REVIEW PAPER

Plant photoreceptors and their signalling components in chloroplastic anterograde and retrograde communication

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Abstract

The red phytochrome and blue cryptochrome plant photoreceptors play essential roles in promoting genome-wide changes in nuclear and chloroplastic gene expression for photomorphogenesis, plastid development, and greening. While their importance in anterograde signalling has been long recognized, the molecular mechanisms involved remain under active investigation. More recently, the intertwining of the light signalling cascades with the retrograde signals for the optimization of chloroplast functions has been acknowledged. Advances in the field support the participation of phytochromes, cryptochromes, and key light-modulated transcription factors, including HY5 and the PIFs, in the regulation of chloroplastic biochemical pathways that produce retrograde signals, including the tetrapyrroles and the chloroplastic MEP-isoprenoids. Interestingly, in a feedback loop, the photoreceptors and their signalling components are targets themselves of these retrograde signals, aimed at optimizing photomorphogenesis to the status of the chloroplasts, with GUN proteins functioning at the convergence points. High light and shade are also conditions where the photoreceptors tune growth responses to chloroplast functions. Interestingly, photoreceptors and retrograde signals also converge in the modulation of dual-localized proteins (chloroplastic/nuclear) including WHIRLY and HEMERA/pTAC12, whose functions are required for the optimization of photosynthetic activities in changing environments and are proposed to act themselves as retrograde signals.

Keywords: Anterograde signals, chloroplast, cryptochrome photoreceptors, GUN mutants, HY5, MEcPP, photomorphogenesis, phytochrome photoreceptors, plastome, retrograde signals, tetrapyrroles.

Abbreviations: CRY, cryptochrome; DXR, DXP REDUCTOISOMERASE; DXS, DXP SYNTHASE; ELIP2, EARLY LIGHT INDUCED PROTEIN; FC1, FERROCHELATASE 1; GUN, GENOMES UNCOUPLED; GLK, GOLDEN2-LIKE protein; HL, high light; HMR, pTAC12/HEMERA; LHCb, light-harvesting complex B; HY5, LONG HYPOCOTYL 5; MEcPP, methylerythritol cyclodiphosphate; MEP, methylerythritol phosphate; PPR, pentatricopeptide domain-containing; PhAPG, photosynthesis-associated plastome gene; PhANG, photosynthesis-associated nuclear gene; PIF, phytochrome-interacting factor; phy, phytochrome; pTAC, PLASMID TRANSCRIPTIONALLY ACTIVE CHROMOSOME; PEP, PLASTID-ENCODED POLYMERASE; ROS, reactive oxygen species; RBCS-1A, ribulose biphosphate carboxylase small subunit; TPR, tetratricopeptide domain-containing; WHY1, WHIRLY1.

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**Introduction**

**Photoreceptor activity is critical to chloroplast development and photosynthetic metabolism**

Plant photoreceptors utilize light to coordinate growth, development, and photosynthetic functions in a changing environment. Mechanistically, both the red/far-red light-sensing phytochromes (phys) and the blue light-sensing cryptochromes (CRYs) are essential in the orchestration of large-scale changes in gene expression to modulate photomorphogenesis (Franklin and Quail, 2010; Yu et al., 2010). Prominently, their transcriptional cascades facilitate the onset of plastid development, greening, the production of photosynthetic pigments, and the set up and maintenance of photosynthetic metabolism, among other light-controlled responses (Franklin and Quail, 2010; Yu et al., 2010).

Beyond the photoreceptors’ downstream activation of thousands of nuclear genes whose protein products have a chloroplastic function including in photosynthesis (Ohgishi et al., 2004; Stephenson and Terry, 2008; Chen and Chory, 2011), recent research hints at the involvement of the phy and the CRY photoreceptors in the global transcriptional, post-transcriptional, and post-translational modulation of plastid-encoded genes (Chen et al., 2010; Oh and Montgomery, 2014; Facella et al., 2017; Yoo et al., 2019; Griffin et al., 2020). Hence, the light photoreceptors not only have a central role in the anterograde (nucleus to plastid) signalling cascades, but also intertwine with the retrograde (plastids to nucleus) signals for the optimization and maintenance of plastid functions and metabolism.

**Phytochromes and cryptochromes in anterograde signalling**

The anterograde signalling pathways are nuclear to chloroplast communication channels involved in setting and tuning chloroplast development and functions, circadian responses, and photosynthesis (Berry et al., 2013; Atkins and Dodd, 2014; Leister and Kleine, 2016). Anterograde signals became necessary following the ancestral endosymbiotic event that originated the chloroplasts. Through evolution, many of the genes from the chloroplast genome (the plastome) were transferred to the nuclear genome (Garrido et al., 2020), but remained functionally associated with the chloroplast. Also, by the acquisition of an N-terminal transit peptide, their protein products gained targeting to the chloroplasts after transcription in the nucleus and translation in the cytoplasm (Wollman, 2016).

The tight regulation of these nuclear genes coding for chloroplast-functioning proteins (globally known as photosynthesis-associated nuclear genes, PhANGs) is critical for chloroplast biogenesis and photosynthesis, and the photoreceptors are essential for tuning their transcriptional responses in changing light environments (Larkin and Ruckle, 2008; Pogson et al., 2015; Calderon and Strand, 2021). Both the phs and the CRYs regulate the global light responsiveness of the PhANGs through the activation or repression of multiple transcription factors including: the bZIP-LONG HYPOCOTYL 5 (HY5) (Osterlund et al., 2000; Toledo-Ortiz et al., 2014); the basic helix–loop–helix phytochrome-interacting factors (PIFs) (Franklin and Quail, 2010; Leivar and Quail, 2011); and the GARP proteins GOLDEN2-LIKE 1 and 2 (GLK1 and GLK2) (Waters et al., 2009; Leister and Kleine, 2016).

HY5 is a master transcription factor in the control of photomorphogenic responses (Gangappa and Botto, 2016) capable of integrating red phy and blue CRY responses. Both photoreceptors tune HY5 abundance in the nucleus by down-regulating the COP1-dependent ubiquitination of HY5 and allowing its accumulation in the light (Osterlund et al., 2000). HY5 binds to the promoters of nearly 4000 genes and controls a wide range of developmental processes including the activation of photosynthesis-associated genes (J. Lee et al., 2007; Gangappa and Botto, 2016), photopigment and antioxidant accumulation (J. Lee et al., 2007; Shin et al., 2007; Toledo-Ortiz et al., 2014), as well as circadian and growth responses (J. Lee et al., 2007; Hajdu et al., 2018).

The PIFs are negative modulators of photomorphogenesis that are degraded in the light after the activation of phy, and are involved in promoting skotomorphogenesis and shade avoidance responses (Leivar and Quail, 2011; Yoo et al., 2019). While their turnover and stability are principally regulated by the phys, CRYs can repress the transcription of PIF4 without affecting its protein stability (Ma et al., 2016), and may also protect PIF5 from phy-mediated degradation in low blue light conditions (Pedmale et al., 2016). PIFs promote skotomorphogenesis (Wang et al., 2022) including the down-regulation of genes involved in photopigment biosynthesis (Shin et al., 2007; Stephenson et al., 2009) and chloroplast development and function (Leivar and Monte, 2014).

The GLK transcription factors target genes involved in light harvesting and chlorophyll biosynthesis through direct binding to their light-sensitive promoters, and are required for chloroplast development (Waters et al., 2009). In addition, GLK1 and GLK2 transcript accumulation is dependent on red phy and blue light, and the glk1 glk2 double mutant has reduced accumulation of transcripts for photosynthetic genes and lower chlorophyll content when grown in blue light (Waters et al., 2009), hinting at their involvement with CRY signalling cascades leading to greening.

Beyond the important role of the CRYs and phys in the transcriptional response of chloroplast functioning genes, recent research provides evidence that the phys are also key regulators of ribosome biogenesis and translation during late leaf development, with a global modulation of mRNAs that code for components of aminoacyl-tRNA biosynthesis, elongation factors, and ribosomal subunits (Romanowski et al., 2021). Active phyB has also been reported to interact with cytosolic RNA-binding proteins, including PENTA1 (PTN1), to inhibit the translation of mRNAs for genes such as
as protochlorophyllide (PORA) involved in chlorophyll biosynthesis (Paik et al., 2012).

