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Two-Component Signaling Elements and Histidyl-Aspartyl Phosphorelays

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Two-component systems are an evolutionarily ancient means for signal transduction. These systems are comprised of a number of distinct elements, namely histidine kinases, response regulators, and in the case of multi-step phosphorelays, histidine-containing phosphotransfer proteins (HPts). Arabidopsis makes use of a two-component signaling system to mediate the response to the plant hormone cytokinin. Two-component signaling elements have also been implicated in plant responses to ethylene, abiotic stresses, and red light, and in regulating various aspects of plant growth and development. Here we present an overview of the two-component signaling elements found in Arabidopsis, including functional and phylogenetic information on both bona-fide and divergent elements.

INTRODUCTION

Protein phosphorylation is a key mechanism for regulating signal transduction pathways in both prokaryotes and eukaryotes. In eukaryotes, regulatory phosphorylation predominantly occurs at serine, threonine, and tyrosine residues (Hunter, 1995; Hunter and Plowman, 1997; Plowman et al., 1999). In contrast, many signal transduction pathways in bacteria employ a so-called "two-component system" that relies upon phosphorylation of histidine and aspartic-acid residues (Mizuno, 1997). Plants also make use of two-component systems and these perform important roles in growth and development (Schaller, 2000; Mizuno, 2005; To and Kieber, 2008).

Two-component systems confer upon bacteria the ability to sense and respond to environmental stimuli and are involved in such diverse processes as chemotaxis, osmotic sensing, oxygen sensing, and host recognition (Parkinson, 1993; Stock et al., 2000; Baker et al., 2006). The simplest form of a two-component system employs a receptor with histidine-kinase activity and a response regulator (Figure 1). The receptor is located in the plasma membrane of the bacterium. In response to an environmental stimulus, the histidine kinase autophosphorylates a conserved histidine residue. This phosphate is then transferred to a conserved aspartic acid residue within the receiver domain of the response regulator. Phosphorylation of the response regulator modulates its ability to mediate downstream signaling. In bacteria, many of the response regulators are transcription factors. Thus, two proteins create a signaling circuit, capable of converting an external stimulus into a change in transcription. There are permutations on the two-component system. Of particular relevance to the plant two-component systems are multi-step phosphorelays (Figure 1) (Swanson et al., 1994; Appleby et al., 1996). These make use of a "hybrid" kinase that contains both histidine kinase and receiver domains in one protein, a histidine-containing phospho-transfer (HPt) protein, and a separate response regulator (Appleby et al., 1996). In these multi-step phosphorelays, the phosphate is transferred from amino acid to amino acid in sequence His ➔ Asp ➔ His ➔ Asp.

Although originally identified in bacteria, two-component signaling elements have also been identified in fungi, slime molds, and plants (Swanson et al., 1994; Loomis et al., 1997; Schaller, 2000; Mizuno, 2005). Interestingly, the canonical histidyl-aspartyl phosphorelay is apparently not found in animals. Analysis using the SMART protein-domain search interface (http://SMART.embl-heidelberg.de) (Schultz et al., 2000) indicates that bona-fide two-component signaling elements are lacking from the genome sequences of *Homo sapiens, Drosophila melanogaster,* and *Caenorhabditis elegans.*

In Arabidopsis, proteins with significant sequence similarities to all elements of the two-component system have been identified, including histidine kinases, response regulators, and HPt proteins (Figure 2) (Schaller, 2000; Mizuno, 2005). Phosphorylation activity has been confirmed for at least one example in each case (Gamble et al., 1998; Imamura et al., 1998; Miyata et al., 1998; Suzuki et al., 1998; Imamura et al., 1999). In recent years, multiple experimental approaches have demonstrated the action of a histidyl-aspartyl phosphorelay in mediating cytokinin signal transduction (Hwang and Sheen, 2001; Higuchi et al., 2004; Nishimura et al., 2004; Mason et al., 2005; Hutchison et al., 2006; Riefler et al., 2006; Yokoyama et al., 2007).

