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Mini Review
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The dual-action mechanism of Arabidopsis cryptochromes∞

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ABSTRACT

Photoreceptor cryptochromes (CRYs) mediate blue-light regulation of plant growth and development. It has been reported that Arabidopsis CRY1and CRY2 function by physically interacting with at least 84 proteins, including transcription factors or co-factors, chromatin regulators, splicing factors, messenger RNA methyltransferases, DNA repair proteins, E3 ubiquitin ligases, protein kinases and so on. Of these 84 proteins, 47 have been reported to exhibit altered binding affinity to CRYs in response to blue light, and 41 have been shown to exhibit condensation to CRY photobodies. The blue light-regulated composition or condensation of CRY complexes results in changes of gene expression and developmental programs. In this mini-review, we analyzed recent studies of the photoregulatory mechanisms of Arabidopsis CRY complexes and proposed the dual mechanisms of action, including the "Lock-and-Key" and the "Liquid-Liquid Phase Separation (LLPS)" mechanisms. The dual CRY action mechanisms explain, at least partially, the structural diversity of CRY-interacting proteins and the functional diversity of the CRY photoreceptors.

Keywords: Arabidopsis, blue light, cryptochrome, CRY1, CRY2, phase separation

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INTRODUCTION

Light is required for not only photosynthesis but also all aspects of plant growth and development. Plants have multiple sensory photoreceptors that perceive photons of different wavelengths. For example, Arabidopsis has at least 13 photoreceptors, including phyA, phyB, phyC, phyD, phyE, cryptochrome 1 (CRY1), CRY2, Phot1, Phot2, ZTL, FKF1, LKP2, and UVR8, which sense solar radiation with the wavelengths ranging from UV-B to far-red spectrum (Chen et al., 2004; Christie, 2007; Kami et al., 2010; Quail, 2010; Zoltowski and Imaizumi, 2014; Han et al., 2019; Podolec et al., 2021). Among this diverse array of plant photoreceptors, cryptochromes are the blue light receptors first discovered in *Arabidopsis* and later found to exist in all plant lineages examined (Ahmad and Cashmore, 1993; Lin et al., 1995; Cashmore, 2003; Lin and Shalitin, 2003; Chaves et al., 2011; Wang and Lin, 2020). Most plant species studied thus far have two types of cryptochromes, CRY1 and CRY2. Arabidopsis CRY1 is the first blue light receptor molecularly defined (Ahmad and Cashmore, 1993; Lin et al., 1995; Malhotra et al., 1995). CRY2 was first discovered for its function in regulating floral initiation and low blue light-induced photomorphogenesis (Guo et al., 1998; Lin et al., 1998). CRY1 exists in both cytosol and nucleus (Wu and Spalding, 2007; Liu et al., 2022), whereas CRY2 is a nuclear protein (Guo et al., 1999; Kleiner et al., 1999; Yu et al., 2007a). Plant CRYs are characterized by the highly conserved N-terminal domain that is referred to as PHR for Photolyase Homologous Region (Lin and Todo, 2005) or CNT for CRY

N-Terminus (Sang et al., 2005). Plant CRYs also possess a less conserved C-terminal domain termed as Cryptochrome C-terminal domain (CCT) (Yang et al., 2000) but later also termed as Cryptochrome C-terminal Extension (CCE) (Yu et al., 2010) to avoid the same name (IntePro# IPR010402 or Pfam# PF06203) of the CCT-family proteins (CONSTANS, CO-LIKE, and TIMING OF CAB EXPRESSION 1) that also play important functions in light signal transduction (Strayer et al., 2000). Although the PHR domain shares high sequence and structure similarity with DNA photolyases, neither CRY1 nor CRY2 has photolyase activity (Lin et al., 1995; Hoffman et al., 1996). However, it has been recently shown that *Arabidopsis* CRYs mediate blue light-enhanced DNA repairing reaction (Guo et al., 2023).

CRYs accept photons through the non-covalently bound chromophore, flavin adenine dinucleotide, which binds to the PHR domain of CRYs (Lin et al., 1995; Malhotra et al., 1995; Cashmore et al., 1999). Photoactivated CRYs undergo rapid oligomerization, phosphorylation, Liquid-Liquid Phase Separation (LLPS) and ubiquitination-induced degradation to transmit light signal and to maintain photosensitivity of plants. Cryptochrome oligomerization is believed to be the first step in CRYs' photoactivation (Sang et al., 2005; Rosenfeldt et al., 2008; Wang et al., 2016; Liu et al., 2020), which is mediated by the PHR domain of CRYs (Sang et al., 2005; Yu et al., 2007b; Shao et al., 2020; Ma et al., 2020a; Palayam et al., 2021). Four PHOTOREGULATORY PROTEIN KINASEs, PPK1-4, mediate phosphorylation of CRYs, primarily at the CCE domain (Shalitin et al., 2002; Liu et al., 2017; Gao et al., 2022). Although phosphorylation of CRYs does not affect their dimerization/oligomerization, it is necessary to maintain phase-separated CRY proteins in the liquid form (Wang et al., 2021; Gao et al., 2022). CRY phosphorylation is required for not only the cellular activities but also ubiquitination and degradation of both CRY1 and CRY2 (Shalitin et al., 2002, 2003; Yu et al., 2007a; Liu et al., 2017; Gao et al., 2022). To avoid unremitting photoresponses, plants have evolved three mechanisms to regulate photosensitivity. First, ubiquitin E3 ligases CONSTITUTIVE PHOTOMORPHOGENIC 1 (COP1) and LIGHT-RESPONSE BRIC-A-BRACK/TRAMTRACK/BROADs (LRBs) mediate degradation of photoactivated CRYs (Ahmad et al., 1998a; Chen et al., 2021; Ma et al., 2021; Miao et al., 2021). Light-induced degradation of CRY1 is relatively slow and requires prolonged high-intensity blue light illumination (Miao et al., 2021). Second, BLUE LIGHT INHIBITOR OF CRYPTOCHROMES 1 (BIC1) and its homolog BIC2 inhibit oligomerization, LLPS, and all known biochemical and physiological activities of CRYs (Wang et al., 2016). Blue light activates transcription of *BIC1* and *BIC2* via the action of HY5, and modestly increases stability of BIC1 and BIC2 proteins (Wang et al., 2017), resulting in a CRY-BIC negative feedback to control photoresponses of plants. Third, photoactivated and oligomerized CRYs undergo dark reversion or thermal relaxation to dissociate into inactive monomers in the absence of blue light (Liu et al., 2020).

