful plant growth and development.

CKs tightly control ethylene biosynthesis

It has been known for decades that CKs play an important role in the regulation of ethylene biosynthesis. However, in contrast to our recent understanding of CKs as predominantly positive regulators of ethylene production, the first relevant studies published in the late 1970s and early 1980s indicated that CKs play a negative role in the process. For example, CK application to carnation flowers was found to induce delays in senescence associated with reductions in ethylene biosynthesis (Eisinger, 1977; Mor *et al.*, 1983). Later, delays in flowering correlating with increases in CK levels and delays in ethylene biosynthesis were observed in petunia (Chang *et al.*, 2003). However, Cary *et al.* (1995) showed that CKs (at 0.5–10 μM) could induce ethylene production and morphological changes resembling the triple response (hypocotyl shortening and thickening with exaggerated hook formation) typically associated with ethylene. Furthermore, at the molecular level, CKs enhance the stability of several ACS, and in 1998, Vogel *et al.* (1998) proposed that CKs may stimulate ACS5 post-transcriptionally. Their data showed only modest and transient upregulation of *ACS5* mRNA levels following CK induction, which appears to be insufficient to account for the strong observed induction of ethylene biosynthesis. Subsequently, CK-mediated stabilization of the ACS5 protein was verified by Chae *et al.* (2003), and Hansen *et al.* (2009) demonstrated that ACS9 is also stabilized by CKs. In addition, recent proteomic analysis of CK effects on roots and shoots has shown that all three remaining enzymes of the ethylene biosynthetic pathway are rapidly upregulated by CKs, namely MET SYNTHASE1 (AtMS1; AT5G17920), MET ADENOSYLTRANSFERASE3 (MAT3; AT2G36880), and ACC OXIDASE2 (ACO2; AT1G62380). Importantly, this CK effect is root specific (Zdarska *et al.*, 2013). The tissue-specific importance of CK effects on ethylene biosynthesis has been confirmed by measurements of endogenous ACC levels, demonstrating that CK treatment does not affect ACC levels in the shoot. In contrast, in roots of non-treated controls, ACC levels are below detection limits, while endogenous ACC amounts can rise to levels comparable to those in the shoot within just 30 min of CK treatment (Zdarska *et al.*, 2013). Besides non-transcriptional regulatory mechanisms, *ACO* activity is also modulated by CK at the mRNA level. For example, Shi *et al.* (2013) found that transcripts of an ACO-like protein (*So-lyc11g045520*) were upregulated 24 h (but not 2 h) after exogenously applying CK to tomato leaves.

In addition to the studies cited above, Heiser *et al.* (1998) proposed that ethylene may be produced independently of the phytochrome signalling and general ethylene biosynthetic pathway. They found that, in the presence of light, riboflavin, and catalytic copper, CKs can induce strong photo-oxidation of fatty acids in the plasma membrane (e.g. α-linolenic acid, according to reported *in vitro* tests), yielding small amounts of ethane and ethylene. However, the importance of this finding for *in planta* ethylene production remains to be clarified (Heiser *et al.*, 1998).

In summary, there is abundant published evidence that CKs can affect ethylene biosynthesis. The possibility that ethylene may affect CK biosynthesis and dynamics has also been considered, although there is little empirical support for the hypothesis as yet. One of the rare studies describes the influence of ethylene on CK content during senescence in *Petunia corolla* (Taverner *et al.*, 1999). In this study, the senescence of petunia is preceded by an accumulation of CK *O*-glucosides. Exogenously applied ethylene was seen to promote the conversion of dihydrozeatin to its *O*-glucosides and zeatin riboside to adenosine and AMP. Thus, it seems that

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ethylene-induced senescence of *P. corolla* is associated with an ethylene-dependent CK inactivation and degradation.

Integration of light, CK, and ethylene signals in multistep phosphorelay (MSP) systems

Signal perception

Organisms of all kingdoms have evolved diverse signalling networks that are essential for appropriate adaptive responses to numerous environmental stimuli. Extensive crosstalk among the pathways is also essential, not only for prompt adaptive responses to environmental changes but also for their tight co-ordination with intrinsic developmental programmes. Accordingly, various findings imply that key developmental pathways in plants, often under the control of hormones such as CK and ethylene, are tightly integrated with light-mediated responses. In the following sections, we discuss several examples demonstrating this emerging phenomenon, emphasizing the integrative role of MSP signalling.

The MSP pathway and CK signalling

Bacteria sense and transduce a plethora of environmental signals, most frequently via two-component signalling pathways. In such systems, signals are recognized by sensor histidine kinases (HKs) that autophosphorylate and transfer the phosphate groups via one-step transphosphorylation to response regulators (RRs), which mostly act as TFs in bacteria. Phosphorylation of RRs activates their respective output domains, leading to changes in the expression of target genes (for a recent review, see Capra and Laub, 2012). Some bacteria have evolved a more advanced system called multistep phosphorelay (MSP), which, with some modifications, was adopted by plants. In MSP, the signal is recognized via hybrid sensor HKs, encompassing both an HK and RR-similar receiver domain (RD). Thus, after signal perception and autophosphorylation, the first transphosphorylation reaction occurs intramolecularly (between a His residue in the HK domain and an Asp residue in the RD of the hybrid sensor HK). Interaction between the phosphorylated RD and small cytoplasmic His-containing phosphotransfer (HPt) proteins subsequently results in transmission of the phosphate from the Asp of the RD to conserved His residues in the HPts. The phosphorylated HPts can relocate from the cytosol to the nucleus, where they putatively allow phosphorylation of a conserved Asp in the RDs of RRs.

Involvement of HK activity in CK signalling was raised by discovery of CYTOKININ-INDEPENDENT 1 (CKI1) (Kakimoto, 1996). The activity of CKI1 was subsequently shown to be constitutive and independent of CK binding, although CKI1 acts through the CK signalling pathway (Hwang and Sheen, 2001; Hejatko *et al.*, 2009). Nonetheless, the idea that CK signalling operates through phosphorylation steps mediated by HKs involved in the MSP pathway was later proven to be correct (Inoue *et al.*, 2001; Higuchi *et al.*, 2004; Nishimura *et al.*, 2004; Riefler *et al.*, 2006).