Arabidopsis also contains divergent two-component-like elements that are unlikely to function in histidyl-aspartyl phosphorelays (e.g. phytochromes and pseudo-response regulators) as they are missing one or more key amino-acid residues involved in a

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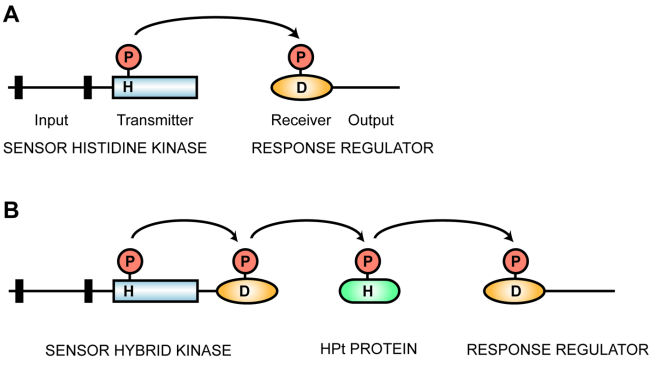

Figure 1. Histidyl-Aspartyl Phosphorelay.

Histidine kinase domains are indicated by rectangles, receiver domains by ovals, HPt proteins by rounded rectangles, and transmembrane domains by black bars. Sites of phosphorylation upon histidine (H) and aspartic acid (D) residues are indicated. Terminology is based on that of Parkinson (1993).

(A) Simple two-component system that employs a histidine kinase and a response regulator.

(B) Multi-step phosphorelay that employs a hybrid histidine kinase with both histidine kinase and receiver domains, a histidine-containing phosphotransfer protein (HPt), and a response regulator.

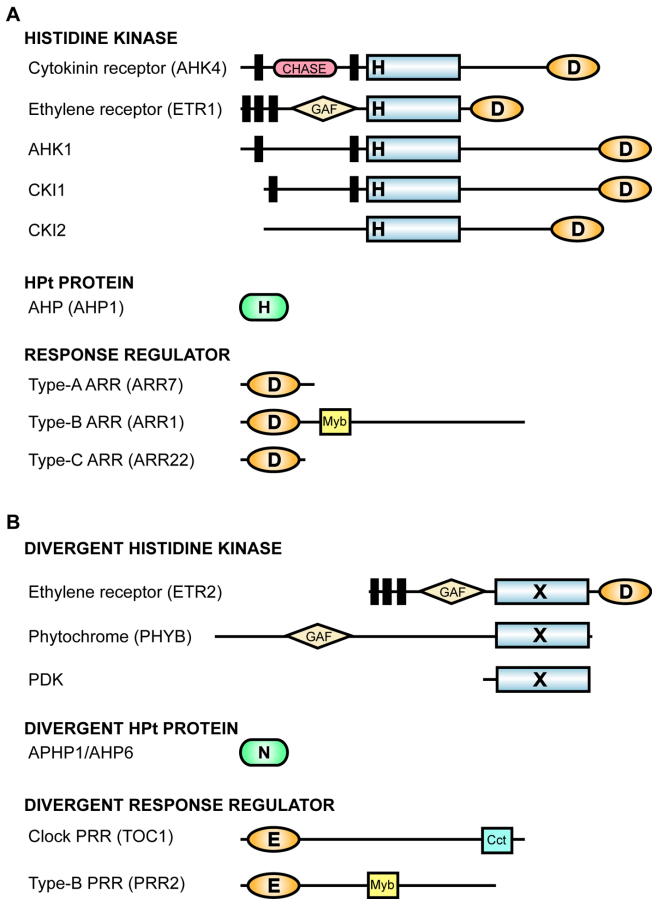

Figure 2. Representative Domain Structures of Arabidopsis Two-Component Signaling Elements.

phosphorelay (Figure 2) (Makino et al., 2000; Schaller, 2000). Plants, like animals, contain pyruvate dehydrogenase kinase; this enzyme is related to histidine kinases but has an altered specificity such that it now phosphorylates serine residues (Popov et al., 1993). Thus, there is evidence from eukaryotes that two-component signaling elements have evolved to fill new functions that no longer rely upon phosphorylation of histidine and aspartic acid residues.