The photoresponsive association and disassociation of CRY complexes are the major signal transduction mechanism of CRYs (Yang et al., 2000; Liu et al., 2008a; Wang and Lin, 2020; Ponnu and Hoecker, 2022). Since reports of the first CRY-interacting protein COP1 (Wang et al., 2001; Yang et al., 2001) and the first blue light-dependent CRY-interacting protein CRYPTOCHROME-INTERACTING BASIC-HELIX-LOOP-HELIX 1 (CIB1) (Liu et al., 2008a), 84 CRY-interacting proteins have been reported (Table 1). Out of these 84 proteins, 47 exhibited photoresponsive (blue light-induced or inhibited) physical interaction with CRYs, 41 were found to be condensed to CRY photobodies, of which nine were shown to undergo blue light-induced LLPS. The existing experimental evidence in *Arabidopsis* supports a proposition that CRY signal transduction involves two different mechanisms. One is the classical "Lock-and-Key" mechanism that involves blue light-induced change of binding activity between CRYs and CRY-interacting proteins, the other is the LLPS mechanism that involves blue light-induced co-condensation of CRYs and CRY-interacting proteins. The present mini-review will focus on the discussion of these two possible mechanisms of CRY signal transduction in *Arabidopsis* (Figures 1, 2).

THE LOCK-AND-KEY MODEL

The Lock-and-Key mechanism was first proposed by Emil Fischer in 1894 (Fischer, 1894). This model proposed that enzymatic catalysis occurs when an enzyme and its substrate exhibit complementary geometric shapes that fit perfectly like a "key in a lock." The Lock-and-Key model has been the paradigm that conceptualizes our understanding of how proteins function. Consistent with this model, CRYs were hypothesized to change conformation upon photon absorption, resulting in "open" conformation, "induced fit" to CRY-interacting proteins and subsequently photo-signal transduction (Yang et al., 2000; Partch and Sancar, 2005; Yu et al., 2007b). This hypothesis has been supported by recent structure studies of CRYs (Ma et al., 2020a, 2020b; Shao et al., 2020). For example, structural analyses have demonstrated complementary structural fits between CRYs and some CRY-interacting proteins, such as BIC2 (Ma et al., 2020b) and COP1 (Lau et al., 2019). About 56% (47/84) of currently known CRY-interacting proteins exhibit photoresponsive alteration of binding affinity to CRYs, supporting "induced fit" version of the "Lock-and-Key" hypothesis (Table 1; Figure 2).

The photoreceptor-COP1/SPA-substrate axis is one of the most extensively studied light-signal transduction mechanisms (Lau and Deng, 2012; Huang et al., 2014; Hoecker, 2017; Podolec and Ulm, 2018; Han et al., 2020; Kerner et al., 2021), and it is also the first reported mechanism of CRY signal transduction (Yang et al., 2000; Wang et al., 2001; Yang et al., 2001). It is a present consensus that a major role of CRYs in photomorphogenesis is to mediate blue

Table 1. Proteins interacting with cryptochromes (CRYs) in *Arabidopsis*

CRY-interacting proteins		Interacting CRY & domain					
Common names	Accession	CRY1	CRY2	Photoresponsive interaction with CRYs	Condense to the CRY photobody	Biochemical activity	Reference
ADA2a	AT3G07740	PHR	PHR	–	Yes	DNA repair	(Guo et al., 2023)
ADA2b	AT4G16420	PHR	PHR	Yes	Yes	DNA repair	(Guo et al., 2023)
AGB1	AT4G34460	PHR	CRY2	Yes	Yes	Trimeric G protein subunit	(Lian et al., 2018)
ANN2	AT5G65020	–	CRY2	–	–	Ca^{2+} binding protein	(Liu et al., 2021)
ANN3	AT2G38760	–	CRY2	–	–	Ca^{2+} binding protein	(Liu et al., 2021)
ARF6	AT1G30330	PHR	–	Yes	Yes	Transcription factor	(Mao et al., 2020)
ARF8	AT5G37020	PHR	–	Yes	Yes	Transcription factor	(Mao et al., 2020)
ARP6	AT3G33520	PHR and CCE	PHR and CCE	Yes	–	H2A.Z deposition	(Mao et al., 2021)
BEE2	AT4G36540	PHR	–	–	Yes	Transcription factor	(Wang et al., 2018a)
BES1	AT1G19350	PHR	PHR and CCE	Yes	Yes	Transcription factor	(Wang et al., 2018b)
BIC1	AT3G52740	PHR	PHR	Yes	–	CRY inhibitor	(Wang et al., 2016)
BIC2	AT3G44450	–	CRY2	–	–	CRY inhibitor	(Wang et al., 2016; Ma et al., 2020b)
BIM1	AT5G08130	PHR	PHR and CCE	Yes	Yes	Transcription regulator	(Wang et al., 2018b)
BIN2	AT4G18710	CCE	–	Yes	–	Protein kinase	(He et al., 2019)
bZIP16	AT2G35530	CRY1	–	Yes	–	Transcription factor	(Norén Lindbäck et al., 2023)
bZIP68	AT1G32150	CRY1	–	–	–	Transcription factor	(Norén Lindbäck et al., 2023)
BZR1	AT1G75080	PHR	PHR and CCE	Yes	Yes	Transcription factor	(Wang et al., 2018b; He et al., 2019)
CIB1	AT4G34530	PHR	CRY2	Yes	Yes	Transcription factor	(Liu et al., 2008a; Liu et al., 2013)
CIB2	AT5G48560	–	CRY2	–	Yes	Transcription factor	(Liu et al., 2013)
CIB4	AT1G10120	–	CRY2	–	Yes	Transcription factor	(Liu et al., 2013)
CIB5	AT1G26260	–	CRY2	Yes	Yes	Transcription factor	(Liu et al., 2008a; Liu et al., 2013)
CIL1	AT1G68920	PHR	–	–	Yes	Transcription factor	(Wang et al., 2018a)
CIS1	AT3G52120	–	PHR	Yes	Yes	Splicing factor	(Zhao et al., 2022)
CIS2	AT1G63980	–	CRY2	–	–	Splicing factor	(Zhao et al., 2022)
CO	AT5G15840	–	CRY2	Yes	Yes	Transcription factor	(Liu et al., 2018)
COP1	AT2G32950	CCE	CCE	No/Yes	Yes	E3 ubiquitin ligase	(Wang et al., 2001; Yang et al., 2001; Holtkotte et al., 2017; Ponnu et al., 2019)
CRY1	AT4G08920	PHR	PHR	Yes	Yes	Blue light receptor	(Sang et al., 2005; Liu et al., 2020; Liu et al., 2022)
CRY2	AT1G04400	PHR	PHR	Yes	Yes, LLPS	Blue light receptor	(Más et al., 2000; Sang et al., 2005; Yu et al., 2009; Liu et al., 2020; Wang et al., 2021)
FIO1	AT2G21070	–	CCE	No	Yes, LLPS	m^6A methyltransferase	(Jiang et al., 2023a)
FIP37	AT3G54170	PHR and CCE	CRY2	No	Yes, LLPS	m^6A methyltransferase	(Wang et al., 2021)
GAI	AT1G14920	PHR and CCE	–	Yes	–	Transcription regulator	(Xu et al., 2021a; Yan et al., 2021; Zhong et al., 2021)