In addition, beyond the activation of the nuclear genome for the production of the chloroplast proteins encoded by it, chloroplast functions require coordination of gene expression with the plastome, wherein essential subunits of the photosynthetic complexes are encoded. As such, part of the anterograde signalling pathways relates to the delivery of information for tuning the plastome genome in response to the environment (Oh and Montgomery, 2014; Facella et al., 2017; Griffin et al., 2020). CRY2 overexpression studies in tomato defined a broad contribution to the plastome expression in long days (58% of the 114 plastome ORFs), with an up-regulation of PSII (psb), PSI (psa), and Cyt b6f (pet) transcripts and down-regulation of multiple large and small ribosomal proteins (rps and rpl). In addition, genes coding for other photosynthetic complexes such as NADH dehydrogenase (ndh) and ATP synthase (atp) showed a mixed regulation (Facella et al., 2017). A similar analysis in Arabidopsis for the phyB mutant in short days revealed an analogous capacity to globally regulate the transcripts of 55 out of 80 plastome-encoded genes (Michael et al., 2008; Griffin et al., 2020). While in most cases phyB function was related to transcript up-regulation, down-regulation of key atp, ndh, psa, and psb transcripts was also detected (Griffin et al., 2020).

Alongside these reports, bioinformatic studies of genomic datasets for Arabidopsis cry1 cry2 and phyabde revealed a significant contribution of red phy and blue CRYs to the light–dependent expression of nuclear-encoded genes whose protein products are linked to the transcriptional, post-transcriptional, and translational control of the plastome (Griffin et al., 2020). Among the light-modulated gene families identified were the sigma factor transcriptional cofactors required for the activity of PLASTID-ENCODED POLYMERASE (PEP) (Oh and Montgomery, 2014; Börner et al., 2015); the pentatricopeptide domain–containing (PPR) and the tetrapeptide domain–containing (TPR) families of RNA-binding proteins with a role in the plastome post-transcriptional events (Lamb et al., 1995; Ruwe et al., 2011). In addition, for the blue CRYs, genes coding for RNA-recognition motif (RRM) RNA-binding proteins with an annotated role in post-transcription and for tRNA ligase and large ribosomal protein (RPL) related to translation were identified (Griffin et al., 2020). In this context, HY5 was singled out as a relevant transcription factor delivering light cues to the ‘plastome-regulatory gene network’. Gene targets include the sigma factors and the PLASMID TRANSCRIPTIONALLY ACTIVE CHROMOSOME class (pTACs), involved in plastome transcription, and the PPR and the TPR proteins probably involved in post-transcriptional processes.

These early studies provide evidence that the photoreceptors and their signalling components are central in the anterograde signalling cascades to tune the global expression of the plastome in response to environmental signals, but the detailed mechanistic insights remain to be understood.

### The chloroplast retrograde signalling pathways

Retrograde signalling pathways are a second type of interorganellar communication channels used by the plastids to relay information to the nucleus in response to a range of stresses or external stimuli for the optimization of growth and for shaping photosynthetic and chloroplast biogenic responses (Kusnetsov et al., 1996; Leister and Kleine, 2016; Hernández-Verdeja and Strand, 2018). Retrograde signalling during chloroplast biogenesis (defined as the transition from etioplasts to proplastids to chloroplasts), germination, or early seedling development, is referred to as biogenic signalling (Pogson et al., 2008). Biogenic signalling tunes-up and -down hundreds of nuclear-encoded genes whose protein products function in the chloroplast (Chan et al., 2016). A variety of intermediates from chloroplastic metabolic pathways, including terpenoids, methylerythritol phosphate (MEP) pathway isoprenoids, phosphoadenosines, carbohydrates, carotenoid oxidation products, and reactive oxygen species (ROS), have been identified as biogenic signals emitted by the chloroplast to deliver information to the nucleus. The biogenic retrograde signalling pathways have been recently reviewed in detail (Chi et al., 2015; Terry and Bampton, 2019).

The crucial contribution of retrograde signalling to seedling survival has been assessed in mutants with impaired retrograde signalling capabilities, and through pharmacological approaches that induce stress in the chloroplasts (Pogson et al., 2008; Chan et al., 2016). Common retrograde signal activators include lincomycin (an inhibitor of plastid translation that blocks plastid development) and norflurazon (an inhibitor of carotenoid biosynthesis that induces photobleached chloroplasts). These chemical agents trigger a reduction in the expression PhANGs, including those coding for light-harvesting complex B (LHCB) proteins and the Rubisco small subunit (RBCS), that are common marker genes for assessing retrograde signal activity (Susek et al., 1993; Ruckel et al., 2012). In Arabidopsis, forward mutagenic screens coupled with the use of norflurazon identified the gun1 (genome uncoupled) mutants with altered accumulation of PhANGs, such as CAB (Chl a/b-binding protein) (Susek and Chory, 1992; Susek et al., 1993; Mochizuki et al., 2001).

A second type of retrograde signalling involves operational signals that occur after chloroplast biogenesis and in response to stress conditions to induce adjustments in chloroplast homeostasis (Pogson et al., 2008; Chan et al., 2016). Examples of identified operational signalling pathways include the regulation of PSII overexcitation via β-cyclocitrinal (Ramel et al., 2012), and the methylerythritol cyclophosphate (MEcPP) pathway (Jiang and Dehesh, 2021).

This review focuses on the involvement of the photoreceptors in the regulation of the biogenic and operational pathways,
including links to the GUN signalling pathways and MEcPP pathway, and novel insights on dual-localized proteins in chloroplast to nuclear signalling (Qin et al., 2010; Martín et al., 2016; Ren et al., 2017; Jiang and Dehesh, 2021).

The intertwining of retrograde signalling and photoreceptor-dependent pathways

While connections between plastid retrograde signalling and light signalling have been made for decades, most of the mechanisms involved remain elusive (Kusnetsov et al., 1996; Larkin and Ruckle, 2008; Xu et al., 2016). In 1996, Kusnetsov et al. examined the effect of the overlap between plastid-derived retrograde signals and light-derived signals on functional PhANG promoter sequences. These authors provided early evidence that chloroplast-derived retrograde signals and light signalling pathways act on the same cis-acting elements (such as L-, I-, and G-boxes), and could regulate the same processes, suggesting an intertwining of the pathways. Since then, G-boxes have been characterized as important light-responsive elements (LREs) bound by multiple phy and CRY downstream signalling components including HY5 and the PIFs (Chattopadhyay et al., 1998; Leivar and Quail, 2011).

Experimental evidence also supports that the activation of retrograde signalling pathways by lincomycin and norflurazon represses or delays plant photoreceptors’ promotion of photomorphogenesis, including chloroplast biogenesis and greening processes (Susek et al., 1993; Ruckle et al., 2012). There is also a clear overlap between the gene targets of the biogenic retrograde signalling pathways and the photomorphogenic cascades initiated by the phy and the CRYs (Ohgishi et al., 2004; Tepperman et al., 2006; Ruckle et al., 2012; Zhao et al., 2019). Examples of common targets include the subunits of LHCB and RBCS (Reed et al., 1994; Mazzella et al., 2001; Vinti et al., 2005; Woodson et al., 2011). Furthermore, RNA-seq experiments with norflurazon have provided evidence that the genes coding for phyA and for light-modulated transcription factors such as HY5 are up-regulated, and PIF4 and PIF7 are down-regulated upon activation of retrograde signal pathways (Zhao et al., 2019), giving support to the hypothesis that photoreceptors and their signalling components and retrograde signals highly intersect and do not operate independently of each other.