The ability of HPts to receive signals from several HKs and mediate specific downstream responses through RRs is an important feature of MSP systems. Thus, HPts could be considered as hubs integrating signals generated by various stimuli into a single MSP pathway. *Arabidopsis* contains six HPts [ARABIDOPSIS HISTIDINE CONTAINING PHOSPHOTRANSMITTERS (AHPs)]. Five of these (AHP1–AHP5) function as positive regulators of CK signalling (Hutchison *et al.*, 2006), while the other (AHP6) lacks the conserved His residue and appears to be a negative regulator of CK signalling in CK-controlled cell fate determination during vascular development. In addition, *AHP6* is negatively controlled by CK signalling, thus closing the regulatory feedback loop (Mahonen *et al.*, 2006). In the *Arabidopsis* nucleus, phosphorylated AHP1–AHP5 activate type B *Arabidopsis* RRs (ARRs-B), which act as TFs mediating expression of the CK primary-response genes, including type A *ARABIDOPSIS RESPONSE REGULATORS* (*ARRs-A*). In turn, ARRs-A function as negative regulators of CK signalling (To *et al.*, 2004; To and Kieber, 2008).

Ethylene signalling pathways

Ethylene is recognized by several membrane-bound ethylene receptors, including ETHYLENE RESPONSIVE1 (ETR1), ETR2, ETHYLENE RESPONSE SENSOR1 (ERS1), ERS2 and ETHYLENE INSENSITIVE4 (EIN4) (Bleecker *et al.*, 1988; Chang *et al.*, 1993; Hua and Meyerowitz, 1998; Hua *et al.*, 1998; Sakai *et al.*, 1998). Ethylene receptors act as negative regulators of ethylene signalling in the absence of ethylene via activation of the Ser/Thr kinase CONSTITUTIVE TRIPLE RESPONSE1 (CTR1) (Kieber *et al.*, 1993), which homodimerizes when activated (Mayerhofer *et al.*, 2012). CTR1 interacts with ETHYLENE INSENSITIVE 2 (EIN2) (Ju *et al.*, 2012) and directly phosphorylates the EIN2 C-terminal end causing its inactivation. EIN2 levels are downregulated with the help of F-box proteins, EIN2 TARGETING PROTEIN 1 and 2 (ETP1/2), through action of the 26S proteasome (Qiao *et al.*, 2009).

In addition, in the nucleus, EIN3-BINDING F BOX PROTEIN 1 and 2 (EBF1/2) target ETHYLENE INSENSITIVE3 (EIN3) and ETHYLENE-INSENSITIVE3-like 1(EIL1), which are positive TF regulators of ethylene signalling, for proteasome-mediated degradation, resulting in repression of downstream responses from this pathway (Guo and Ecker, 2003, 2004; Potuschak *et al.*, 2003; Gagne *et al.*, 2004).

In the presence of ethylene, binding of the hormone inactivates the receptors and the kinase activity of CTR1 via an as yet unknown mechanism. The CTR1 inactivation precludes the phosphorylation of EIN2, and the C-terminal end of non-phosphorylated EIN2 (EIN2C) is cleaved and translocates to the nucleus (Ju *et al.*, 2012; Qiao *et al.*, 2012; Wen *et al.*, 2012) where it stabilizes EIN3/EIL1 while promoting degradation of EBF1/2 proteins. Based on the available evidence, EIN3 and EIL1 seem to function as homodimers (Solano *et al.*,

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1998; Li *et al.*, 2012) and activate expression of ethylene-response genes, including the TF ERF1, which then activates a downstream transcriptional cascade resulting in activation or inhibition of many ethylene-target genes (Alonso *et al.*, 2003; Konishi and Yanagisawa, 2008; for detailed reviews see, for instance, Chen *et al.*, 2005b; Merchante *et al.*, 2013; Cho and Yoo, 2015).

Receptors: functions and localization

CK, ethylene, and light receptors: is there something in common?

The CK receptors AHK2, AHK3, and AHK4 (Higuchi *et al.*, 2004; Nishimura *et al.*, 2004; Riefler *et al.*, 2006) are fully functional HKs, consisting of N-terminal transmembrane domains and an extracellular CHASE domain that allows CK sensing via direct CK binding. The CHASE domain is common to transmembrane receptors of prokaryotes, lower eukaryotes, and plants (Anantharaman and Aravind, 2001; Mougel and Zhulin, 2001; Ueguchi *et al.*, 2001). AHK2, AHK3, and AHK4 contain a conserved His residue in the HK domain, which becomes phosphorylated after CK binding, and a conserved Asp in the RD domain to which the phosphate is transferred (Mougel and Zhulin, 2001; Yamada *et al.*, 2001).

The ethylene receptors are generally divided into two groups according to the structure of their intracellular domains. Subfamily I includes ETR1 and ERS1 receptors, both of which contain a functional HK domain. Subfamily II includes ETR2, ERS2, and EIN4, which possess a divergent HK domain lacking the conserved His residue (Bleecker, 1999). Accordingly, receptors of subfamily II act not as HKs but as Ser/Thr kinases (Moussatche and Klee, 2004). ETR1 was the first identified member of the ethylene receptor family (Chang *et al.*, 1993) and is also the only one that seems to exclusively exhibit HK activity (Gamble *et al.*, 1998; Moussatche and Klee, 2004). Although ERS1 can phosphorylate the conserved His residue *in vitro*, the biological relevance of its HK activity *in vivo* is questionable (Moussatche and Klee, 2004). Furthermore, ERS1 lacks the RD. Thus, the only ethylene receptor capable of transducing signals via His/Asp autophosphorylation seems to be ETR1, as it is the only one with both HK activity and an RD (Etheridge *et al.*, 2006). Consequently, ETR1 is the best candidate for a potential functional link between ethylene perception and MSP-mediated CK signalling. However, triple-response assays reported by Cho and Yoo (2007) with an *etr1-7* null mutant containing transformed cDNA of ETR1 affected in the codon for the only phosphorylatable His (H353) (Moussatche and Klee, 2004) have shown that HK activity of ETR1 is not required for ethylene signalling responses. Further analysis of a kinase-active and kinase-inactive form of ETR1 has revealed that both can rescue the constitutive ethylene triple-response phenotype of *etr1-9 ers1-3* double mutants in ethylene-free atmospheres ('air') and hence restore normal growth. This corroborates the hypothesis that HK activity of ETR1 is not directly required for ethylene signalling responses (Hall *et al.*, 2012). On the other hand, expression analyses of kinase-active and kinase-inactive constructs fused with a luciferase (LUC) reporter (ARR6–LUC; Hwang and Sheen, 2001) have indicated that ETR1 can activate the MSP pathway via the conserved HK (H353) and response regulator (D659) residues, thereby supporting plant growth (Cho and Yoo, 2007). In addition, the *etr1-9 ers1-3* mutants complemented with the kinase-inactive form of ETR1 showed ethylene sensitivity that was weaker than WT in the growth response assays, and slightly lower CTR1 levels in the 'air', suggesting that the HK activity of ETR1 contributes in some way to modulation of ethylene responses (Hall *et al.*, 2012). Overall, since the main impact of ETR1 on the ethylene response is mediated via the CTR1/EIN2 pathway, the modulatory effect might be conveyed through crosstalk of ETR1 with MSP signalling (Schaller *et al.*, 2011).