Continued

Table 1. Continued

CRY-interacting proteins		Interacting CRY & domain					
Common names	Accession	CRY1	CRY2	Photoresponsive interaction with CRYs	Condense to the CRY photobody	Biochemical activity	Reference
GBF1	AT4G36730	CRY1	–	–	–	Transcription factor	(Norén Lindbäck et al., 2023)
GID1a	AT3G05120	PHR and CCE	–	Yes	–	GA receptor	(Xu et al., 2021a; Yan et al., 2021; Zhong et al., 2021)
GID1b	AT3G63010	PHR and CCE	–	Yes	–	GA receptor	(Xu et al., 2021a; Zhong et al., 2021)
GID1c	AT5G27320	PHR and CCE	–	Yes	–	GA receptor	(Xu et al., 2021a; Zhong et al., 2021)
HBI1	AT2G18300	PHR	PHR	Yes	Yes	Transcription factor	(Wang et al., 2018a)
HsfA1a	AT4G17750	CRY1	–	–	–	Transcription factor	(Gao et al., 2023)
HsfA1b	AT5G16820	CRY1	–	–	–	Transcription factor	(Gao et al., 2023)
HsfA1d	AT1G32330	PHR and CCE	CRY2	–	–	Transcription factor	(Gao et al., 2023)
HsfA1e	AT3G02990	CRY1	–	–	–	Transcription factor	(Gao et al., 2023)
IAA3	AT1G04240	PHR	–	–	–	Transcription regulator	(Xu et al., 2018)
IAA7	AT1G04250	PHR	CRY2	Yes	Yes	Transcription regulator	(Xu et al., 2018; Mao et al., 2020)
IAA12	AT1G04550	PHR	–	Yes	Yes	Transcription regulator	(Xu et al., 2018; Mao et al., 2020)
IAA13	AT2G33310	CRY1	–	–	–	Transcription regulator	(Xu et al., 2018)
IAA17	AT1G04250	PHR	CRY2	Yes	Yes	Transcription regulator	(Xu et al., 2018; Mao et al., 2020)
LRB1	AT2G46260	CRY1	CRY2	Yes	–	E3 ubiquitin ligase	(Chen et al., 2021; Ma et al., 2021; Miao et al., 2021)
LRB2	AT3G61600	CRY1	CCE	Yes	–	E3 ubiquitin ligase	(Chen et al., 2021; Ma et al., 2021; Miao et al., 2021)
LRB3	AT4G01160	CRY1	CRY2	Yes	–	E3 ubiquitin ligase	(Ma et al., 2021; Miao et al., 2021)
LWD1	AT1G12910	–	CRY2	No	Yes	Transcription regulator	(Mo et al., 2022)
LWD2	AT3G26640	–	CRY2	No	Yes	Transcription regulator	(Mo et al., 2022)
MAC3A	AT1G04510	CRY1	PHR and CCE	No	Yes, LLPS	Transcription regulator	(Jiang et al., 2023b)
MAC3B	AT2G33340	CRY1	CRY2	No	Yes, LLPS	Transcription regulator	(Jiang et al., 2023b)
MTA	AT4G10760	CRY1	PHR and CCE	No	Yes, LLPS	m^6A methyltransferase	(Wang et al., 2021)
MTB	AT4G09980	–	CRY2	No	Yes, LLPS	m^6A methyltransferase	(Wang et al., 2021)
NF-YC5	AT5G50490	–	CRY2	No	–	Transcription factor	(Wang et al., 2023)
NF-YC7	AT5G50470	–	CRY2	No	–	Transcription factor	(Wang et al., 2023)
NF-YC8	AT5G27910	–	CRY2	No	–	Transcription factor	(Wang et al., 2023)
PhyA	AT1G09570	CRY1	–	–	–	Far-red light receptor	(Ahmad et al., 1998b)
PhyB	AT2G18790	PHR	CRY2	Yes	Yes	Red light receptor	(Más et al., 2000; Hughes et al., 2012)
PIF4	AT2G43010	CRY1	CRY2	LBL	Yes	Transcription factor	(Ma et al., 2016; Pedmale et al., 2016)
PIF5	AT3G59060	CRY1	PHR	LBL	Yes	Transcription factor	(Pedmale et al., 2016)
PPK1	AT3G13670	PHR and CCE	CRY2	Yes	Yes	Protein kinase	(Liu et al., 2017; Mo et al., 2022; Gao et al., 2022)
PPK2	AT5G18190	CRY1	CRY2	Yes	–	Protein kinase	(Liu et al., 2017; Gao et al., 2022)

Continued

Table 1. Continued

CRY-interacting proteins		Interacting CRY & domain					
Common names	Accession	CRY1	CRY2	Photoresponsive interaction with CRYs	Condense to the CRY photobody	Biochemical activity	Reference
PPK3	AT3G03940	CRY1	CRY2	Yes	–	Protein kinase	(Liu et al., 2017; Gao et al., 2022)
PPK4	AT2G25760	CRY1	CRY2	Yes	–	Protein kinase	(Liu et al., 2017; Gao et al., 2022)
PRR9	AT2G46790	No	PHR	Yes	Yes	Transcription regulator	(He et al., 2022)
RGA	AT2G01570	PHR and CCE	–	Yes	–	Transcription regulator	(Yan et al., 2021; Zhong et al., 2021; Xu et al., 2021a)
RGL1	AT1G66350	CRY1	–	–	–	Transcription regulator	(Yan et al., 2021; Zhong et al., 2021)
RGL2	AT3G03450	CRY1	–	–	–	Transcription regulator	(Yan et al., 2021; Zhong et al., 2021)
RGL3	AT5G17490	CRY1	–	–	–	Transcription regulator	(Yan et al., 2021; Zhong et al., 2021)
SINAT1	AT2G41980	CRY1	–	–	–	E3 ubiquitin ligase	(Hu et al., 2021)
SINAT2	AT3G58040	PHR and CCE	–	Blue-inhibited	–	E3 ubiquitin ligase	(Hu et al., 2021)
SINAT3	AT3G61790	CRY1	–	–	–	E3 ubiquitin ligase	(Hu et al., 2021)
SINAT4	AT4G27880	CRY1	–	–	–	E3 ubiquitin ligase	(Hu et al., 2021)
SINAT5	AT5G53360	PHR and CCE	–	Blue-inhibited	–	E3 ubiquitin ligase	(Hu et al., 2021)
SMC5	AT5G15920	CRY1	CRY2	Yes	Yes	DNA repair	(Guo et al., 2023)
SPA1	AT2G46340	PHR and CCE	PHR and CCE	Yes	Yes, LLPS	Positive regulator of COP1	(Lian et al., 2011; Liu et al., 2011; Zuo et al., 2011; Ponnu et al., 2019; Jiang et al., 2023a)
SWC6	AT5G37055	PHR and CCE	PHR and CCE	Yes	–	H2A.Z deposition	(Mao et al., 2021)
TCP2	AT4G18390	PHR	–	Yes	–	Transcription factor	(He et al., 2016)
TCP17	AT5G08070	PHR	–	–	–	Transcription factor	(Zhou et al., 2019)
TCP22	AT1G72010	–	CRY2	No	Yes, LLPS	Transcription factor	(Mo et al., 2022)
TCP5	AT5G60970	CRY1	–	–	–	Transcription factor	(Zhou et al., 2019)
TOE1	AT2G28550	PHR and CCE	PHR and CCE	Yes	Yes	Transcription factor	(Du et al., 2020)
TOE2	AT5G60120	PHR and CCE	PHR and CCE	Yes	Yes	Transcription factor	(Du et al., 2020)
UBP12	AT5G06600	–	–	–	–	Deubiquitinase	(Hu et al., 2023)
UBP13	AT3G11910	–	CRY2	Yes	–	Deubiquitinase	(Hu et al., 2023)
ZTL	AT5G57360	CCE	–	–	–	Blue light receptor, E3 ubiquitin ligase	(Jarillo et al., 2001)