Beyond the chemical activators of retrograde signals, high light (HL) is also an important trigger (Szczygłowska-Hebda and Karpfiski, 2013), and photoreceptors are part of the perception and responsiveness to HL (Kreslavski et al., 2020). ROS including hydrogen peroxide (H$_2$O$_2$), superoxide anions (O$_2^{-}$), and singlet oxygen (O$_2$^{'}) are chemical derivatives of O$_2$ produced by metabolic processes in plants (Apel and Hirt, 2004). In HL irradiances, chloroplasts increase H$_2$O$_2$ production by PSI and O$_2$ production by PSII (Kanervo et al., 2005; Krieger-Liszkay, 2005). While H$_2$O$_2$ has been shown to move out of isolated chloroplasts in vitro, providing it with the capacity to act as an initiator of retrograde signalling (Mubarakshina et al., 2010), O$_2$ cannot leave the chloroplast due to its short half-life (Gorman and Rodgers, 1992), and therefore secondary messengers yet to be identified must be involved in the transmission of the O$_2$ signal to the nucleus.

In addition to ROS, HL stress also generates 12-oxophytodienoic acid (OPDA) and oxylipin-derived retrograde signals (Gollan and Aro, 2020). Among the targets of these retrograde signalling cascades is EARLY LIGHT INDUCIBLE PROTEIN1 (ELIP1) (Gollan and Aro, 2020), a thylakoid protein induced during de-etiolation and in response to HL stress (Rossini et al., 2006). ELIPs may participate in enhancing the photoprotective capacity of the plant (Casazza et al., 2005; Rossini et al., 2006) and, under HL, CRY1 and HY5 modulate the induction of ELIP1 (Kleine et al., 2007). As part of these cascades, a second cross-regulatory point is the modulation of heat shock protein (HSP) chaperones (including HSP90) which are HY5 targets and participate in the tetrapyrrole-mediated plastid signalling to repress PhANGs under oxidative stress (Kindgren et al., 2012).

These examples illustrate that photoreceptor activity is crucial for the set up of the protective responses against HL stress, as well as for the communication channels activated by high irradiances. Likewise, phys and CRYs promote the activation of nuclear genes for the biosynthesis of carotenoids and anthocyanins to deal with excess light (Kreslavski et al., 2020). Accordingly, the cry1phyA1B1 and phyAB1B2 mutants in Solanum lycopersicum present additive HL stress phenotypes, including reductions in photopigment content and photosynthetic activity; and lower transcript accumulation of photosynthesis-associated genes encoded in both the plastome and the nuclear genome (PhANGs and PhAPGs) (Kreslavski et al., 2020). Furthermore, the more acute HL damage observed for cry1phyA1B1 may point to a larger contribution of CRY1 to HL tolerance and responsive mechanisms in tomato plants.

Studies in Arabidopsis further support this primary role of CRY1 in managing photoprotective and HL responses, and single out HY5, whose transcript and protein accumulate in HL, as one of the light signalling components involved (Kleine et al., 2007). In addition to a HL-sensitive phenotype including the photo-inactivation of PSII, the cry1 mutant exhibits at a transcriptomic level misregulation of 77 HL-induced genes, with 26 of them also misregulated in hy5 (Kleine et al., 2007). Interestingly, a further 39 genes showed altered patterns of accumulation in hy5, but not in cry1, indicating that HY5 participates in both HL–CRY1-dependent and HL-responsive but CRY-independent pathways.

Additional evidence from studies in emerging rice seedlings grown under high blue or high red light and lincomycin supports both an integration and a differential contribution of light quality and photoreceptor activity to seedling photomorphogenesis and non-photochemical quenching mechanisms to tolerate the excess light (Duan et al., 2020). In this context, in high red light conditions, retrograde signal activators induced photobleaching, but in high blue light, enhanced carotenoid
and chlorophyll production contributed to a stronger HL stress tolerance, in a mechanism likely to be dependent on CRYs (Kleine et al., 2007; Duan et al., 2020; Richter et al., 2020).

In summary, HL responses involve both photoreceptors (CRYs and phyS) and light signalling components (such as HY5) capable of sensing and responding to both HL and retrograde signals to tune growth and development with the status of the chloroplast. Current studies also support the conservation of these HL-induced retrograde signalling cascades between monocot and dicot plants (Duan et al., 2020).

**Photoreceptors, HY5, and GUN1 in the convergence of photomorphogenesis and retrograde signalling**

The GUN genes (GUN1–GUN6) were identified in the ‘gun mutant screens’ using norflurazon to activate retrograde signals (Susek and Chory, 1992; Susek et al., 1993; Mochizuki et al., 2001; Woodson et al., 2011). GUN2–GUN6 play roles in the tetrapyrrole biosynthesis pathway and, while the full functional role of GUN1 remains to be addressed, experimental evidence also supports GUN1 modulation of tetrapyrroles by direct binding to both haem and porphyrins (Shimizu et al., 2019).

Tetrapyrroles, as either bilins or porphyrins, have important functions in multiple biological processes, including respiration and photosynthesis, and are active in light absorption, electron transfer, and oxygen binding (Shimizu et al., 2019). Tetrapyrrole biosynthesis takes place in the plastids and involves two key pathways branching from protoporphyrin IX: the chlorophyll branch, ending in production of Chls $a$ and $b$; and the haem branch, ending in phytochromobilin (the chromophore used by the red and far-red light phyD photoreceptors) (Bae and Choi, 2008; Li et al., 2011). A tight regulation of tetrapyrrole biosynthesis is required to avoid cellular damage by the generation of ROS.

As the gun mutants involve mutations within the tetrapyrrole biosynthetic pathway, the metabolites therein are considered key retrograde signals for chloroplast development (Leister and Kleine, 2016). In the chlorophyll branch of the tetrapyrrole biosynthesis pathway, GUN5 encodes a gene for the H subunit of magnesium chelatase (MgCh), involved in the transition between protoporphyrin IX (ProtoIX) and magnesium protoporphyrin IX (Mg-ProtoIX) (Mochizuki et al., 2001). GUN4 encodes an activator of MgCh that also contributes to the accumulation of Mg-ProtoIX (Larkin et al., 2003). Mg-ProtoIX has been proposed as one of the important signalling molecules for retrograde signalling (Kindgren et al., 2011), linked to the reduction in transcript levels of PhaNGs, including LHCB and RBCS (Shimizu et al., 2019). However, beyond gun4 and gun5, other mutants for genes encoding subunits for the Mg-ProtoIX complex do not display a gun phenotype, making the role of this metabolite in retrograde signalling unclear at present (Mochizuki et al., 2001; Wu and Bock, 2021).

The haem branch of tetrapyrrole synthesis is initiated by GUN6 (also known as plastid FERROCHELATASE 1, FC1) that converts ProtoIX to protohaem by inserting Fe$^{2+}$. Protohaem is converted first to biliverdin IX by GUN2 (encoding haem oxygenase), and finally to 3Z-phytochromobilin by GUN3 (phytochromobilin synthase). Evidence that haem may function as a second type of retrograde signalling molecule has been provided by the characterization of gun6-1D, a dominant mutant allele overexpressing FC1, and promoting the flow of tetrapyrroles into the haem branch, with consequent up-regulation of PhaNG transcripts (Woodson et al., 2011).

While the specific mechanisms through which photoreceptor signalling pathways are involved in the generation, regulation, and response to GUN retrograde signals have yet to be fully elucidated, tetrapyrrole biosynthesis is induced by light, as previously reviewed (Kobayashi and Masuda, 2016), with the contribution of light signalling transcription factors including HY5 (K.P. Lee et al., 2007; Kobayashi et al., 2012a, b), the PIFs (Shin et al., 2009; Leivar and Quail, 2011), and GLK1 and GLK2 (Waters et al., 2009).

In particular, GUN1 is a gene of high interest as an integratory point for light and retrograde signalling pathways. GUN1 encodes a chloroplast-localized protein containing a PPR (Koussevitzky et al., 2007). PPRs are known post-transcriptional regulators of plastid gene expression (Ruwe et al., 2011), but the functional role of GUN1 protein is still under exploration. Of all gun mutants, gun1 exhibits the strongest de-repression of PhaNG expression in lincomycin (Koussevitzky et al., 2007), and GUN1 transcript accumulation is light responsive and dependent on the phys in red light (Hu et al., 2013). During de-etiolation, GUN1 is active and involved in cotyledon expansion and hypocotyl elongation (Ruckle et al., 2007; Ruckle and Larkin, 2009), with gun1 also displaying a delayed greening phenotype. As such, GUN1 probably represents a crosstalk point between the photoreceptor signalling cascades and the plastid signals that tune chloroplast greening and growth responses (Mochizuki et al., 1996; Ruckle et al., 2007; Pesaresi and Kim, 2019; Wu et al., 2019; Wu and Bock, 2021).