HISTIDINE KINASES

Analysis of the Arabidopsis genome supports the existence of eight histidine kinases that contain all the conserved residues required for enzymatic activity (Table 1, Figures 2 and 3), as well as additional diverged histidine-kinase like proteins that lack residues essential to histidine kinase activity. Some of the functional histidine-kinases have been identified as receptors for the plant hormones cytokinin (AHK2, AHK3, and AHK4) and ethylene (ETR1 and ERS1), but the ligands for the other three bona-fide histidine kinases (AHK1, CKI1, and CKI2) have yet to be determined.

Cytokinin Receptor Family

The cytokinin receptor family is composed of three histidine kinases: AHK2, AHK3, and AHK4 (also called WOL1 or CRE1). Initial evidence that this family functions in cytokinin perception came from the study of AHK4 transgenically expressed in bacteria and yeast, where it was shown that AHK4 could bind cytokinins and that ligand-binding stimulated the receptor's ability to signal through a phosphorelay (Inoue et al., 2001; Suzuki et al., 2001; Ueguchi et al., 2001; Yamada et al., 2001). All three receptors contain transmembrane domains, are thought to be localized to the plasma membrane, and contain a CHASE (cyclases/histidine kinases associated sensing extracellular) domain in their predicted extracellular portion that functions in cytokinin binding (Anantharaman and Aravind, 2001; Heyl et al., 2007). The isolation and characterization of T-DNA insertion mutations has demonstrated roles for the cytokinin receptors in diverse cytokinin-regulated processes including cell division,

Figure 2. (continued)

Histidine kinase domains are indicated by rectangles, receiver domains by ovals, HPt proteins by rounded rectangles, and transmembrane domains by black bars. Additional domains are as indicated and are described in the text.

(A) Bona-fide signaling elements likely to participate in phosphorelays. Sites of phosphorylation upon histidine (H) and aspartic acid (D) residues are indicated.

(B) Divergent signaling elements from Arabidopsis that lack residues normally associated with participation in a two-component phosphorelay. An X in a histidine-kinase-like domain indicates that it lacks multiple residues implicated in histidine kinase activity. The divergent HPt (APHP1) contains an Asn (N) substitution for the His that normally gets phosphorylated. The divergent response regulators typically contain a Glu (E) substitution for the Asp that normally gets phosphorylated.

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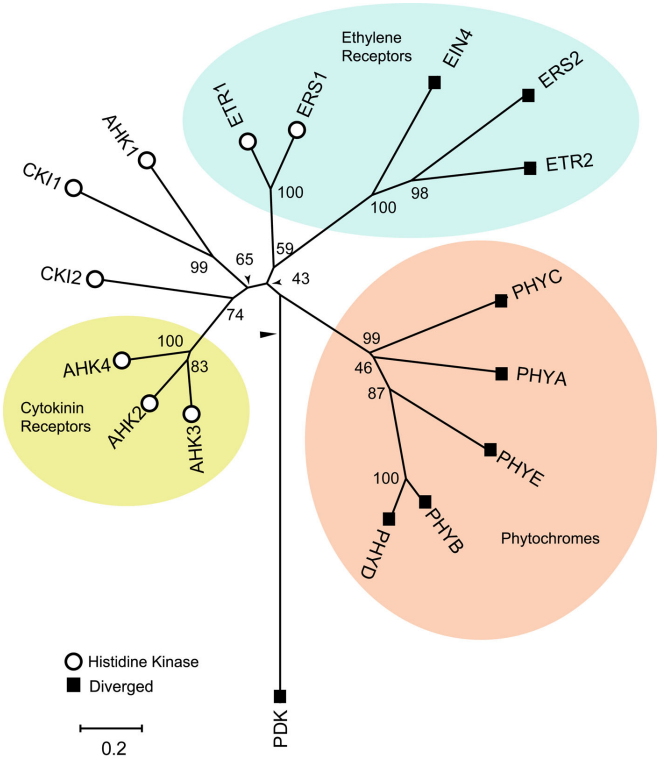

Figure 3. Phylogenetic Relationship of Histidine Kinases.