Note: "–", not determined; GA, gibberellic acid; LBL, limiting blue light; LLPS, Liquid-Liquid Phase Separation; m6A, N^6-methyladenosine; PHR, Photolyase Homologous Region. It should be noted that not all condensations are in liquid phase (LLPS), which should be tested according to spherality, mobility, reversibility and so on.

light-induced inhibition of $CUL4^{COP1/SPAs}$ (Lau and Deng, 2012; Hoecker, 2017; Podolec and Ulm, 2018; Han et al., 2020; Wang and Lin, 2020). COP1 is an evolutionarily conserved core subunit of the E3 ubiquitin ligase $CUL4^{COP1/SPAs}$. SUPPRESSOR OF PHYA-105 (SPA) was originally identified as a genetic suppressor of *phyA* mutant (Hoecker et al., 1999), which interacts with COP1 to positively regulate COP1 activity (Hoecker and Quail, 2001; Saijo et al., 2003; Saijo et al., 2008; Zhu et al., 2008). The SPA gene family contains four members, SPA1-4, and *spa* quadruple mutants exhibit *cop1*-like photomorphogenesis phenotype (Laubinger et al., 2004). The WD domain of COP1 interacts with the VP motif of its substrates to recruit substrate proteins, such as HY5, LAF1, CO and CRYs, to $CUL4^{COP1/SPAs}$ for polyubiquitination and degradation (Ang et al., 1998; Osterlund et al., 2000; Holm et al., 2001; Seo et al., 2003; Liu et al., 2008b; Uljon et al., 2016; Lau et al., 2019; Ponnu et al., 2019). CRYs interact with both COP1 and SPAs (Wang et al., 2001; Yang et al., 2001; Lian et al., 2011; Liu et al., 2011; Zuo et al., 2011; Holtkotte et al., 2017; Ponnu et al., 2019), and compete with COP1 substrates for COP1 binding via VP motif at the CCE domain of CRYs (Lau et al., 2019; Ponnu et al., 2019).