Further support for this possibility has been provided by additional gun genetic screens, where an allele of cry1 that shares similar phenotypes with gun1-1, including defects in plastid to nucleus signalling affecting LHCB and RBCS transcript accumulation, was identified (Ruckle et al., 2007). Double mutant analysis of gun1-101 cry1 grown in HL showed an additive phenotype for their effects on LHCB accumulation and deficiencies in chlorophyll accumulation, indicating that GUN1 and CRY1 may be partially redundant in modulating LHCB via parallel pathways that converge. A similar phenotype of defective LHCB accumulation was observed for the gun1-101 hy5 double mutant, suggesting that this CRY1-dependent pathway requires HY5. Likewise, phyB gun1-1 double mutants accumulated more LHCB than gun1-1 single mutants when treated with lincomycin, providing evidence that phyB may also be a gun mutant, contributing to the repression of LHCB, but only when GUN1 is inactive (Ruckle et al., 2007).
In summary, the light/photoreceptor-dependent modulation of GUN1, together with the additive phenotypes between gun1 and photoreceptor mutants, point at signal integration between the light cascades and the retrograde signals via GUN1, with HY5 as a potential ‘convergence of signals point’ for which full mechanistic insights await full dissection.

Phytochrome-dependent GLK tuning of PhANGs is antagonized by GUN signalling

An additional molecular link identified between the GUN pathways and the photoreceptor signalling cascades during de-etiolation was recently uncovered (Martín et al., 2016). These authors showed that during de-etiolation, the phy photomorphogenic signals and the GUN1 biogenic retrograde signalling pathways converge to antagonistically control photomorphogenesis. Notably, Arabidopsis plants grown in red or white light, with inhibition of chloroplast biogenesis induced by lincomycin or norflurazon, showed elongated hypocotyls and unexpanded cotyledons lacking chlorophyll—phenotypes associated with dark-grown seedlings. These observations give support to a retrograde signal-dependent tuning down of light-dependent pathways with suppression of photomorphogenic development.

Interestingly, genomic studies showed that >343 photomorphogenesis-associated genes involved in de-etiolation and greening are co-repressed both by lincomycin-induced/ GUN1-derived retrograde signals and by the PIFs in the dark. This transcriptional effect was further supported by the characterization of the pifq (pif1 pif3 pif4 pif5) mutant, for which treatment with lincomycin restored the transcriptomic profile of PIF-repressed genes to wild-type levels, indicating a parallel pathway to GUN1 in response to chloroplast dysfunction (Martín et al., 2016). An analysis of the DNA-binding motifs in the promoters of the genes co-repressed by both lincomycin-induced/ GUN1-derived retrograde signals and by the PIFs in the dark showed enrichment in GLK-binding motifs (Martín et al., 2016). GLK1 encodes a transcription factor that is both phy/light induced and PIF repressed, and whose down-regulation by retrograde signals in a GUN1/GUN5-dependent manner is reported (Kakizaki et al., 2009; Waters et al., 2009). In addition, characterization of overexpressing lines for GLK1 and GLK2 placed them as gun mutants themselves (Leister and Kleine, 2016). As part of the GUN1/GLK1-mediated responses, the B-box gene BBX16 has been identified as a directly induced target of GLK1 for the promotion of photomorphogenesis, and whose transcription is repressed in a GUN1/GLK1-dependent manner upon chloroplast damage, as well as in response to norflurazon treatment (Zhao et al., 2019; Veciana et al., 2022).

Along with the links between retrograde signalling and GUN signalling in the light, evidence also suggests that these pathways may operate in darkness, with the involvement of COP1 and the PIFs. Support for this possibility comes from experiments on etiolated Arabidopsis pifq seedlings that, when grown in the presence of lincomycin, show a restoration to phenotypes present in wild-type etiolated seedlings, including suppression of cotyledon separation and sustainment of apical hook curvature and of appressed cotyledons (Martín et al., 2016). In addition, lincomycin also reduces the transcript accumulation of photomorphogenesis–associated genes such as LHCB1 in dark–grown cop1, and of 354 transcripts in dark-grown pifq mutants (Sullivan and Gray, 1999; Martín et al., 2016). Also, recent studies of dark–grown etioplasts and proplasts revealed the presence of GUN1 protein in the dark, and transcriptomic studies on dark–grown wild type and gun1-102 indicate that GUN1–mediated signals regulate nuclear gene expression in the dark with up to 4425 genes, including subunits of PSI (PSA) and LHCB, differentially expressed in dark-grown gun1-101 compared with the wild type. These results support a significant role for GUN1 in tuning the expression in the dark of genes involved in the build-up of the photosynthetic apparatus (Hernández-Verdeja et al., 2022).

Therefore, while the molecular connections between the GUN1 retrograde signalling and the phy cascades are only beginning to be addressed, progress in the area points to retrograde signals acting as an antagonistic pathway to suppress phy-induced photomorphogenesis. In this context, GUN1 can integrate retrograde signals downstream of COP1 to tune the initiation of photomorphogenesis, including those that modulate the transcriptional responses of transcription factors required for de-etiolation and for chloroplast development such as GLK1, HY5, PIF1, PIF4, PIF5, and PIF8 (Hernández-Verdeja et al., 2022).

Photoreceptors and the MECPP retrograde signalling pathway

Along with their roles in initiating greening and tetrapyrrole biosynthesis, phfs are downstream targets of MECPP, an isoprenoid derivative of the chloroplastic MEP pathway, and a powerful operational retrograde signalling molecule (de Souza et al., 2017; Jiang et al., 2019; Jiang and Dehesh, 2021) for the expression of nuclear genes involved in stress responses in plastids (Xiao et al., 2012; de Souza et al., 2017). The plastidial accumulation of MECPP is induced in response to oxidative stress, HL, wounding, high temperature, and heavy metals in plants and eubacteria (Xiao et al., 2012; Wang et al., 2017).

A genetic screen in Arabidopsis to identify genes involved in the regulation of HYDROPEROXIDE LYASE (HPL), a stress-inducible protein in the oxylipin pathway, identified the constitutively expressing HPL (ech1) mutant (Xiao et al., 2012). ech1 has a mutation in HMBPP synthase (HDS) that catalyses the conversion of MECPP to HMBPP (Ostrovsky et al., 1998; Rodríguez-Concepción, 2006; Xiao et al., 2012), and displays short hypocotyls in the light (Jiang et al., 2019, 2020). This phenotype is caused by higher phyB protein levels induced by the overaccumulation of MECPP (Jiang et al., 2020). Higher phyB levels lead to the repression of PIF4 and PIF5 activity and to an
altered accumulation of ethylene and auxin biosynthetic genes such as ACS4, 5, 8, and YUC8 (Jiang et al., 2019, 2020). Interestingly, the short hypocotyl phenotype of ceh1 mutants was also present in seedlings grown under blue light, supporting the possibility that blue light-sensing CRYs are also linked to MEcPP accumulation and signalling (Jiang et al., 2019).

While phyB is a downstream target of a MEcPP retrograde signal, phyB and transcription factors acting downstream of phyB are also critical regulators of MEP pathway genes [e.g. DXP SYNTHASE (DXS), DXP REDUCTOISOMERASE (DXR), and HMBPP REDUCTASE (HDR)] from which MEcPP is derived (Chenge-Espinosa et al., 2018). In particular, red light signals from phy and HY5, antagonistically transduced by PIFs, are involved in the transcriptional control of DXS and DXR, the genes in the MEP pathway that are considered rate-limiting steps and flux-controlling points (Wright et al., 2014; Chenge-Espinosa et al., 2018).