Generally, phytochromes can be considered to be composed of an N-terminal part consisting of PAS, GAF, and PHY domains and a C-terminal part containing a PAS-related domain (PRD) and an HK-related domain (HKRD). In comparison to similar photosensors from other organisms, plant phytochromes have an N-terminal extension domain, which inhibits dark conversion, i.e. spontaneous switching from the Pfr to the Pr form in darkness (Vierstra, 1993). Moreover, the plant phytochromes contain two additional PAS domains that are important for nuclear localization (Chen *et al.*, 2005a). A relationship of phytochromes with MSP signalling is indicated by similarities between the HK domain of sensor HKs and both phytochrome HKRD and PRD domains (Yeh and Lagarias, 1998). In cyanobacterial phytochrome receptors, point mutations in the kinase domain of both phyA and phyB eliminate their biological activity (Quail, 1997). Moreover, the cyanobacterial photoreceptor Cph1 is autophosphorylated after light perception and transphosphorylates its cognate RR Rcp1 during signal transduction (Yeh *et al.*, 1997). Altogether, the bacterial phytochromes seem to act as a classical two-component signalling system. In contrast, the C-terminal HKRD domain of plant phytochromes has low similarity to a functional HK domain, and the important His residue is replaced by Ser. Accordingly, plant phytochromes possess Ser/Thr kinase activity, allowing their light-dependent autophosphorylation (Yeh and Lagarias, 1998). Furthermore, the kinase domain of *Arabidopsis* phyB is not directly involved in light signal transduction, but dimerization and nuclear relocalization of N-terminally located domains is necessary and sufficient to trigger light-induced responses (Matsushita *et al.*, 2003).

Nevertheless, autophosphorylation of phyA plays an important role in regulation of plant phytochrome signalling through the regulation of phyA protein stability (Han *et al.*, 2010). Thus, although the importance of phytochrome kinase activity in light signalling in plants is still uncertain, it might play a role via indirect modulation of light perception and provide an important link to other (signalling) pathways. Accordingly, several phytochrome kinase substrates have been discovered in studies including *in vitro* assays. These include cryptochromes (blue light photoreceptors), especially CRYPTOCHROME 1 (CRY1) and CRY2. Both CRY1 and CRY2 are phosphorylated by phyA *in vitro* and interact with

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Arabidopsis phyA in the yeast two-hybrid system (Ahmad *et al.*, 1998). PHYTOCHROME KINASE SUBSTRATE 1 (PKS1) also serves as a substrate for light-dependent kinase activity of phyA and phyB *in vitro*. Interestingly, PKS1 interacts with both phyA and phyB at their most similar positions to HKs. Moreover, *in vivo* experiments have shown that PKS1 participates in negative regulation of phytochrome signalling (Fankhauser *et al.*, 1999). Conversely, FAR-RED ELONGATED HYPOCOTYL 1 (FHY1) and its homolog FHY1-LIKE (FHL) are positive regulators of phyA signalling and both directly interact with phyA, as shown by bimolecular fluorescence complementation. FHY1 is rapidly phosphorylated in response to R light in a phyA-dependent manner, and is then a target for proteasome-mediated degradation (Shen *et al.*, 2009).

To summarize, phytochromes are Ser/Thr kinases that interact with and phosphorylate numerous substrates. In several cases, phytochrome-mediated phosphorylation, including autophosphorylation, is associated with changes in protein stability.

Position matters: localization of individual receptors

As mentioned above, an N-terminal transmembrane domain is possessed by ethylene and CK receptors but not by phytochromes (Schaller *et al.*, 2008). When inactive, both phyA and phyB are localized in the cytosol, where they sense light stimuli, leading to their photoactivation and translocalization to the nucleus (Yamaguchi *et al.*, 1999; Nagy and Schafer, 2000; Kircher *et al.*, 2002; reviewed by Rockwell *et al.*, 2006). The nuclear localization signal of phyB is located on its C-terminal part, which possesses Ser/Thr kinase activity (Matsushita *et al.*, 2003). In the nucleus, the phytochromes form highly dynamic nuclear bodies, with altered responses to light. The accumulation of nuclear bodies seems to play a role in phytochrome-regulated signalling, but their exact functions remain to be clarified (Kircher *et al.*, 2002).

All ethylene receptors are localized predominantly in the endoplasmic reticulum (ER) membrane (Grefen *et al.*, 2008). The N-terminal portion, responsible for ethylene perception, is transmembrane and the C-terminal portion, including the HK and RD domains, is orientated towards the cytosol (Shakeel *et al.*, 2013). ERS1, ERS2, and EIN4 receptors are located mostly in ER regions close to the nucleus, and none is located at the plasma membrane in *Arabidopsis* (Grefen *et al.*, 2008). However, tobacco NTHK1, an ethylene receptor homologous to subfamily II *Arabidopsis* ethylene receptors, is present in the plasma membrane of tobacco protoplasts (Xie *et al.*, 2003). In parallel to a prevailing ER localization, ETR1 has also been observed in Golgi apparatus membranes of *Arabidopsis* root-hair cells (Dong *et al.*, 2008).