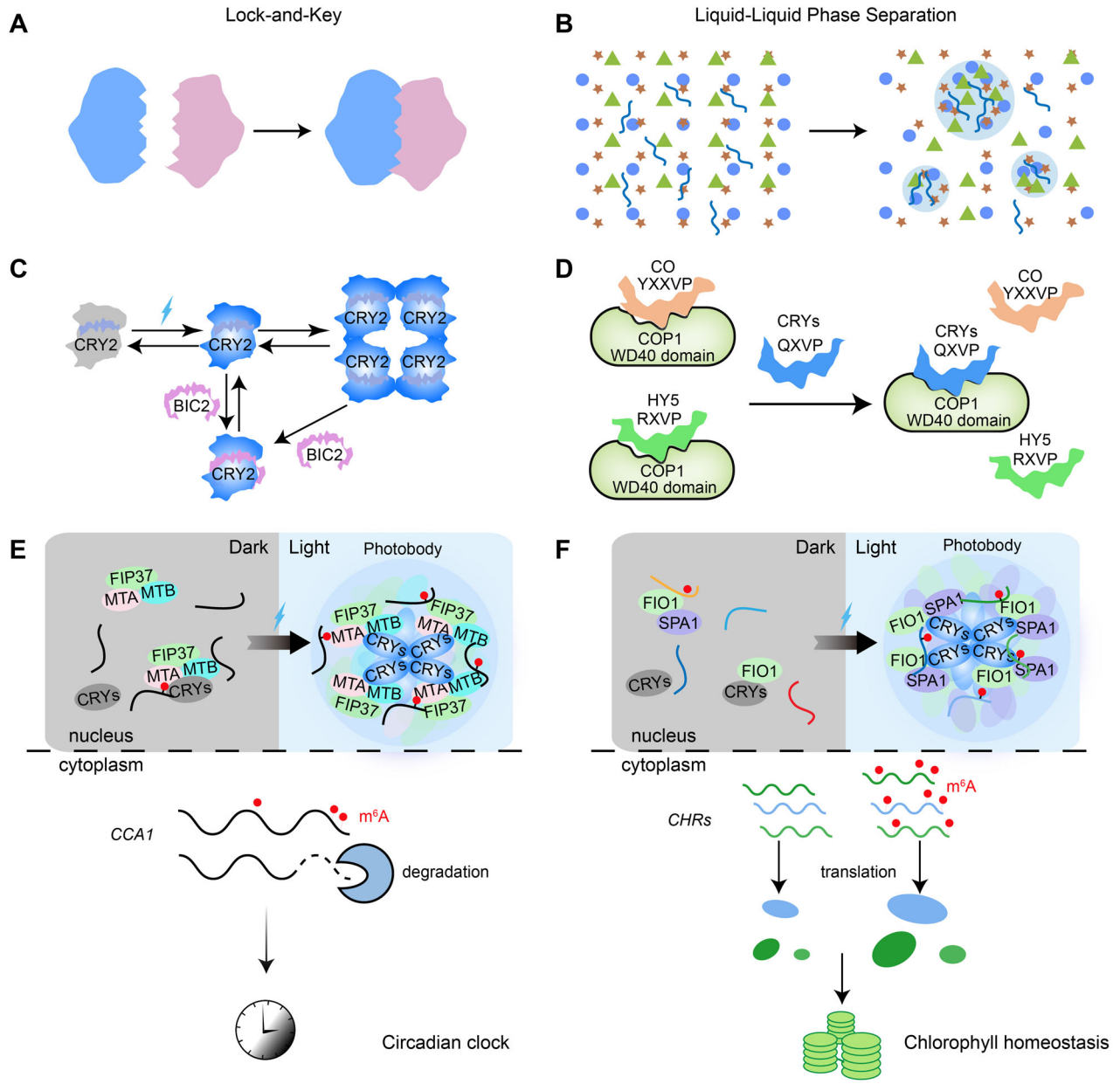

Figure 1. Two functional models of cryptochromes (CRYs) signaling

(A) Lock-and-Key model indicates complementary structures between CRYs and their interacting proteins. **(B)** Liquid-Liquid Phase Separation (LLPS) model indicates that macromolecules get together leading to a solution being demixed into different phases. **(C** and **D)** Examples of Lock-and-Key model. Photoactivated CRY2 Photolyase Homologous Region (PHR) domain undergoes minor conformational changes and forms an oligomer. BLUE LIGHT INHIBITOR OF CRYPTOCHROMES 2 (BIC2) wraps around CRY2, leading to inhibition of electron transfer, preventing CRY2 oligomerization and facilitating CRY2 oligomerization to return to monomer **(C)**. The C-terminal VP motif of CRYs has a higher affinity to WD domain of CONSTITUTIVE PHOTOMORPHOGENIC 1 (COP1), leading to competitive binding and disassociating CO and HY5 from COP1 **(D)**. **(E** and **F)** Example of LLPS model. Blue light induces co-condensation of CRYs/MTA/MTB/FIP37 **(E)** and CRY2/FIO1 with the help of SPA1 **(F)**, leading to increased m^6A methylation of *CCA1* and *CHRs*, respectively. N^6-methyladenosine (m^6A) methylation enhances messenger RNA (mRNA) stability of *CCA1* and translation efficiency of *CHRs* to regulate circadian clock and chlorophyll homeostasis, respectively.

Therefore, CRYs may mediate photoresponsive inhibition of $CUL4^{COP1/SPAs}$ by at least two mechanisms. First, blue-light stimulates CRY-SPA interaction to suppress the SPA-dependent activation of COP1. Second, the photoresponsive CRY-SPA interaction enhances the CRY-COP1 interaction to heighten CRY-dependent competitive inhibition of COP1.

However, the exact photoreactions underlying the blue light- and CRY-dependent inhibition of COP1 may be more complex than these seemingly oversimplified models. First, it was initially reported that CRY1 undergoes light-independent interaction with COP1 (Yang et al., 2000; Wang et al., 2001; Yang et al., 2001), but light-dependent CRYs/COP1