Together, these findings support a cross-regulation between the photoreceptors and the MEcPP retrograde signalling pathways, with phyB as both a key target of retrograde signals in red light and a regulator of their generation, in a feedback loop that adjusts photomorphogenic responses to the status of the chloroplast.

**HY5 emergence as an important integratory factor for light and multiple retrograde signalling pathways**

HY5 is a master modulator of plant photomorphogenesis, including the control of de-etiolation, photopigment accumulation, hormonal levels, anthocyanin production, and tuning of reactive oxygen stress responses (Kobayashi et al., 2012; Toledo-Ortiz et al., 2014; Gangappa and Botto, 2016). In the light, several pieces of evidence support the signal integratory capacity of CRY and phys signal via HY5 with retrograde signalling (Ruckle et al., 2007; Kindgren et al., 2012; Richter et al., 2020). As such, HY5 transcript accumulation increases in response to retrograde signal activators (Zhao et al., 2019), and HY5 has been proposed to alternate between an activator and a repressor of nuclear-encoded gene expression in response to plastid dysfunction (K.P. Lee et al., 2007; Ruckle et al., 2007; Ruckle and Larkin, 2009).

In addition, HY5 mediates the GUN1-triggered rapid light-dependent inhibition of PhANGs, induced by singlet oxygen retrograde signals derived from the photo-excitation of Mg-porphyrins and the accumulation of the chlorophyll intermediate Mg-ProtoIX (Strand et al., 2003; Kindgren et al., 2012; Richter et al., 2020). Mg-ProtoIX interaction with cytosolic HSP90 proteins leads to the repression or inactivation of nuclear-encoded PhANGs in a HY5-dependent manner (Kindgren et al., 2012). In this pathway, GUN5–HSP90.2–HY5 is emerging as a convergence point for light and retrograde signalling cascades for the modulation of PhANGs. HY5 may also form—together with GUN1 and HSP90.1 (Wu et al., 2019; Wu and Bock, 2021)—a second integratory node for light retrograde signals, whose full biological significance remains to be investigated.

Additionally, together with CRYs, HY5 also participates in the coordination of light and retrograde signals for anthocyanin and flavonoid accumulation (Shin et al., 2007; Zhang et al., 2016; Richter et al., 2020). In this respect, current evidence shows that in norflurazon-treated Arabidopsis plants, GUN1/GUN5 retrograde signals can tune down the transcription accumulation of flavonoid/anthocyanin biosynthesis (FAB) genes, including LEUCANTHOCYANIDIN DIOXYGENASE (LDOX), a gene whose activation depends on CRY1 and HY5 (Richter et al., 2020).

As such, current studies support the participation of CRY1 and HY5 in abiotic stress-triggered retrograde signalling cascades necessary for enabling chloroplast stress responsiveness, the modulation of photoprotective pigment accumulation, and repression of the expression of the PhANGs.

Another reported link between HY5 and the tetrapyrrrole biosynthesis-derived retrograde signalling cascades involves the sigma factors. The sigma transcriptional cofactors are nuclear-encoded genes required for the activity of the PEP (Berry et al., 2013; Börner et al., 2015). In Arabidopsis, there are six members of the sigma factor family, with five of them (SIG1, 2, 3, 5, and 6) showing red phy-, blue CRY-, or red/blue HY5-dependent transcript accumulation (Oh and Montgomery, 2013; Griffin et al., 2020). For SIG2 and SIG5, links to retrograde signalling are emerging (Woodson et al., 2013; Oh et al., 2018) with SIG2 modulation of the expression of tRNA-Glu, an early step in tetrapyrrrole, biosynthesis (Woodson et al., 2013), and a reduced accumulation of PhANG transcripts (including RBCS and LHCB genes) in sig2, a phenotype that is alleviated by haem feeding. Transcriptomic studies for SIG2 have also identified under red light >2000 nuclear-encoded misregulated genes, some with roles in growth, hormonal crosstalk, stress responses, and photosynthesis (Oh et al., 2018). The enrichment in sig2 of misregulated chloroplastic/red light-responsive genes that are targets of retrograde signals supports an intersection of both pathways for the modulation, in particular, of chloroplastic acting genes and of genes active during in photomorphogenesis.

A second sigma factor, SIG5, is a light quality- and HLeight-responsive gene that is sensitive to DCMU-dependent retrograde signals (Mellenthin et al., 2014). SIG5 transcript accumulation is induced by CRY1 in blue light and is phy dependent in red light, with HY5 contributing to its transcriptional response in both light qualities (Mellenthin et al., 2014; Griffin et al., 2020). Following DCMU activation of retrograde signals derived from the inhibition of electron flow in PSII (Metz et al., 1986; Mellenthin et al., 2014), the accumulation of SIG5 is down-regulated. These early studies indicate the capacity of SIG5 to integrate inputs from light and retrograde signals; however, the mechanistic insights
into signal integration and biological outputs remain to be investigated. Yet, SIG2 and SIG5 as HY5- and retrograde signal-sensitive genes, have a good potential to be part of the anterograde and retrograde pathways to tune the plastid genome and the PhANG transcriptional responses with the blue and red photoreceptor light signals.

Fig. 1. Phytochromes (phys), cryptochromes (CRYs), and HY5 integrate light and retrograde signals from the chloroplast to tune nuclear genome responses to a changing environment. (A) MEcPP tuning of phyB-modulated growth responses. Chloroplast stress-induced MEcPP accumulation increases the abundance of phyB-Pr protein. Red light-activated phyB-Pfr translocates to the nucleus to inhibit PIF activity, and target hormonal pathways to halt hypocotyl elongation. In addition to inhibiting PIF activity, phyB promotes HY5 accumulation. In a feedback loop, HY5 and PIFs antagonistically regulate the transcriptional accumulation of DXS and DXR, two of the rate-limiting steps in the MEP pathway from which MEcPP derives. (B) High light- (HL) induced stress responses are dependent on photoreceptor and HY5 activity. HL stress induces damage to the photosynthetic apparatus, triggering the release of retrograde signalling molecules including H2O2 and oxylipins, which target the phy-, CRY-, and HY5-dependent activation of PhANG expression and photoprotective responses including chlorophyll and carotenoid biosynthesis. (C) A GUN1-dependent pathway inhibits PhANG accumulation to halt photomorphogenesis in response to chloroplast stress. GUN1 antagonistically inhibits phy-mediated photomorphogenesis through a GUN1:GLK1 complex that down-regulates BBX16-mediated PhANG expression. CRY1 and HY5 also co-target GUN1-dependent PhANG accumulation in a converging pathway, contributing to the responsiveness of PhANGs to chloroplast stress.
HY5 and phyB in the shade-induced retrograde signalling pathways

In addition, HY5’s involvement in retrograde signals to avoid shade and optimize photosynthetic performance has been reported (Roig-Villanova et al., 2007; Cagnola et al., 2012; Bou-Torrent et al., 2015; Ortiz-Alcaide et al., 2019). In this context, HY5 is reported to respond to retrograde signals derived from functional chloroplasts to tune hypocotyl elongation, in a manner similar to its induction by phyA in low red:far red conditions to suppress elongation (Bou-Torrent et al., 2015; Ortiz-Alcaide et al., 2019). On the other hand, under shade, signals derived from challenged chloroplasts to de-activate phyB stimulate the activity of the PIFs to promote hypocotyl elongation and avoid shade (Ortiz-Alcaide et al., 2019).

Studies using norflurazon or lincomycin treatments indicate a higher transcript accumulation of HY5, and HY5 protein can be detected in white- and in far-red light-enriched environments simulating canopies, but only when retrograde signals derived from functional chloroplasts are active (Ortiz-Alcaide et al., 2019). Interestingly, in the absence of functional chloroplasts, phyB inactivation in response to far-red treatments is delayed, with the consequent reduction in the transcripts of shade-induced genes involved in elongation (Roig-Villanova et al., 2007; Ortiz-Alcaide et al., 2019).