Sequences containing conserved histidine-kinase domains (open circles) and diverged histidine kinase domains (filled squares) were identified in Arabidopsis. An unrooted bootstrapped tree is shown based on amino-acid alignment of the histidine-kinase domain sequences. The histidine kinase domain was defined as the sequence extending from the phospho-acceptor domain through the ATPase domain.

vascular differentiation, leaf senescence, seed size, and stress responses (Higuchi et al., 2004; Nishimura et al., 2004; Riefler et al., 2006; Tran et al., 2007).

Ethylene Receptor Family

The ethylene receptor family of Arabidopsis (ETR1, ERS1, ETR2, ERS2, and EIN4) also contains proteins with histidine kinase domains (Chang et al., 1993; Hua et al., 1995; Hua et al., 1998; Sakai et al., 1998). ETR1 and ERS1 have been demonstrated to bind ethylene when transgenically expressed in yeast (Schaller and Bleecker, 1995; Rodriguez et al., 1999; Hall et al., 2000) and both contain functional histidine kinase domains (Gamble et al., 1998; Moussatche and Klee, 2004). Although histidine-kinase activity has been implicated in subtle modulations of the ethylene response, no major role has yet been identified in ethylene signal transduction (Wang et al., 2003; Binder et al., 2004; Qu and Schaller, 2004). Mutational analysis indicates that, rather than relying on a histidyl-aspartyl phosphorelay, ethylene signal transduction incorporates the Raf-like kinase CTR1, the membrane-bound Nramp-like protein EIN2, and the EIN3 family of transcription factors (Chen et al., 2005). Histidine kinase activity of the ethylene receptors could play a direct but lesser role in ethylene signal transduction. Alternatively, histidine kinase activity could allow for cross-talk between ethylene perception and other two-component signaling pathways such as cytokinin signal transduction.

The ethylene-receptor family also includes three members (ETR2, ERS2, and EIN4) that contain divergent histidine-kinase domains (Bleecker, 1999; Schaller, 2000). Thus, one protein family of related function contains both bona-fide and divergent histidine kinases. Based on in-vitro phosphorylation assays, ETR2, ERS2, and EIN4 are now thought to function as ser/thr kinases (Moussatche and Klee, 2004). In the same study ERS1 was found to phosphorylate serine in addition to histidine, suggesting that it might be bi-functional.

CKI1

CKI1 was initially identified in a mutant screen where it was found that its ectopic expression results in cytokinin-independent greening and shoot induction in callus cultures (Kakimoto, 1996). However CKI1 is not closely related to the cytokinin-receptor family and lacks the CHASE domain involved in cytokinin binding. Thus, the cytokinin-related phenotype resulting from CKI overexpression may arise due to non-physiological cross-talk with the cytokinin-signaling pathway. Analysis of loss-of-function mutations has clarified the role of *CKI1* in plant growth and development, although a regulatory ligand for this putative receptor has not been identified. The homozygous *cki1* mutation is lethal and examination of the mutant indicates that *CKI1* is required for megagametogenesis, consistent with expression data that indicate *CKI1* is expressed in developing ovules (Pischke et al., 2002; Hejatko et al., 2003).

CKI2

CKI2, like *CKI1,* can induce cytokinin responses when ectopically expressed (Kakimoto, 1996), but is also not thought to be directly involved in cytokinin signaling. *CKI2* shows strong expression in the root and weaker expression in flowers (Iwami et al., 2007). Loss-of-function mutations in *CKI2* exert a subtle phenotype in which root elongation is more sensitive to growth inhibition in response to ethylene, suggesting possible cross-talk with the ethylene receptors (Iwami et al., 2007).