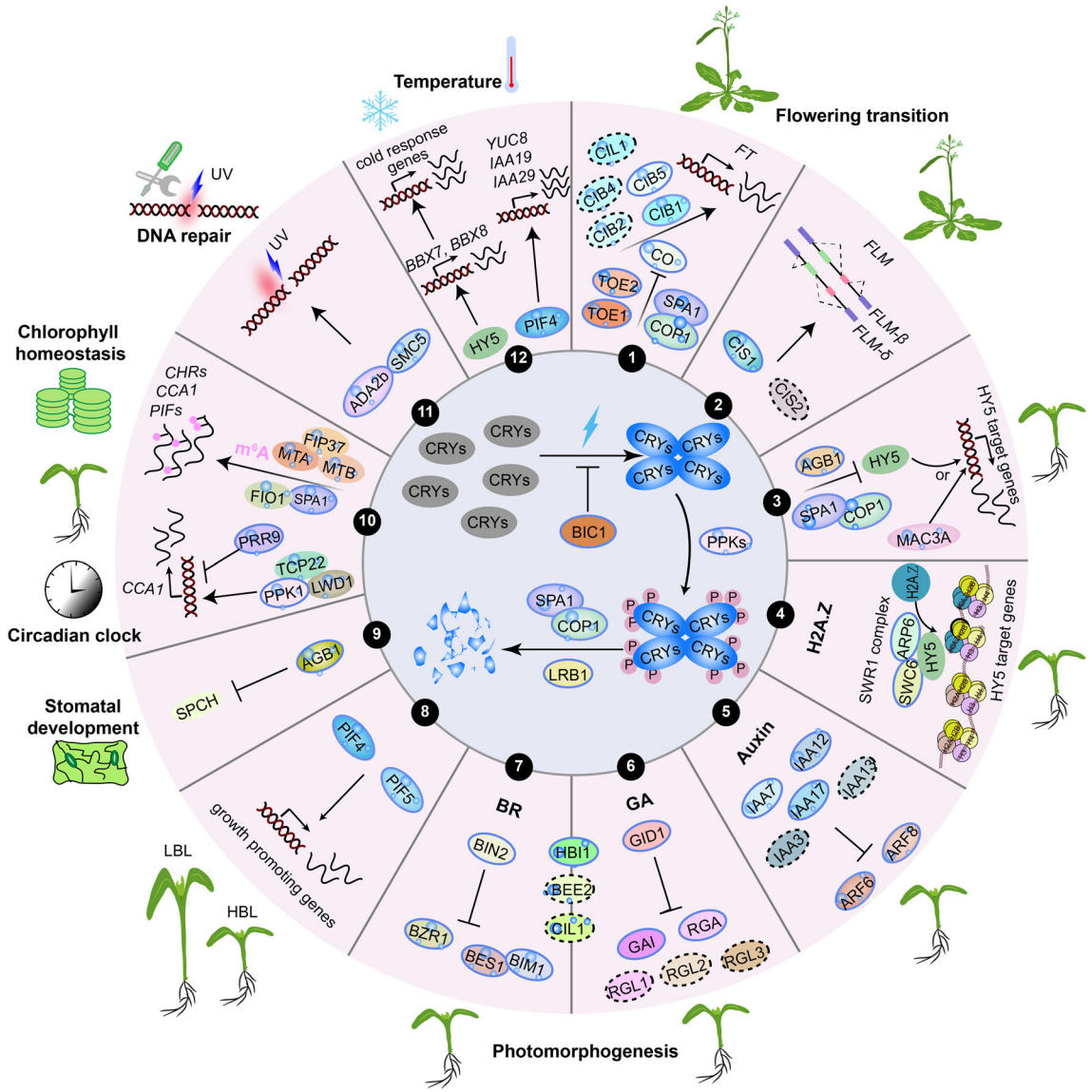

Figure 2. Detailed network of cryptochromes (CRYs) signaling

Light-activated CRYs undergo oligomerization and PHOTOREGULATORY PROTEIN KINASE (PPK)-mediated phosphorylation for light signaling. BIC1 inhibited oligomerization and CONSTITUTIVE PHOTOMORPHOGENIC 1/SUPPRESSOR OF PHYA-105 1 (COP1/SPA1) and LIGHT-RESPONSE BRIC-A-BRACK/TRAMTRACK/BROAD 1 (LRB1) synergistically mediated degradation of activated CRYs desensitize persistent light responses. For flowering transition, light-activated CRY2 activates expression of *FT* through transcriptional factor CRYPTOCHROME-INTERACTING BASIC-HELIX-LOOP-HELIX 1 (CIB1) and its homologs (①). Meanwhile, CRY2 stabilizes or alleviates inhibition on CO, activator of *FT*, through competitive binding with its ubiquitin E3 ligase COP1/SPA1 or repressor TARGET OF EAT 1/2 (TOE1/2), respectively (①). Furthermore, CRY2 regulates alternative splicing of flowering repressor *FLM* through CRY2 INTERACTING SPLICING FACTOR 1/2 (CIS1/2) (②). For photomorphogenesis, CRYs stabilizes and activates HY5 through competitive binding with COP1/SPA1 and disassociating HY5 from repressor Arabidopsis G-Protein β Subunit 1 (AGB1), respectively (③). Meanwhile, co-condensation of CRYs/MAC3A (MOS4-ASSOCIATED COMPLEX SUBUNIT 3A) facilitates MAC3A competitively binding to HY5 targets, leading to attenuated HY5 activity (③). Moreover, CRYs enhance interaction between SWC6 and ACTIN RELATED PROTEIN 6 (ARP6) to facilitate H2A.Z deposition on HY5 target genes (④). In addition, CRYs stabilize auxin/indole-3-acetic acid (AUX/IAAs) and repress ARFs through promoting their interaction with AUX/IAAs or directly inhibiting their DNA binding activity, to repress auxin induced hypocotyl elongation (⑤). CRYs interact with gibberellic acid (GA) GA-INSENSITIVE DWARF 1 (GID1) and DELLAs to disassociate DELLAs from GID1s, leading to stabilize DELLAs to repress GA signaling (⑥). CRYs suppress brassinosteroid (BR) signaling through interacting with BRI1-EMS SUPPRESSOR1 (BES1) and BRASSINAZOLE-RESISTANT 1 (BZR1) to inhibit their DNA binding activity or transcriptional activity (⑦). And CRYs facilitate interaction between BRASSINOSTEROID INSENSITIVE 2 (BIN2) and BZR1 to promote phosphorylation and inactivation of BZR1 (⑦). CRYs also interact with PHYTOCHROME INTERACTING FACTORs (PIFs) to regulate photomorphogenesis under low blue light (⑧). For stomatal development, CRYs disassociate the master transcriptional factor SPEECHLESS (SPCH)from repressor AGB1 (⑨). CRYs also regulate the circadian clock, chlorophyll homeostasis and photomorphogenesis through co-condensation with TCP22/LWD1/PPK1, MTA/MTB/FIP37 or FIO1/SPA1 to regulate expression of *CCA1* or N^6-methyladenosine (m^6A) modification of *CCA1*, *CHRs*, and *PIFs*, which affect messenger RNA (mRNA) stability or translation efficiency (⑩). For DNA repair, CRYs interact and enhance interaction between ADA2b and SMC5, and recruit SMC5 to the DNA damage site (⑪). For temperature response, CRYs enhance freezing tolerance through HY5 regulated expression of cold response genes and suppress thermomorphogenesis through repressing PIF4 activity (⑫). Blue oval frame indicates blue light dependent interaction with CRYs. Black dotted oval frame indicates undetermined light dependence for their interaction. Light blue circles inside oval frame indicate co-condensation with photoactivated CRYs. LBL, limiting blue light. HBL, high blue light.

interaction was also reported more recently (Holtkotte et al., 2017; Ponnu et al., 2019). Second, interaction between CRY1 and SPA1 disassociates COP1/SPA complex (Lian et al., 2011; Liu et al., 2011), but interaction between CRY2 and SPA1 enhances affinity between COP1 and SPA1 (Zuo et al., 2011). Third, COP1 and SPA1 are inter-dependent on interacting with CRY1, but not with CRY2 (Holtkotte et al., 2017). Moreover, how light-induced COP1 subcellular distribution (von Arnim and Deng, 1994; Pacín et al., 2013) affects CRY-inhibition of COP1 also remains to be elucidated. Another interesting but unsolved puzzle of the CRY-COP1/SPA axis concerns the "nuclear speckles" of COP1, SPAs and CRYs. COP1 and its substrates, such as HY5 and HFR1, are co-condensed into the COP1 nuclear speckles (von Arnim and Deng, 1994; Ang et al., 1998; Yang et al., 2005); SPAs and COP1 are often condensed together to the same nuclear speckles (Seo et al., 2003; Zhu et al., 2008); CRYs can be recruited to the COP1 nuclear speckles via VP motif or to the SPA1 nuclear speckles via either PHR or CCE domains (Lian et al., 2011; Liu et al., 2011; Zuo et al., 2011; Ponnu et al., 2019). Exactly how the COP1/SPAs nuclear speckles are structurally or functionally associated with light-induced LLPS of CRYs remains to be further investigated.

CRYs appear to directly regulate photoresponsive transcriptional changes by blue light-dependent interaction with transcription factors or co-factors. Transcription factor CIB1 is the first reported blue light-dependent CRY-interacting protein (Liu et al., 2008a). CIB1 and its homologous proteins CIB2, CIB4, CIB5 and CIL1 (CIB1 LIKE PROTEIN 1) interact with photoactivated CRY2 to co-activate florigen *FLOWERING LOCUS T* (*FT*) expression (Liu et al., 2008a; Liu et al., 2013, 2018; Wang et al., 2018a). CRY2 interacts with AP2-type transcriptional repressor TARGET OF EAT 1/2 (TOE1/2) to suppress their DNA binding activity and disassociate CO, activator of *FT*, from TOE1/2 in response to blue light (Zhai et al., 2015; Zhang et al., 2015; Du et al., 2020). Photoactivated CRY2 also regulates the circadian clock through interacting with PSEUDO-RESPONSE REGULATOR 9 (PRR9), which attenuates interaction of PRR9 with its co-repressor TOPLESS (TPL) and its protein kinase PPKs (He et al., 2022). In addition, under a shade condition with limited blue light or high temperature condition, CRYs interact with PHYTOCHROME INTERACTING FACTOR 4 (PIF4) and PIF5 to regulate hypocotyl elongation (Ma et al., 2016; Pedmale et al., 2016). Photoactivated CRYs interact with Arabidopsis G-Protein β Subunit 1 (AGB1), which interacts with HY5 to inhibit DNA-binding activity of HY5, to attenuate interaction between AGB1 and HY5 (Lian et al., 2018). Similarly, CRY1 disassociates SPEECHLESS (SPCH), the master transcription factor driving stomatal initiation and proliferation, from AGB1 to promote stomatal development (Cao et al., 2021).