In summary, current studies indicate antagonistic effects of phyB/PIFs and phyA/HY5 for the proper modulation of elongation responses upon impending competition. Yet, in this setting, chloroplast retrograde signals are also critical for the tuning of light quality/shade perception to the status of the chloroplast.

Photoreceptors regulate retrograde signalling-dependent dual-localized proteins

Likewise, there is also evidence to support the involvement of the photoreceptors in the regulation of multiple dual-localized proteins that can communicate information between the nucleus and the chloroplast to tune chloroplast needs and photomorphogenic responses. WHIRLY1 (WHY1) is among such dual-localized proteins with potential to act as a retrograde signal based on a functional role in chloroplast biogenesis and a capability for translocation from the chloroplast back to the nucleus (Isemer et al., 2012).

WHIRLY proteins are a small family of three genes in Arabidopsis, coding for ssDNA-binding proteins (Desveaux et al., 2002; Krause et al., 2005). WHY1 and WHY3 are targeted to chloroplast, and WHY2 localizes to the mitochondria (Krause et al., 2005). WHY1 is involved in the transcriptional modulation of plastid-encoded and nuclear-encoded genes (Desveaux et al., 2002, 2005; Isemer et al., 2012). In the chloroplast, WHY1 forms part of the pTAC complexes involved in plastome transcription, and in the nucleus WHY1 stimulates the expression of pathogen response genes by an unknown mechanism (Isemer et al., 2012).

The role of WHY1 as a retrograde signal occurs in response to redox changes in the thylakoid electron transport chain (Foyer et al., 2014). WHY1’s alternative subcellular localization depends on light via the phyA-dependent regulation of the Calcineurin B-Like-Interacting Protein Kinase14 gene (CIPK14) (Qin et al., 2010), coding for a protein that phosphorylates and modifies WHY1 binding affinity for different promoters (Ren et al., 2017). Interestingly, CIPK14 transcript accumulation is dependent on multiple light inputs, including transient activation by far-red light and time-dependent modulation by blue and red light (Qin et al., 2010). At present, only the response to far-red light and the dependence on phyA have been investigated, but based on current studies it can be hypothesized that this phyA–CIPK14–WHY1 regulatory module may be important for the far-red blocking of the greening response. It remains to be established if the observed red light induction of CIPK14 is phyB dependent, but the blue light induction of CIPK14 is not dependent on CRY1 CRY2 (Qin et al., 2010).

A second example of the involvement of photoreceptors in the control of nuclear–chloroplastic dual-localized proteins include pTAC12/HEMERA (HMR), a member of the pTAC family that regulates PEP (Pfälz et al., 2006; Chen et al., 2010). HMR transcript accumulation is light responsive and dependent on the phy in red light and on the CRYs in blue light (Griffin et al., 2020). In the nucleus, HMR acts as a transcriptional co-activator to regulate light-responsive genes, while in the plastids it associates with the PEP to induce plastid-encoded gene expression (Pfälz et al., 2015; Qiu et al., 2015). HMR first localizes to the plastids, like WHY1 (Grabowski et al., 2008; Isemer et al., 2012), and its relocation to the nucleus is proposed as part of the activation of the retrograde signal cascades (Yoo et al., 2020). Currently this possibility, including the potential crosstalk with photoreceptor signalling mechanisms, remains to be fully investigated.

In summary, research supports the involvement of phy in the modulation of the activity of nuclear–chloroplastic proteins that directly or indirectly impact on the expression of the nuclear and plastid genomes. At present, only the role of phy has been studied, but the integration of the CRYs in the retrograde signalling pathways that tune photomorphogenesis in blue light make them interesting candidates to assess for their role in controlling dual-localized proteins that may be retrograde signals.

Conclusions

The research highlighted in this review supports an emerging view that the phy and CRY photoreceptor signalling, including through transcription factors such as PIFs and HY5, intertwine with both the anterograde and retrograde signalling pathways. This crosstalk is essential for the tuning of the nuclear and plastid genomes in response to environmental cues (Fig. 1).

As part of the anterograde signalling cascades, the photoreceptors and their signalling components contribute to both nuclear and plastid transcription, post-transcription, and translational mechanisms. On the other hand, in retrograde signalling, they are not only contributors to the activation of pathways involved
in the emission of retrograde signals, such as the tetrapyrrole and MEcPP pathways, but are also targets of themselves of the retrograde signals (Fig. 1A). These dual functionalities are probably part of their extended capacity to optimize plant growth in response to environmental cues. In particular, phyA and HY5 transcript accumulation and phyB protein abundance increased in response to retrograde signal activators such as norflurazon and the MEcPP pathway. Additionally, GUN1 signalling tunes CRY1 and HY5 transcript abundance and intersects with the photoreceptors in the control of de-etiolation responses. However, at present, the full reach of these cross-regulations remains to be explored, although the identification of cry1 as a gim mutant hint towards a wide involvement of CRYs in plastid to nucleus signalling (Fig. 1C).

CRYs, phy, and HY5 are also part of the chloroplast responsiveness to environmental cues, including the set up and the control of photoprotective mechanisms against the detrimental effects of HL. HL is emerging as a condition where the crosstalk between photoreceptors and retrograde signals is essential to optimize plastid functions, including the management of stress (Fig. 1C). Additionally, as part of the perception of light quality, phy, PIFs, and HY5 participate in the modulation of the shade avoidance syndrome elongation responses that are tuned via retrograde signals to the status of the chloroplast.

Finally, dual-localized proteins with capacity to act as retrograde signals, such as WHY1 and HMR, are also light quality responsive, but the impact of the phy and CRYs on their regulation is just starting to emerge.

**Author contributions**

JHCG and GTO designed and wrote the manuscript.

**Conflict of interest**

The authors report no conflict of interest.

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**References**

Apel K, Hirt H. 2004. Reactive oxygen species: metabolism, oxidative stress, and signal transduction. Annual Review of Plant Biology 55, 373–399.

Atkins KA, Dodd AN. 2014. Circadian regulation of chloroplasts. Cell Signalling and Gene Regulation 21, 43–50.

Bae G, Choi G. 2008. Decoding of light signals by plant phytochromes and their interacting proteins. Annual Review of Plant Biology 59, 281–311.

Berry JO, Yerramsetty P, Zielinski AM, Mure CM. 2013. Photosynthetic gene expression in higher plants. Photosynthesis Research 117, 91–120.

Börner T, Aleynikova AY, Zuo YO, Kusnetsov VV. 2015. Chloroplast RNA polymerases: role in chloroplast biogenesis. Biochimica et Biophysica Acta 1847, 761–769.

Bou-Torrent J, Toledo-Ortiz G, Ortiz-Alcaide M, Cifuentes-Esquível N, Halliday KJ, Martínez-García JF, Rodríguez-Concepcion M. 2015. Regulation of carotenoid biosynthesis by shade relies on specific subsets of antagonistic transcription factors and cofactors. Plant Physiology 169, 1584–1594.

Cagnona JL, Ploschuk E, Bencich-Arnold T, Finlayson SA, Casal JJ. 2012. Stem transcriptome reveals mechanisms to reduce the energetic cost of shade-avoidance responses in tomato. Plant Physiology 160, 1110–1119.

Calderon RH, Strand A. 2021. How retrograde signaling is intertwined with the evolution of photosynthetic eukaryotes. Cell Signaling and Gene Regulation 63, 102093.

Cassaza AP, Rossini S, Rosso MG, Soave C. 2005. Mutational and expression analysis of ELIP1 and ELIP2 in Arabidopsis thaliana. Plant Molecular Biology 58, 41–51.

Chan XX, Phua SY, Crisp P, McNicoll R, Pogson BJ. 2016. Learning the languages of the plastid: retrograde signaling and beyond. Annual Review of Plant Biology 67, 25–53.

Chattopadhyay S, Ang L-H, Puente P, Deng X-W, Wei N. 1998. Arabidopsis bZIP protein HY5 directly interacts with light-responsive promoters in mediating light control of gene expression. The Plant Cell 10, 673–683.

Chen M, Chory J. 2011. Phytochrome signaling mechanisms and the control of plant development. Trends in Cell Biology 21, 664–671.