AHK1

AHK1 was initially proposed to function as a plant osmosensor based on its ability to complement function of the yeast osmosensor SLN1, a histidine kinase that regulates the HOG1 MAP-kinase pathway for osmosensing in yeast (Urao et al., 1999). However it was subsequently found that other histidine kinases of Arabidopsis, including the cytokinin receptors, can complement yeast *SLN1* mutations, indicating that this assay is not necessarily diagnostic of plant function (Reiser et al., 2003; Tran et al.,

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Table 1. Histidine Kinase-like Proteins of Arabidopsis

Gene Names	Synonyms	Chrom. Locus[a]	Features[b]	Family	References[c]
ETR1		At1g66340	C_2H_4, GAF, HK, Rec	Ethylene Receptor	Chang et al. 1993
ERS1		At2g40940	C_2H_4, GAF, HK	Ethylene Receptor	Hua et al. 1995
ETR2		At3g23150	C_2H_4, GAF, HKL, Rec	Ethylene Receptor	Sakai et al. 1998b
ERS2		At1g04310	C_2H_4, GAF, HKL	Ethylene Receptor	Hua et al. 1998
EIN4		At3g04580	C_2H_4, GAF, HKL, Rec	Ethylene Receptor	Hua et al. 1998
AHK4	WOL1, CRE1	At2g01830	CHASE , HK, Rec	Cytokinin Receptor	Mähönen et al. 2000, Inoue et al. 2001, Suzuki et al. 2001
AHK2		At5g35750	CHASE , HK, Rec	Cytokinin Receptor	Ueguchi et al. 2001
AHK3		At1g27320	CHASE , HK, Rec	Cytokinin Receptor	Ueguchi et al. 2001
CKI1		At2g47430	HK, Rec		Kakimoto, 1996, Pischke et al. 2002
AHK1	ATHK1	At2g17820	HK, Rec		Urao et al. 1999
CKI2	AHK5	At5g10720	HK, Rec		Kakimoto, 1996, Iwama et al. 2007
PHYA		At1g09570	GAF, HKL	Phytochrome	Sharrock and Quail, 1989
PHYB		At2g18790	GAF, HKL	Phytochrome	Sharrock and Quail, 1989
PHYC		At5g35840	GAF, HKL	Phytochrome	Sharrock and Quail, 1989
PHYD		At4g16250	GAF, HKL	Phytochrome	Sharrock et al. 1994
PHYE		At4g18130	GAF, HKL	Phytochrome	Sharrock et al. 1994
PDK		At3g06483	HKL	Pyruvate dehydrogenase kinase	Thelen et al. 2000

[a]Chromosome loci are given by the MIPS designation.
[b]Features noted are conserved histidine-kinase domain (HK), diverged histidine-kinase like domain (HKL), receiver domain (Rec), ethylene-binding domain (C_2H_4), CHASE domain for cytokinin binding (CHASE), and GAF domain which in phytochromes serves as the chromophore-binding site.
[c]References are chosen based on initial descriptions of genes and their synonyms

2007). Rather, genetic analysis indicates that *AHK1* modulates plant growth and stress responses based on the finding that an *ahk1,ahk2,ahk3* triple mutant (i.e. a combination of *ahk1* with two cytokinin receptor mutations) is reduced in size compared to the *ahk2,ahk3* double mutant (Tran et al., 2007). *AHK1* is induced by dehydration and acts as a positive regulator of drought and salt stress responses, in contrast to the cytokinin receptors which are also induced by dehydration but act as negative regulators of these responses (Tran et al., 2007).

Phytochrome Family

The phytochromes, which act as red light receptors (Sharrock and Quail, 1989; Clack et al., 1994; Rockwell et al., 2006), are divergent histidine kinases that possess ser/thr kinase activity rather than histidine kinase activity (Yeh and Lagarias, 1998).

Pyruvate dehydrogenase kinase

Pyruvate dehydrogenase kinase retains the most highly conserved residues found in histidine kinases, but has nevertheless diverged significantly in other residues, resulting in an ability to phosphorylate its substrate, pyruvate dehydrogenase, at a serine residue (Thelen et al., 2000).