CK receptors were originally predicted to be localized in the plasma membrane, which has been supported by observation of the AHK3–GFP fusion protein at the plasma membrane in *Arabidopsis* protoplasts (Kim *et al.*, 2006). CKI1, a sensor HK that contributes to CK signalling, is also reportedly present exclusively in the plasma membrane (Hwang and Sheen, 2001). Conflicting recent data suggest that the ER is the main subcellular site to which the *Arabidopsis* CK receptors AHK2, AHK3, and AHK4 (Caesar *et al.*, 2011; Wulfetange *et al.*, 2011) and the maize CK receptor ZmHK1 (Lomin *et al.*, 2011) are targeted, although minor plasma membrane localizations cannot be excluded (Caesar *et al.*, 2011; Wulfetange *et al.*, 2011). However, the topology and functional importance of ER-located CK receptors is still unclear, unlike ethylene receptors, for some of which the topology is known, and the interaction of ETR1 with its downstream partner EIN2 in the ER membrane has been described (Bisson *et al.*, 2009; Bisson and Groth, 2010). Recent insights into CK signalling suggest that CKs could be perceived in the ER lumen and that the signal is further transduced to the nucleus via cytosolic AHPs. In support of these hypotheses, the optimal pH for CK binding to the CHASE domain, around pH 6.5 (Romanov *et al.*, 2006), corresponds well to the pH in the ER lumen. Nevertheless, this model remains to be confirmed experimentally.

Collectively, these findings suggest that CK, ethylene, and light sensors cover a wide spectrum of signalling cues originating from both inside and outside plant cells. While the ER seems to be a subcellular compartment where CK and ethylene signals could potentially integrate, the cytoplasm and/or nucleus might be of similar importance for interactions between CK and light signalling. The possible molecular mechanisms and experimental evidence supporting such signal integration are discussed in the following section.

Integration of CK, ethylene, and light signals in the MSP pathway

The hypothesis that CK and ethylene signalling may be integrated in the MSP signalling pathway arose from yeast two-hybrid assays suggesting that ETR1 can interact with AHP1 and AHP3 and through them with ARR4. Other ethylene receptors, including ERS1, do not interact with any of the AHPs (Urao *et al.*, 2000). Later analysis showed that full-length ETR1 and AHP1 form a complex *in vitro.* Truncated ETR1 lacking a C-terminal RD does not interact with AHP1, implying that the ETR1 RD is involved in AHP1–ETR1 interaction (and possible phosphoryl group signalling) (Scharein *et al.*, 2008). Analysis of the phosphorylation status of both interacting partners showed that the ETR1–AHP1 complex formation is phosphorylation dependent. The affinity between ETR1 and AHP1 is very limited when both interactors are in their phosphorylated or non-phosphorylated form, but ETR1–AHP1 complex formation is promoted when either one of these proteins is phosphorylated (Scharein and Groth, 2011). Moreover, this interaction requires the ETR1 receptor in a functional dimeric state (Schaller and Bleecker, 1995; Scharein and Groth, 2011). These observations support the hypotheses that ETR1–AHP1 interaction may occur *in planta* and participate in signal transduction. Probably the most direct evidence of MSP involvement in ethylene signalling is provided by indications that the B-type response regulator ARR2 contributes not only to CK signalling but also to ethylene signalling (Hass *et al.*, 2004). The loss-of-function mutant *arr2* displays reduced sensitivity to exogenously applied CK as well as to ACC treatment, and the

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hyposensitive phenotype is complemented by *ARR2* overexpression. Moreover, analysis of the primary ethylene-responsive element of the *ETHYLENE RESPONSE FACTOR 1* (*ERF1*) promoter in an *Arabidopsis* protoplast assay showed that ARR2 contributes to regulation of *ERF1* expression, which subsequently influences ethylene signal-targeted genes. Finally, the ability of ARR2 to function in ethylene signalling was shown to depend on phosphorylation of its conserved Asp residue, and, importantly, ETR1 has been identified as an upstream regulator of ARR2 phosphorylation (Hass *et al.*, 2004).

A direct link between MSP-mediated CK signalling and light was discovered in a study demonstrating a key role for the A-type RR ARR4 in R light signalling (Sweere *et al.*, 2001). White and R light induce expression of *ARR4* in a phyB-dependent manner. ARR4 interacts specifically with the N-terminal part of phyB, leading to formation of a phyB–ARR4 complex *in vivo*. ARR4 thereby stabilizes the active (Pfr) form of phyB by retarding its dark conversion. Moreover, the accumulation of active phyB in *ARR4*-overexpressing plants results in hypersensitive responses to R light but not to FR light, suggesting that ARR4 modulates phyB-mediated R light signalling (Sweere *et al.*, 2001). A later study showed that the conserved Asp of ARR4 is necessary for its role in photomorphogenesis (Mira-Rodado *et al.*, 2007). The ability of ARR4 to act in phyB stabilization was shown to be CK dependent and mediated by AHKs acting as CK receptors. Another possible connection between CK and light in MSP signalling through ARR4 is based on the interplay of CK and light signals during photomorphogenesis. In *Arabidopsis*, CK increases levels of the TF LONG HYPOCOTYL 5 (HY5), probably by reducing its COP1-dependent degradation (Vandenbussche *et al.*, 2007). The HY5-stabilizing CK signal is mediated further by ARR4 through multiple signalling intermediates via an unknown mechanism involving COP1 and other components (Vandenbussche *et al.*, 2007). Overall, these findings imply that ARR4 represents a direct point of convergence between light and CK signalling.

Other recent work, reported by Marchadier and Hetherington (2014), has revealed roles of CK signalling elements in light-induced stomatal opening. The AHP2 protein is localized in the cytoplasm and nucleus of guard cells, and its deficiency leads to a significantly narrower stomatal aperture after light stimulation. Conversely, overexpression of *AHP2* in plants induces widening of the aperture. Furthermore, analyses of AHK mutants indicate that AHK2 and AHK3 are involved in this process, as single *AHK2* and *AHK3* mutants exhibit hypersensitivity to abscisic acid-induced stomatal closure. Interestingly, this effect is not observed in *ahk2-2 ahk3-3* double mutants. However, during light-induced stomatal opening, the apertures reached WT widths in all *AHK* mutants that the cited authors tested.