Chen M, Galvão RM, Li M, Burger B, Bugeja J, Bolado J, Chory J. 2010. Arabidopsis HEMERA/pTAC12 initiates photomorphogenesis by phytochromes. Cell 141, 1230–1240.

Chenge-Espinoza M, Cordoba E, Romero-Guido C, Toledo-Ortiz G, León P. 2018. Shedding light on the methylerythritol phosphate (MEP)-pathway: long hypocotyl 5 (HY5)/phytochrome-interacting factors (PIFs) transcription factors modulating key limiting steps. The Plant Journal 96, 828–841.

Chi W, Feng P, Ma J, Zhang L. 2015. Metabolites and chloroplast retrograde signaling. Current Opinion in Plant Biology 25, 32–38.

de Souza A, Wang J-Z, Dehes K. 2017. Retrograde signals: integrators of interorganellar communication and orchestrators of plant development. Annual Review of Plant Biology 68, 85–108.

Desveaux D, Allard J, Brisson N, Sygusch J. 2002. A new family of plant transcription factors displays a novel ssDNA-binding surface. Nature Structural Biology 9, 512–517.

Desveaux D, Maréchal A, Brisson N. 2005. Whirly transcription factors: defense gene regulation and beyond. Trends in Plant Science 10, 95–102.

Duan L, Ruiz-Sola MA, Cossu A, Veciana N, Monte E. 2020. Red and blue light differentially impact retrograde signaling and photoprotection in rice. Philosophical Transactions of the Royal Society B: Biological Sciences 375, 20190402.

Facella P, Carbone F, Placido A, Perrotta G. 2017. Cryptochrome 2 extensively regulates transcription of the chloroplast genome in tomato. FEBS Open Bio 7, 456–471.

Foyer CH, Karpinska B, Krupinska K. 2014. The functions of WHIRLY1 and REDOX-RESPONSIVE TRANSCRIPTION FACTOR 1 in cross tolerance responses in plants: a hypothesis. Philosophical Transactions of the Royal Society B: Biological Sciences 369, 20130226.

Franklin KA, Quail PH. 2010. Phytochrome functions in Arabidopsis development. Journal of Experimental Botany 61, 11–24.

Gangappa SN, Botto JF. 2016. The multifaceted roles of HY5 in plant growth and development. Molecular Plant 9, 1353–1365.

Garrido C, Caspari OD, Choquet Y, Wollman F-A, Lafontaine I. 2020. Evidence supporting an antimicrobial origin of targeting peptides to endosymbiotic organelles. Cells 9, 1795.

Gollan PJ, Aro E-M. 2020. Photosynthetic signalling during high light stress and recovery: targets and dynamics. Philosophical Transactions of the Royal Society B: Biological Sciences 375, 20190406.

Gorman AA, Rodgers MA. 1992. Current perspectives of singlet oxygen detection in biological environments. Journal of Photochemistry and Photobiology B 14, 159–176.
Grabowski E, Miao Y, Mulisch M, Krupinska K. 2008. Single-stranded DNA-binding protein whirly1 in barley leaves is located in plastids and the nucleus of the same cell. Plant Physiology 147, 1800–1804.

Griffin JHC, Prado K, Sutton P, Toledo-Ortiz G. 2020. Coordinating light responses between the nucleus and the chloroplast, a role for plant cryptochromes and phytochromes. Physiologia Plantarum 169, 515–528.

Hajdu A, Dobos O, Domijan M, Bálint B, Nagy I, Nagy F, Kozma-Bognár L. 2018. ELONGATED HYPOCOTYL 5 mediates light signalizing to the Arabidopsis circadian clock. The Plant Journal 96, 1242–1254.

Hernández-Verdeja T, Strand A. 2018. Retrograde signals navigate the path to chloroplast development. Plant Physiology 176, 967–976.

Hernández-Verdeja T, Vujoriški L, Jin X, Vergara A, Dubreuil C, Strand A. 2022. GENOMES UNCOUPLED1 plays a key role during the de-etiolation process in Arabidopsis. New Phytologist 235, 188–203.

Hu W, Franklin KA, Sharrock RA, Jones MA, Harmer SL, Lagarias JC. 2013. Unanticipated regulatory roles for Arabidopsis phytochromes revealed by null mutant analysis. Proceedings of the National Academy of Sciences, USA 110, 1542–1547.

Isemer R, Krause K, Grabe N, Kitahata N, Asami T, Krupinska K. 2012. Plastid located WHIRLY1 enhances the responsiveness of Arabidopsis seedlings toward abscisic acid. Frontiers in Plant Science 3, 283.

Jiang J, Dehesh K. 2021. Plastidial retrograde modulation of light and hormonal signaling: an odyssey. New Phytologist 230, 931–937.

Jiang J, Yao X, Chen H, Hu W, Zeng L, Ke H, Ditengou FA, Devisetty U, Palme K, Maloof J, Dehesh K. 2020. Retrograde Induction of phyB orchestrates ethylene–auxin hierarchy to regulate growth. Plant Physiology 183, 1268–1280.

Jiang J, Zeng L, Ke H, De La Cruz B, Dehesh K. 2019. Orthogonal regulation of phytochrome B abundance by stress-specific plastidial retrograde signaling metabolite. Nature Communications 10, 2904.

Kakizaki T, Matsumura H, Nakayama K, Che F-S, Terauchi R, Inaba T. 2007. Signals from chloroplasts control light regulation of Mg-chelatase H subunit in plastid-to-nucleus signal transduction. Proceedings of the National Academy of Sciences, USA 104, 10270.

Leister D, Kleine T. 2016. Definition of a core module for the nuclear retrograde response to altered organellar gene expression identifies GLK overexpressors as gun mutants. Physiologia Plantarum 157, 297–309.

Leivar P, Monte E. 2014. PIFs: systems integrators in plant development. The Plant Cell 26, 56–78.

Leivar P, Quail PH. 2011. PIFs: pivotal components in a cellular signaling hub. Trends in Plant Science 16, 19–28.

Li T, Bonkovsky HL, Guo J-T. 2011. Structural analysis of heme proteins: implications for design and prediction. BMC Structural Biology 11, 13.

Ma D, Li X, Guo Y, Chu J, Fang S, Yan C, Noel JP, Liu H. 2016. Cryptochrome 1 interacts with PIF4 to regulate high temperature-mediated hypocotyl elongation in response to blue light. Proceedings of the National Academy of Sciences, USA 113, 224–229.

Martin G, Leivar P, Ludevid D, Pepperman JM, Quail PH, Monte E. 2016. Phytochrome and retrograde signaling pathways converge to antagonistically regulate a light-induced transcriptional network. Nature Communications 7, 11431.

Mazzella MA, Cerdán PD, Staneloni RJ, Staneloni RJ, Casal JJ. 2001. Hierarchical coupling of phytochromes and cryptochromes reconciles stability and light modulation of Arabidopsis development. Development 128, 2291–2299.

Mellenthin M, Eilersiek U, Börger A, Baier M. 2014. Expression of the Arabidopsis sigma factor SIG5 is photoreceptor and photosynthesis controlled. Plants 3, 359–391.

Metz JG, Pakrasi HB, Seibert M, Arntzer CJ. 1986. Evidence for a dual function of the herbicide-binding D1 protein in photosystem II. FEBS Letters 205, 269–274.

Michael TP, Breton G, Hazen SP, Priest H, Mockler TC, Kay SA, Chory J. 2008. A morning-specific phytohormone gene expression program underlies anther-mediated plant growth. PLoS Biology 6, e225.

Mochizuki N, Brusslan JA, Larkin R, Nagatani A, Chory J. 2001. Arabidopsis genomes uncoupled (GUN) mutant reveals the involvement of Mg-chelatase H subunit in plastid-to-nucleus signal transduction. Proceedings of the National Academy of Sciences, USA 98, 2053.

Mochizuki N, Susek R, Chory J. 1996. An intracellular signal transduction pathway between the chloroplast and nucleus is involved in de-etiolation. Plant Physiology 112, 1465–1469.