CRYs regulate plant growth and development by mediating light regulation of the signaling of plant hormones, such as auxin, brassinosteroid (BR) and gibberellic acid (GA). Auxin is perceived by receptor TRANSPORT INHIBITOR RESPONSE 1 (TIR1) or its homolog AUXIN SIGNALING F-boxes (AFB1-AFB5), substrate-recognizing subunit of ubiquitin E3 ligase complex. After binding auxin, TIR1/AFBs recognize and mediate ubiquitination of transcriptional repressors Aux/IAA (indole-3-acetic acid), allowing transcription factors AUXIN RESPONSE FACTORs (ARFs) to regulate expression of auxin response genes (Yu et al., 2022). Photoactivated CRYs represses auxin signaling by at least two mechanisms. First, photoactivated CRY1 interacts with and stabilizes AUX/IAAs (Xu et al., 2018). Second, CRY1 interacts with ARFs to inhibit their DNA binding activities, and CRY1 also promotes interaction between ARFs and IAAs to further inhibit activity of ARFs (Mao et al., 2020).

Brassinosteroid promotes hypocotyl elongation, and BRASSINAZOLE-RESISTANT 1 (BZR1) and BRI1-EMS SUPPRESSOR1 (BES1) are the main transcription factors regulating expression of BR-responsive genes. Under lower BR level, BRASSINOSTEROID INSENSITIVE 2 (BIN2) phosphorylates and inactivates BZR1 and BES1 (Nolan et al., 2020). Photoactivated CRYs interact with BIN2, BZR1 and BES1 to inhibit BR signaling (Wang et al., 2018b; He et al., 2019). On the one hand, CRY1 enhances interaction between BIN2 and BZR1 to promote phosphorylation of BZR1 (He et al., 2019). On the other hand, CRYs preferentially interact with unphosphorylated active BZR1 and BES1 to inhibit their DNA binding activity and transcriptional activation activity (Wang et al., 2018b; He et al., 2019). In addition, CRYs interact with BES1-INTERACTING MYC-LIKE PROTEIN1 (BIM1), which interacts with BES1 and facilitates its binding to target genes, to attenuate DNA binding activity of BES1 (Wang et al., 2018b).

Gibberellic acid promotes hypocotyl elongation, whereas CRYs inhibit GA signaling to promote photomorphogenesis. After binding GA, receptor GA-INSENSITIVE DWARF 1 (GID1) containing GID1a, GID1b and GID1c, interacts with DELLA proteins, GA INSENSITIVE (GAI), REPRESSOR OF ga1-3 (RGA), RGA-LIKE 1 (RGL1), RGL2 and RGL3, resulting in their degradation mediated by ubiquitin E3 ligase SLEEPY1 (SLY1) (Murase et al., 2008; Daviere and Achard, 2013). Photoactivated CRY1 interacts with GID1 and DELLA proteins, inhibiting interaction of DELLAs with GID1 and SLY1 to stabilize DELLA proteins (Xu et al., 2021a; Yan et al., 2021; Zhong et al., 2021). In addition, CIB1 homolog HOMOLOG OF BEE2 INTERACTING WITH IBH 1 (HBI1) functions downstream of BR and GA signaling to promote hypocotyl elongation. CRYs interact with HBI1 to inhibit its activity (Wang et al., 2018a). And CRY1 was co-localized with other CIB1 homologs CIB1 LIKE PROTEIN 1 (CIL1) and BR ENHANCED EXPRESSION 2 (BEE2), indicating that CRYs maybe regulate hypocotyl elongation partly through CIL1 and BEE2 in a similar manner (Wang et al., 2018a).

In addition to directly interacting with transcription factors and co-factors, CRYs may also regulate gene expression by modulating chromosome structure or alternative splicing. H2A.Z is a variant of histone H2A in the nucleosome. SWC6 and ACTIN RELATED PROTEIN 6 (ARP6) are core subunits of chromatin remodeling complex SWI2/SNF2-RELATED 1

(SWR1), which mediates H2A.Z deposition to affect chromatin status and gene expression. Photoactivated CRYs interact with SWC6 and ARP6 to enhance their interaction and activity of SWR1 (Mao et al., 2021). Furthermore, CRYs promote accumulation of HY5 that interacts with both SWC6 and ARP6 to guide H2A.Z deposition (Mao et al., 2021). In addition, CRYs interact with CRY2 INTERACTING SPLICING FACTOR 1 (CIS1), which controls alternative splicing of *FLOWERING LOCUS M* (*FLM*) pre-mRNA (messenger RNA), to enhance its RNA-binding activity to regulate thermosensory flowering (Zhao et al., 2022). Photoactivated CRYs also interact with STRUCTURAL MAINTENANCE OF CHROMOSOME 5 (SMC5) and ADA2b, components of DNA damage repairing complex, to enhance their interaction and recruitment of SMC5 to DNA damaged sites to facilitate DNA repair (Guo et al., 2023).

THE LLPS MODEL

The current CRY-signaling hypothesis asserts that blue light alters the protein conformation of CRYs and their affinity to CRY-interacting proteins to initiate signal transduction (Wang and Lin, 2020; Ponnu and Hoecker, 2022). This is a classical "induced fit" version of the Lock-and-Key model. More than half of the CRY-interacting proteins (47/84) have been shown to exhibit blue light-dependent change of affinity to CRYs (Table 1), supporting the "induced fit" hypothesis for CRY signaling mechanism. On the other hand, some proteins interact with CRYs in a light-independent manner, such as MTA, MTB, FKBP12-INTERACTING PROTEIN 37 (FIP37), FIONA1 (FIO1), TEOSINTE BRANCHED1-CYCLOIDEA-PCF 22 (TCP22), MOS4-ASSOCIATED COMPLEX SUBUNITS 3A/3B (MAC3A/3B) and LIGHT-REGULATED WD 1 (LWD1) (Wang et al., 2021; Mo et al., 2022; Jiang et al., 2023a, 2023b), which could not be explained by the Lock-and-Key model. Moreover, the Lock-and-Key model also has difficulties in explaining the important function of the CCE domain of CRYs, which is an intrinsically disordered region (IDR) without stable tertiary structure (Brautigam et al., 2004; Ma et al., 2020a; Shao et al., 2020; Palayam et al., 2021; Wang et al., 2021). LLPS has emerged to explain the action mechanism of IDR-bearing proteins (Wright and Dyson, 2015; Liu et al., 2023), including photoreceptor CRYs (Wang et al., 2021; Mo et al., 2022; Jiang et al., 2023a; Jiang et al., 2023b; Ma et al., 2023) and phytochromes (Pardi and Nusinow, 2021; Chen et al., 2022; Kim et al., 2023).