CK-mediated regulation of phyA provides further clear links between CK and light signalling. Cotton *et al.* (1990) showed that exogenous application of the aromatic CK benzyladenine can downregulate *PHYA* mRNA. However, an opposite effect of benzyladenine on *PHYA* transcripts has been observed in genome-wide transcriptome profiling experiments (Brenner *et al.*, 2005, 2012). These experiments suggest a link between CK and light signalling via CK-mediated regulation of phyA signalling, e.g. by CK-mediated upregulation of *PHYTOCHROME-A SIGNAL TRANSDUCTION* (*PAT1*), which acts as a positive regulator of phytochrome signalling (Brenner *et al.*, 2005). PAT1 is a member of the GRAS protein family, but physiological changes observed under FR light indicate that, unlike other members of the family, PAT1 specifically controls the phyA signalling pathway (Bolle *et al.*, 2000). A later transcriptional profiling study (Brenner and Schmulling, 2012) revealed CK-mediated upregulation of genes encoding *SUPPRESSOR OF PHYA-105 1* (*SPA1*) and the *COP1* regulatory protein. These two proteins seem to contribute to very rapid degradation of active phyA, which, together with CK-mediated downregulation of *PHYA* transcription, probably leads to a reduction in phyA levels (Brenner and Schmulling, 2012). Finally, it has been proposed that light-mediated upregulation of CK signalling interferes with auxin in the regulation of stem cell activity during shoot apical meristem organogenesis (Yoshida *et al.*, 2011); however, no molecular details are known.

Indications that interactions between light and ethylene signalling include mutual effects have also been reported recently. Notably, transcript analyses have demonstrated the light-dependent upregulation of *ETR1* and *EIN4*, and downregulation of *ETR2* and *ERS2* gene expression in *Arabidopsis* seedlings (Grefen *et al.*, 2008). Interestingly, a distinct role of ETR1 in germination under FR light conditions has also been discovered recently (Wilson *et al.*, 2014b). It is known that WT seeds generally fail to germinate under FR light exposure or in darkness. However, seeds of loss-of-function *etr1* mutants can germinate better than WT seeds under these conditions, suggesting that ETR1 represses seed germination under FR and in darkness. Moreover, analysis of a double mutant has revealed that ETR1 and ETR2 receptors are involved and that they play opposing roles in regulation of FR-mediated germination. The exact mechanism of this interaction is not clear, but the participation of ETR1 RD has been excluded, and epistasis analyses imply a possible genetic interaction of ETR1 with phyA and phyB in the control of germination and growth (Wilson *et al.*, 2014b).

In parallel with receptor-level interactions, crosstalk between light and ethylene signalling also seems to occur at the level of more downstream signalling components. COP1, a key light signalling component, degrades a number of TFs, such as the basic leucine zipper domain TFs HY5 and HYH. However, COP1 also allows accumulation of other TFs, e.g. the bHLH protein family of PIFs: PIF1, PIF3, and PIF4 (Alabadi and Blazquez, 2008). Similarly, COP1 positively regulates levels of EIN3 (Zhong *et al.*, 2009) and significantly affects transcription of genes acting downstream of EIN3 (Liang *et al.*, 2012). However, details of the regulatory mechanism remain to be elucidated.

In summary, the MSP pathway seems to integrate CK, ethylene, and light signalling (Fig. 1). This could provide plants possibilities to co-ordinate CK- and ethylene-controlled developmental responses to changes in environmental

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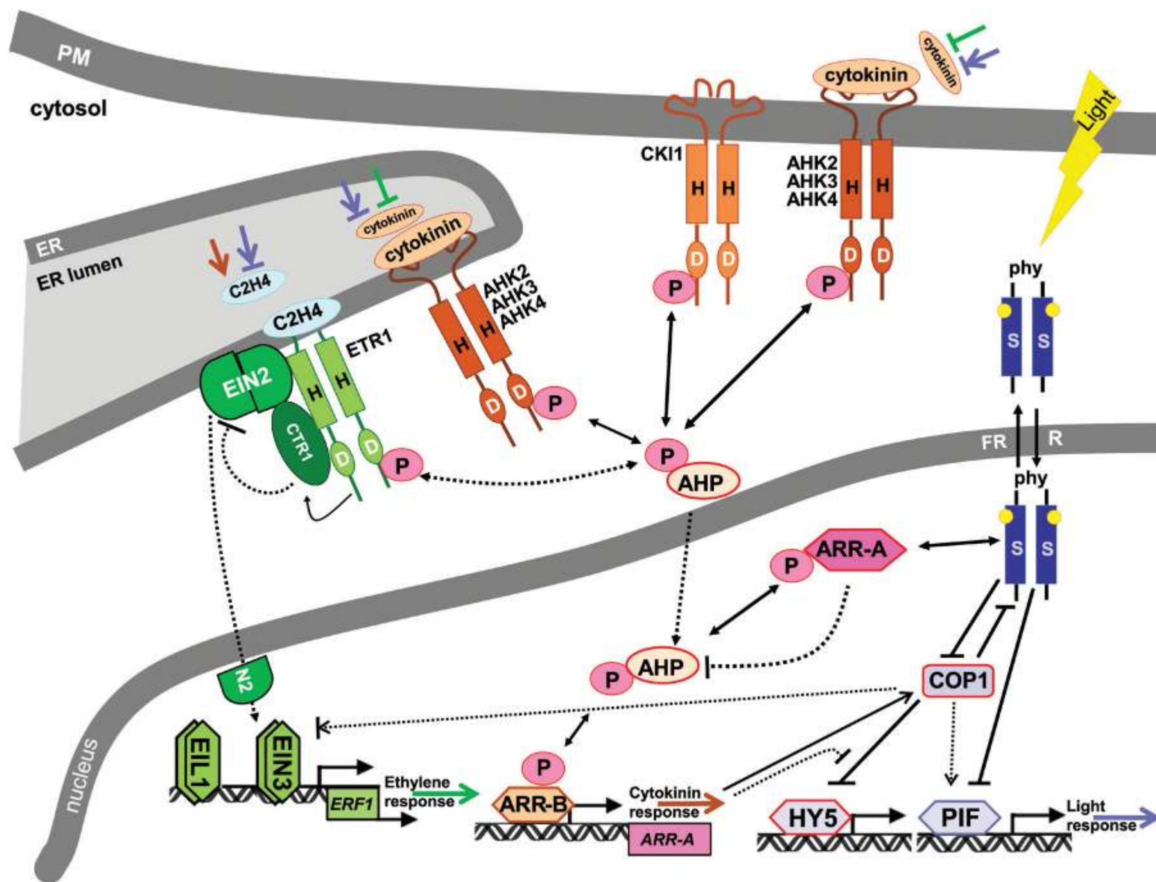