Mubarakshina MM, Ivanov BN, Naydov IA, Hillier W, Badger MR, Krieger-Liszkay A. 2010. Production and diffusion of chloroplastic H2O2 and its implication to signalling. Journal of Experimental Botany 61, 3577–3587.
Oh S, Montgomery BL. 2013. Phytochrome-induced SIG2 expression contributes to photoregulation of phytochrome signaling and photomorphogenesis in Arabidopsis thaliana. Journal of Experimental Botany 64, 5457–5472.

Oh S, Montgomery BL. 2014. Phytochrome-dependent coordinate control of distinct aspects of nuclear and plastid gene expression during antero-grade signaling and photomorphogenesis. Frontiers in Plant Science 5, 171.

Oh S, Strand DD, Kramer DM, Chen J, Montgomery BL. 2018. Transcriptome and phenotyping analyses support a role for chloroplast stress factor 2 in red-light-dependent regulation of growth, stress, and photosynthesis. Plant Direct 2, e00043.

Ogishi M, Saji K, Okada K, Sakai T. 2004. Functional analysis of each blue light receptor, cry1, cry2, phot1, and phot2, by using combinatorial multiple mutants in Arabidopsis. Proceedings of the National Academy of Sciences, USA 101, 2223.

Ortiz-Alcaide M, Llamas E, Gomez-Cadenas A, Nagatani A, Martinez-Garcia JF, Rodriguez-Concepcion M. 2019. Chloroplasts modulate elongation responses to canopy shade by retrograde pathways involving HY5 and abscisic acid. The Plant Cell 38, 384–398.

Pfälz J, Holtzegel U, Barkan A, Weisheit W, Mittag M, Pfannschmidt T. 2013. ZmpTAC12 binds single-stranded nucleic acids and is essential for accumulation of the plastid-encoded polymerase complex in maize. New Phytologist 200, 1024–1037.

Pfalz J, Liere K, Kandlbinder A, Dietz K-J, Oelmüller R. 2006. pTAC2, -6, and -12 are components of the transcriptionally active plastid chromosome that are required for plastid gene expression. The Plant Cell 18, 176–197.

Pogson BJ, Ganguly D, Albrecht-Borst V. 2015. Insights into chloroplast biogenesis and development. Biochimica et Biophysica Acta 1847, 1017–1024.

Pogson BJ, Woo NS, Förster B, Small ID. 2008. Plastid signalling to the nucleus and beyond. Trends in Plant Science 13, 602–609.

Qiu Y, Li M, Pasoreck EK, et al. 2015. HEMERA couples the proteolysis and transcriptional activity of PHYTOCHROME INTERACTING FACTORs in Arabidopsis photomorphogenesis. The Plant Cell 27, 1409–1427.

Ramel F, Birtic S, Ginies C, Soubigou-Taconnat L, Triantaphyllides C, Havaux M. 2012. Carotenoid oxidation products are stress signals that mediate gene responses to singlet oxygen in plants. Proceedings of the National Academy of Sciences, USA 109, 5535.

Reed JW, Nagatani A, Fau - Elich TD, Elich T, Fau - Fagan M, Fagan M, Fau - Chory J, Chory J. 1994. Phytochrome A and phytochrome B have overlapping but distinct functions in Arabidopsis development. Plant Physiology 104, 1139–1149.

Ren Y, Li Y, Jiang Y, Wu B, Miao Y. 2017. Phosphorylation of WHIRLY1 by CIPK14 shifts its localization and dual functions in Arabidopsis. Molecular Plant 10, 749–763.

Richter AS, Thöge T, Fernie AR, Grimm B. 2020. The genomes uncoupled-dependent signalling pathway coordinates plastid biogenesis with the synthesis of anthocyanins. Philosophical Transactions of the Royal Society B: Biological Sciences 375, 20190403.
Toledo-Ortiz G, Johansson H, Lee KP, Bou-Torrent J, Stewart K, Steel G, Rodriguez-Concepcion M, Halliday KJ. 2014. The HY5–PIF regulatory module coordinates light and temperature control of photosynthetic gene transcription. PLoS Genetics 10, e1004416.

Veciana N, Martín G, Leivar P, Monte E. 2022. BBX16 mediates the repression of seedling photomorphogenesis downstream of the GUN1/GLK1 module during retrograde signalling. New Phytologist 234, 93–106.

Vinti G, Fournier N, Bowyer JR, López-Juez E. 2005. Arabidopsis cue mutants with defective plastids are impaired primarily in the photoregulation of expression of photosynthesis-associated nuclear genes. Plant Molecular Biology 57, 343–357.

Wang J-Z, Li B, Xiao Y, et al. 2017. Initiation of ER body formation and indole glucosinolate metabolism by the plastidial retrograde signaling metabolite, MEcPP. Molecular Plant 10, 1400–1416.

Wang P, Abid MA, Qanmber G, et al. 2022. Photomorphogenesis in plants: the central role of phytochrome interacting factors (PIFs). Environmental and Experimental Botany 194, 104704.

Waters MT, Wang P, Korkaric M, Capper RG, Saunders NJ, Langdale JA. 2009. GLK transcription factors coordinate expression of the photosynthetic apparatus in Arabidopsis. The Plant Cell 21, 1109–1128.

Wollman F-A. 2016. An antimicrobial origin of transit peptides accounts for early endosymbiotic events. Traffic 17, 1322–1328.

Woodson JD, Perez-Ruiz Juan M, Chory J. 2011. Heme synthesis by plastid ferrochelatase I regulates nuclear gene expression in plants. Current Biology 21, 897–903.

Woodson JD, Perez-Ruiz JM, Schmitz RJ, Ecker JR, Chory J. 2013. Sigma factor-mediated plastid retrograde signals control nuclear gene expression. The Plant Journal 73, 1–13.

Wright LP, Rohwer JM, Ghirardo A, Hammerbacher A, Ortiz-Alcaide M, Raguschke B, Schnitzler J-P, Gershenzon J, Phillips MA. 2014. Deoxyxylulose 5-phosphate synthase controls flux through the methylenetriol 4-phosphate pathway in Arabidopsis. Plant Physiology 165, 1488–1504.

Wu G-Z, Bock R. 2021. GUN control in retrograde signaling: how GENOMES UNCOUPLED proteins adjust nuclear gene expression to plastid biogenesis. The Plant Cell 33, 457–474.

Wu G-Z, Meyer EH, Richter AS, et al. 2019. Control of retrograde signaling by protein import and cytosolic folding stress. Nature Plants 5, 525–538.

Xiao Y, Savchenko T, Baidoo EE, Chehab WE, Hayden DM, Tolstikov V, Corwin JA, Kliebenstein DJ, Keasing JD, Dehesh K. 2012. Retrograde signaling by the plastidial metabolite MEcPP regulates expression of nuclear stress-response genes. Cell 149, 1525–1535.

Xu X, Chi W, Sun X, et al. 2016. Convergence of light and chloroplast signals for de-etiolation through ABI4–HY5 and COP1. Nature Plants 2, 16066.

Yoo CY, Han S, Chen M. 2020. Nucleus-to-plastid phytochrome signaling in controlling chloroplast biogenesis. Annual Plant Reviews 3, 251–280.

Yoo CY, Pasoreck EK, Wang H. 2019. Phytochrome activates the plastid-encoded RNA polymerase for chloroplast biogenesis via nucleus-to-plastid signaling. Nature Communications 10, 2629.

Yu X, Liu H, Klejnot J, Lin C. 2010. The cryptochrome blue light receptors. The Arabidopsis Book 8, e0135.

Zhang H-N, Li W-C, Wang H-C, Shi S-Y, Shu B, Liu L-Q, Wei Y-Z, Xie J-H. 2016. Transcriptome profiling of light-regulated anthocyanin biosynthesis in the pericarp ofitchi. Frontiers in Plant Science 7, 963.

Zhao X, Huang J, Chory J. 2019. GUN1 interacts with MORF2 to regulate plastid RNA editing during retrograde signaling. Proceedings of the National Academy of Sciences, USA 116, 10162–11067.