LLPS describes a phenomenon that many interacting macromolecules aggregate to a condense phase, albeit accompanied by a dilute phase (Dignon et al., 2020; Emenecker et al., 2020, 2021; Liu et al., 2023), resulting in intuitively higher velocity of biochemical reactions. LLPS has emerged as a ubiquitous framework to explain organizations and functions of many membraneless organelles or protein condensates, such as stress granules, processing body (P-body), nucleoli, nucleosome arrays, DNA damage foci, paraspeckles, autophagosomes, photobodies, and so on (Emenecker et al., 2020, 2021; Pardi and Nusinow, 2021; Xu et al., 2021b; Liu et al., 2023). Phytochromes and CRYs are known to form light-induced nuclear speckles or nuclear bodies (Yamaguchi et al., 1999; Más et al., 2000; Kircher et al., 2002; Yu et al., 2009; Pardi and Nusinow, 2021), termed as phytochrome photobodies (Chen and Chory, 2011) and CRY photobodies (Zuo et al., 2012), respectively. It has become clear that photobodies result from light-induced LLPS of photoreceptor proteins or photoreceptors and their interacting proteins (Wang et al., 2021; Chen et al., 2022; Mo et al., 2022; Kim et al., 2023). And it has been proposed that blue light-induced LLPS increases local concentration of CRY complexes to enhance their biochemical activities, whereas it is also important to keep CRY condensates from aggregating into inactive gel or solid phases. The PHR and CCE domains play different roles in the light-induced LLPS of CRYs. The PHR domain of CRY2 alone is sufficient to cause light-induced condensation, but the CCE domain of CRY2 and protein kinase PPKs are required to maintain condensed CRY2 in a liquid phase (Wang et al., 2021; Liu et al., 2022; Ma et al., 2023). Although photobodies and LLPS of phytochromes and cryptochromes are usually studied using overexpressed photoreceptors fused to fluorescent proteins such as green fluorescent protein (GFP) or red fluorescent protein, endogenous CRY2 has been shown to condense to photobodies in response to blue light (Yu et al., 2009). It has been reported that blue light-induced LLPS of CRYs regulates the circadian clock, photomorphogenesis and chlorophyll homeostasis (Wang et al., 2021; Mo et al., 2022; Jiang et al., 2023a; Yang et al., 2023), supporting the hypothesis that light-induced LLPS is another photoregulatory action mechanism of CRYs.

N^6-methyladenosine (m^6A) modification is a reversible and the most abundant internal modification of mRNA, regulating RNA stability, alternative polyadenylation, microRNA maturation, translational efficiency and chromatin state in eukaryotic organisms (Zhao et al., 2017; Shen et al., 2019; Tang et al., 2023). Blue light enhances m^6A deposition (Wang et al., 2021; Yang et al., 2023), which was proposed to result from co-condensation of m^6A writer MTA/MTB/FIP37 or FIO1 with photoactivated CRYs (Wang et al., 2021; Jiang et al., 2023a). Condensation of MTA/MTB/FIP37/CRY2 promotes m^6A deposition to mRNA of CIRCADIAN CLOCK ASSOCIATED 1 (CCA1), a core component of the molecular oscillator, to regulate the circadian clock (Wang et al., 2021). Condensation of MTA/MTB/FIP37/CRY1 may enhance RNA-binding activity of FIP37 to increase m^6A deposition in *PIF3*, *PIF4*, and *PIF5* mRNAs, promoting their degradation and photomorphogenesis (Yang et al., 2023). In addition, LLPS of MAC3A/CRY2 enhances DNA binding activity of MAC3A to suppress transcription of *YUC8* and *IAA19* and hypocotyl elongation (Jiang et al., 2023b). The TBS motif of *CCA1* gene facilitates LLPS of PPK1/TCP22/LWD1/CRY2 to activate transcription of *CCA1*, which may represent another mechanism underlying CRY-mediated blue-light regulation of the circadian clock (Mo et al., 2022).

The Lock-and-Key and LLPS models are not mutually exclusive. There is at least one example that the two mechanisms synergistically mediate blue-light responses in *Arabidopsis*. It was proposed that the light-induced interacting protein SPA1 facilitates condensation of CRY2/SPA1/FIO1, stimulating m^6A deposition and translation of *CHLOROPHYLL HOMEOSTASIS REGULATORs* (*CHRs*) mRNAs to maintain normal chlorophyll homeostasis in *Arabidopsis* grown in blue light (Jiang et al., 2023a).

FUTURE PERSPECTIVES

In 2020, we raised three problems about CRY photoreceptors (Wang and Lin, 2020). Two of those three problems have been, at least partially, solved. CRYs are no longer among the structurally least understood proteins and we have added the control of mRNA methylation to the arsenal of CRY-mediated light regulation of gene expression. However, the newly discovered LLPS mechanism of CRYs raises new questions. For example, some newly reported CRY-interacting proteins, such as MTA, TCP22 and MAC3A, interact with CRYs constitutively. So one may wonder whether these CRY complexes have biochemical and cellular activities in darkness. Plant CRYs have been known for their blue light-independent activities, but those activities were often measured in plants grown in red or far-red light, and they were attributed to the co-action of phytochromes and CRYs (Devlin and Kay, 2000; Botto et al., 2003; Yang et al., 2008). More recently, both phytochromes and CRYs were shown to exhibit "dark activity" in the absence of light (Carlson et al., 2019; Li and Hiltbrunner, 2021; Jiang et al., 2023a). For example, tomato red/far-red light receptor phyA has been shown to regulate carbon flux in dark-grown tomato seedlings (Carlson et al., 2019). Similarly, CRYs may also have "dark activity," because 10^2 to 10^3 genes are altered in transcriptome, mRNA methylation or proteome in dark-grown Arabidopsis cry1cry2 mutant seedlings (Jiang et al., 2023a). Understanding how CRYs may affect plant growth and development in the absence of light would help us better understand how CRYs act in response to blue light. And continuous study of CRY-interacting proteins that interact with CRYs in light or darkness would help us to solve the problems raised 3 years ago and the problems raised here.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

G.P.Q. wrote the original manuscript and made the figures. G.P.Q., B.J. and C.L. revised the manuscript. All authors read and approved of its content.

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