Fig. 1. Integration of light, cytokinin and ethylene signalling in the MSP pathway. For detailed descriptions of individual signalling pathways and corresponding references see the main text. Briefly, AHK cytokinin (CK) receptors are found in both the endoplasmic reticulum (ER) and the plasma membrane (PM) (although higher proportion seems to localize to ER). Binding of CKs to AHK proteins triggers the downstream phosphorelay. From AHKs, signals are transferred via AHPs into the nucleus, where ARR-Bs are phosphorylated and activate expression of CK primary response genes, including ARR-As. Phosphorylation stabilizes the ARR-As, which act in turn as inhibitors of CK signalling by an unclear mechanism. Ethylene is perceived by the ER-integrated receptors ETR1, ETR2, ERS1, ERS2, and EIN4. In contrast to CK-recognizing AHKs (which are inactive in the absence of CKs), ethylene receptors as well as their downstream target CTR1 are active in the absence of ethylene, resulting in the 26S proteasome-mediated degradation of positive regulators of ethylene signalling EIN2, EIN3, EIL1 and ERF1, and repression of ethylene signalling. Binding of ethylene inhibits the activity of ethylene receptors and subsequently S/T activity of CTR1. The C-terminal portion of non-phosphorylated EIN2 is cleaved and translocates into the nucleus, leading to stabilization of EIN3, EIL1 and ERF1 TFs that directly regulate the expression of ethylene responsive genes. Interestingly, it seems that ETR1, CTR1 and EIN2 form a complex facilitating to switch between the two different modes of ethylene signalling pathway. Phytochromes (phys) are the major photoreceptors that perceive red (R) and far-red (FR) light. Light activates phys, which then translocate to the nucleus. The interaction of phys with bHLH TFs PIFs and their subsequent phosphorylation is responsible for rapid proteasome-mediated degradation of PIFs and regulation of gene expression (both activation and inhibition). Activated phys also mediate light-regulated suppression of the E3 ubiquitin ligase COP1. COP1 targets multiple light-responsive TFs (e.g. HY5) for degradation, but it also allows accumulation of other TFs such as PIFs. As a result of reduced COP1 activity in the light, the bZIP TF HY5 accumulates and promotes expression of light-responsive genes. **CK-ethylene crosstalk:** ETR1 interacts with AHPs and, possibly through AHPs, phosphorylates ARR2 which contributes to regulation of *ERF1* and thus to ethylene44 induced expression. CKs also stimulate expression and stabilization of key ethylene biosynthetic enzymes. On the other hand, ethylene is responsible for CK conversion and degradation. **CK-light crosstalk:** CKs induce downregulation of *PHYs* and upregulation of COP1, resulting in phys degradation. On the other side, CKs upregulate HY5, probably by reducing its COP1-dependent degradation. ARR4 specifically interacts with phyB *in vivo*, stabilizing its active (Pfr) form and prolonging responses specifically to R light. Light upregulates endogenous CK levels but also promotes CK degradation by inducing CKX activity. **Light-ethylene crosstalk:** Light controls expression levels of key proteins in the ethylene signalling pathway, upregulates *ETR1* and *EIN4*, but downregulates *ETR2* and *ERS2*. It also stimulates accumulation of EIN3 in a COP1-dependent manner, while interfering with EIN3-mediated transcription. High intensity light cause reductions in ethylene content, whereas low intensity light promotes ethylene production. Dashed lines indicated proposed or uncertain regulatory mechanisms. Coloured arrows indicate regulation at biosynthetic level. Green, brown and blue colours indicate ethylene-, CK- and light-mediated signalling pathways, respectively.

conditions associated not only with diurnal and seasonal fluctuations in light intensities but also with changes in light wavelengths, e.g. in shade avoidance responses triggered by changes in the R:FR ratio (Quail, 1998). However, the functional importance of such signal integration mostly remains to be discovered.

Impact of CK/ethylene/light crosstalk on seedling growth and development

Hormonal crosstalk influences plant development throughout their life cycle. In this chapter, we highlight a few of the key processes known to be affected by CKs, ethylene, and

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light crosstalk, such as seed germination and early seedling development.

Germination

Germination involves complex morphological and physiological changes resulting in embryo activation. Water, light, storage compounds, and proteins are all essential for the process. Moreover, phytohormones and light play key roles in its initiation.

Early experiments with lettuce (*Lactuca sativa* L. cv. Grand Rapids) not only elucidated some aspects of light-dependent germination but also led to the discovery of phytochromes (Borthwick *et al.*, 1952; Butler *et al.*, 1959). An important finding of these experiments is that R light induces germination of lettuce seeds, but its effect can be suppressed by an immediately following FR pulse. As mentioned above, R light promotes an increase in iP levels in Scots pine (*Pinus sylvestris* L.) seeds, while an FR pulse reduces the endogenous iP pool, suggesting that the R light-induced breaking of dormancy might be CK dependent (Qamaruddin and Tillberg, 1989). The influence of CK/light crosstalk on dormancy breaking and initiation of germination has been described in many plant species (for detailed reviews see, for instance, Thomas *et al.*, 1997; Kucera *et al.*, 2005; Miransari and Smith, 2014). CKs alone can break dormancy of many plant species' seeds, as summarized by Cohn and Butera (1982). However, in thermo-inhibited lettuce and *Striga* seeds, CKs probably break dormancy by upregulating ethylene biosynthesis (Saini *et al.*, 1989; Babiker *et al.*, 2000). Interestingly, ethylene and light treatment during germination seem to induce CK production in *Spergula arvensis* seeds, suggesting that CK production could also be involved in dormancy breaking, but CK treatment alone cannot initiate *Spergula* germination (Staden *et al.*, 1973).

In *Arabidopsis*, it is well known that ethylene stimulates germination (Bleecker *et al.*, 1988; Wilson *et al.*, 2014b). However, under salt stress conditions, ETR1 acts as an inhibitor and ETR2 as a stimulator of germination after FR light illumination (Wilson et al., 2014a, b). Genetic evidence indicates that interactions of *ETR1* with *PHYA* and *PHYB* participate in the control of seed germination and hypocotyl growth, as mentioned in the previous section. On the other hand, the effect of ETR1 on germination seems to be light independent, suggesting that ethylene also participates in the regulation of germination in parallel with the phytochrome pathway (Wilson *et al.*, 2014a).

Skotomorphogenesis

The apical hook protects the shoot apical meristem during germination and soil penetration until it reaches the soil surface. The organ is shaped by asymmetric cell division and elongation on opposite sides of the hypocotyl. Three phases of the process can be readily distinguished under *in vitro* conditions: hook formation, maintenance, and opening.

The involvement of ethylene in apical hook development has been known for more than 50 years. Hook opening is induced by light together with a decrease in ethylene production (Goeschl *et al.*, 1967; Kang *et al.*, 1967). Enhanced ethylene signalling (e.g. in *ctr1* mutants) or ethylene biosynthesis (e.g. in *eto1* and *eto2* mutants) results in exaggerated hook formation (Bleecker *et al.*, 1988; Guzman and Ecker, 1990; Kieber *et al.*, 1993). In contrast, ethylene-insensitive mutants (*etr1-1* and *ein2-1*) cannot form any hook curvature (Bleecker *et al.*, 1988; Guzman and Ecker, 1990). Real-time imaging has revealed that ethylene delays the transition between the formation and maintenance phases (Vandenbussche *et al.*, 2010; Zadnikova *et al.*, 2010; Gallego-Bartolome *et al.*, 2011). In addition, ethylene production in the apical hook is localized asymmetrically, as are transcripts of two ACOs—*PsACO1* on the concave and *AtACO2* on the convex side (Peck *et al.*, 1998; Raz and Ecker, 1999)—while the ethylene reporter *EBS::GUS* indicates that ethylene responsiveness is the same on both sides of the hypocotyl (Stepanova *et al.*, 2007). Nevertheless, ethylene application leads to different growth responses on the two sides of the apical hook (Vandenbussche *et al.*, 2010; Zadnikova *et al.*, 2010; Muday *et al.*, 2012). A putative *N*-acetyltransferase, HOOKLESS1 (HLS1), may play a crucial role during hook development, as ethylene treatment increases *HLS1* mRNA levels (Lehman *et al.*, 1996) while light represses its transcription. Moreover, HLS1 protein levels decrease dramatically upon illumination during the hook opening phase (Li *et al.*, 2004), so HLS1 seems to act as an interconnecting point between ethylene and light signalling in the regulation of apical hook development. The *hls1* mutant lacks well-established auxin maxima in the apical zone, and *AUXIN RESPONSE FACTOR 2* (*ARF2*) has been identified (through analysis of an *arf2* mutant) as a suppressor of *hls1* (Li *et al.*, 2004). Thus, it appears that HLS1 acts by influencing auxin responses.

Depending on light conditions, ethylene regulates hypocotyl elongation in two opposite ways: as an inducer in the light (Smalle *et al.*, 1997; Alonso *et al.*, 1999) and an inhibitor in the dark (Bleecker *et al.*, 1988; Ecker, 1995). Under light conditions, the ethylene-insensitive mutants *ein2* and *ein3 eil1* display shortened hypocotyls, whereas transgenic plants overexpressing *EIN3* exhibit elongated hypocotyls similar to the constitutive ethylene-response mutant *ctr1* (Zhong *et al.*, 2012). Moreover, *ein3 eil1* is insensitive to ACC treatment, like *pif3*. Subsequent genetic studies support a role for PIF3 downstream of EIN3 and EIL1 in the regulation of ethylene-promoted hypocotyl elongation in the light. By analogy with EBF2 and ERF1, direct target genes of EIN3 (Solano *et al.*, 1998; Konishi and Yanagisawa, 2008), *PIF3* expression has been predicted to be under the control of EIN3. Bioinformatic analysis, chromatin immunoprecipitation, and yeast one-hybrid assays have revealed that EIN3 binds specifically to the *PIF3* promoter region and activates *PIF3* gene expression (Zhong *et al.*, 2012). EIN3 and EIL1 are required for the dual actions of ethylene in the light and dark, as upstream regulators of *PIF3* or *ERF1*. In etiolated seedlings, mechanical pressure of the soil enhances ethylene production, and EIN3 protein accumulation corresponds with soil depth (Zhong *et al.*, 2014). Ethylene stimulates *ERF1*, via EIN3, in the hypocotyl. The ERF1 pathway inhibits cell elongation,

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and thus hypocotyl elongation, thereby protecting the shoot apical meristem in deep soil. As soil depth diminishes, ethylene production gradually declines, and the hypocotyl can elongate more rapidly without risk of damage (Zhong *et al.*, 2014). Moreover, ERF1 protein is clearly unstable in the dark and becomes stabilized by light exposure (Zhong *et al.*, 2012), which corresponds with a rapid inhibition of hypocotyl elongation after dark-to-light transition. Simultaneously, EIN3 activates *PIF3* expression in cotyledons and the upper part of the hypocotyl under soil. The PIF3 pathway leads to the pre-assembly of photosynthetic machinery in the cotyledon, particularly biosynthesis of protochlorophyllide (Zhong *et al.*, 2014). Thus, PIF3–ERF1 circuitry seems to balance tissue-specific development in etiolated seedlings.

COP1–HY5 interaction provides another means of regulating hypocotyl elongation (Yu *et al.*, 2013). The *Arabidopsis hy5* mutant produces a longer hypocotyl than WT (Col-0) seedlings in the light but a hypocotyl of comparable length in the dark, suggesting that HY5 acts as a negative regulator of hypocotyl elongation in the light. The HY5 protein level is regulated in a light-dependent manner by COP1-mediated degradation in the nucleus. Importantly, genetic and biochemical analyses have revealed that both COP1 and HY5 act downstream of EIN3, indicating that the COP1–HY5 complex integrates light and ethylene signalling during hypocotyl elongation in the light (Yu *et al.*, 2013).

CKs also reportedly affect hypocotyl elongation and its dependence on light conditions. In the dark, CKs suppress hypocotyl elongation (Su and Howell, 1995) by inducing ethylene production (Cary *et al.*, 1995), whereas under light conditions, CKs have no effect on hypocotyl elongation (Su and Howell, 1995). However, in combination with blocked ethylene perception in the presence of Ag^+, CKs promote hypocotyl elongation via the upregulation of cell elongation in light-grown seedlings, mainly in the bottom part of the hypocotyl. This occurs with no changes in cell number per cell file and thus with no alteration in cell division (Smets *et al.*, 2005).

Photomorphogenesis

As the apical hook opens, cotyledons start to become green and seedling development is switched to photomorphogenesis. This transition is associated with a dramatic reprogramming of seedling metabolism, leading to a switch from heterotrophic to autotrophic growth. Ethylene plays a crucial role in this process by facilitating the greening of etiolated seedlings upon light irradiation (Zhong *et al.*, 2009). For this, EIN3/EIL1 activation is essential, and EIN3 protein accumulation is partially enhanced in a COP1-dependent way but is reduced by light (Zhong *et al.*, 2009). *EIN3* overexpression can also reverse the inhibition of greening triggered by the *cop1* mutation or FR light irradiation. In addition, EIN3/EIL1 induces expression of genes encoding two key enzymes in the chlorophyll biosynthesis pathway, PROTOCHLOROPHYLLIDE OXIDOREDUCTASE A and B (PORA/B). Chromatin immunoprecipitation and electrophoretic mobility shift assays have shown that EIN3 binds directly to the *PORA* and *PORB* promoters. Moreover, genetic studies have revealed that EIN3/EIL1 co-operate with PIF1 in promoting cotyledon greening (Zhong *et al.*, 2009). Specifically, PIF1 binds to the promoter of *PORC* and simultaneously inhibits accumulation of protochlorophyllide (Moon *et al.*, 2008).

Root apical meristem (RAM) length (cell division and differentiation)

Root growth is controlled and balanced by the mitotic activity of cells in the RAM and cell differentiation in the transition zone. This important balance between cell division and cell differentiation establishes the size of the RAM (Dolan *et al.*, 1993; Beemster and Baskin, 1998; Dello Ioio *et al.*, 2007a), as reviewed in detail by Petricka *et al.* (2012). CKs have been shown to reduce RAM size by promoting cell differentiation in the transition zone (Dello Ioio *et al.*, 2007b). Based on phenotypic assays addressing long-term CK effects, it has been proposed that CK effects on RAM size are ethylene independent (Růžička *et al.*, 2009), and ethylene's repression of root growth is mediated exclusively by inhibition of cell elongation in the cell elongation zone (Růžička *et al.*, 2007). However, a recent study indicated an unexpected role for ethylene in the regulation of RAM size during the early stages of CK-induced root shortening, as the ethylene biosynthetic mutant lines *atms1* and *aco2* exhibited resistance to CK-mediated reduction of RAM length (Zdarska *et al.*, 2013).

Phytochromes and root development

It has long been known that roots as well as shoots can sense and respond to light. It is also known that blue light receptors, cryptochromes, and phytochromes are present in them (Okada and Shimura, 1992; Somers and Quail, 1995; Kiss *et al.*, 2003). Functions of phytochromes in the root are less clearly understood than their roles in hypocotyl and shoot development, but they are involved in several aspects of root growth and development, e.g. root-hair formation (De Simone *et al.*, 2000), lateral root orientation (Kiss *et al.*, 2002), and both gravitropic responses and elongation of roots (Correll and Kiss, 2005). For example, Correll and Kiss (2005) found that irradiation with R light reduced the elongation of etiolated roots to 35 and 20% of the lengths observed in WT and *phy* mutants, respectively, and that phyA and phyB play important roles in this response. Nevertheless, other phytochromes (phyC and phyE) might also be involved in light-mediated control of root elongation. Primary roots of etiolated *phyA phyB* double mutants are shorter than those of WT seedlings, implying the involvement of inactive (Pr) phytochromes in the control of root growth. Accordingly, recent reports indicate that both root- and shoot-localized phyA and phyB affect seminal root elongation in rice (Shimizu *et al.*, 2009; Zheng *et al.*, 2013).

Taken together, the available data clearly show that phytochromes influence root elongation, although the downstream components involved remain unknown. Light signals may be transported from the shoot to the root, and/or the

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Pr forms of root-localized phytochromes may directly control root development. As mentioned above, PIFs might be involved in downstream connections between light and hormonal signalling pathways. However, their exact roles in root elongation remain to be clarified.

Future prospects

The crosstalk among light, CK, and ethylene signalling pathways appears to be strongly involved in the regulation of many crucial plant growth and development processes. Available data indicate that light affects both CK and ethylene levels, but the downstream molecular mechanisms of these interactions remain mostly unclear. Further knowledge is required of: the signalling intermediates acting downstream of phytochromes in the regulation of hormonal metabolism; mechanisms that mediate effects of light at tissue and cell levels; and the specificity of these phenomena in developmental contexts. Promisingly, recent methodological improvements in hormonal measurements now permit quantification of hormones in minimal amounts of tissues, as reviewed by Tarkowska *et al.* (2014). Such measurements, combined with analyses of recently available mutants deficient in various phytochrome signalling components should allow us to examine the role of light in hormonal biosynthesis in much more detail.

A number of findings indicate that extensive crosstalk occurs between light and both CK and ethylene signal transduction pathways at multiple levels. We propose that MSP may be a backbone signalling pathway that integrates CK, ethylene, and light signals, generating a common signalling output, with AHPs acting as signalling hubs, as they interact not only with CK but also with the ethylene receptor ETR1. It is still not clear if phytochromes can also utilize AHP signalling hubs, but the CK RRs, ARRs-A, link all the signalling pathways. In this context, it is worth noting that oat phyA (AsphyA) can physically interact with and phosphorylate Rcp1, the RR and substrate of the cyanobacterial phytochrome Cph1 (Yeh *et al.*, 1997; Yeh and Lagarias, 1998). In addition, phyA is not an HK but a Ser/Thr kinase, and Rcp1 phosphorylation is light independent and does not involve the conserved Asp (Yeh and Lagarias, 1998). Thus, these findings might imply the ability of phytochromes to modulate MSP signalling via the phosphorylation of pathway members at other amino acids and then the conserved His and Asp residues, thus controlling MSP signalling via the regulation of, for example, protein stability. This, however, remains to be addressed experimentally. Nevertheless, many other questions remain to be answered. How are the individual signals integrated into a single signalling output? How is the signal specificity determined? Are there other mechanisms allowing (for example) not only CK-mediated signalling to control light sensitivity but also light-mediated control of CK signalling and responses, as suggested recently (Yoshida *et al.*, 2011)? What are the roles of the inactive Pr forms of phytochromes, and might they be involved in the MSP signalling pathway? These and other questions remain challenges to address in future work on the importance of light and its modulation of hormone-directed plant development.

Importantly, light-induced dynamic changes influenced by separate hormonal pathways can remain largely hidden within complex phenotypes. Thus, the acquisition of a deeper understanding will require methodological advances allowing us to clearly elucidate these pathways, their effects, and (hence) the nature and adaptive functions of the tight cooperation between light and CK/ethylene signalling in plant growth and development.

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