HISTIDINE-CONTAINING PHOSPHOTRANSFER PROTEINS

Histidine-containing phosphotransfer (HPt) proteins function in multi-step phosphorelays, acting as signaling intermediates between hybrid histidine kinase and response regulators (Figure 1). The Arabidopsis genome encodes five HPt proteins (AHP1 through 5) that contain the conserved residues required for activity, as well as one pseudo-HPt (APHP1/AHP6) that lacks the histidine phosphorylation site (Table 2, Figures 2 and 4) (Miyata et al., 1998; Suzuki et al., 1998; Suzuki et al., 2000). The HPt proteins have been shown capable of participating in a phosphorelay with Arabidopsis response regulators (Suzuki et al., 1998). In addition, two-hybrid analysis has demonstrated their ability to interact with both hybrid histidine kinases and response regulators (Imamura et al., 1999; Urao et al., 2000; Tanaka et al., 2004; Dortay et al., 2007), consistent with an ability to function in a multi-step phosphorelay.

Analysis of loss-of-function mutations has revealed that *AHP1, AHP2, AHP3,* and *AHP5* function as redundant positive regulators of cytokinin signaling (Hutchison et al., 2006). *AHP4* only contributes slightly to the cytokinin responses, and in some cases appears to act as a negative regulator (Hutchison et al., 2006). The AHPs have been shown to accumulate in the nucleus in response to exogenous cytokinin (Hwang and Sheen, 2001; Yamada et al., 2004). *APHP1,* which encodes a pseudo-HPt lacking the

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Table 2. HPt Proteins of Arabidopsis

Gene Names	Synonyms	Chrom. Locus[a]	Features[b]	References
AHP1	ATHP3	AT3g21510	HPt	Suzuki et al. 1998, Miyata et al. 1998
AHP2	ATHP1	AT3g29350	HPt	Suzuki et al. 1998, Miyata et al. 1998
AHP3	ATHP2	AT5g39340	HPt	Suzuki et al. 1998, Miyata et al. 1998
AHP4		AT3g16360	HPt	Suzuki et al. 2000
AHP5		At1g03430	HPt	Suzuki et al. 2000
APHP1	AHP6	At1g80100	pseudo-HPt	Suzuki et al. 2000, Mähönen et al. 2006

[a]Chromosome loci are given by the MIPS designation.
[b]Features indicate whether the protein contains a conserved histidine-containing phosphotransfer domain (HPt) or a pseudo-HPt lacking the His that is phosphorylated

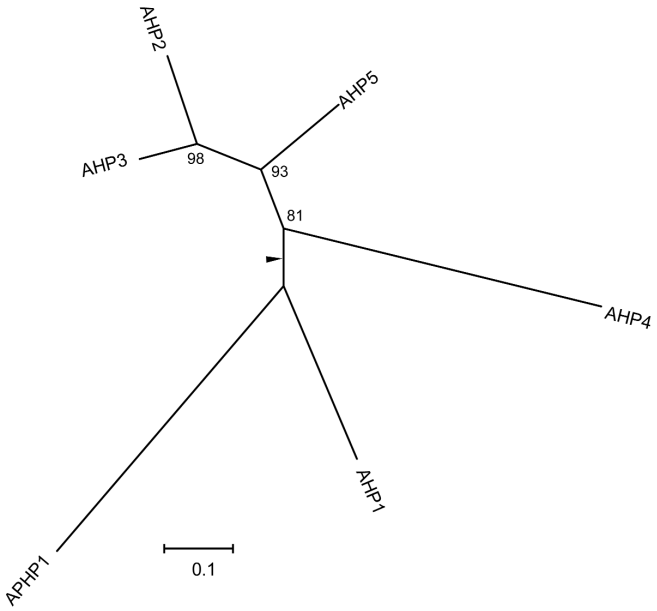

Figure 4. Phylogenetic Relationship of HPt Proteins.

An unrooted bootstrapped tree is shown based on amino-acid alignment of HPt domain sequences.

phosphorylation site, acts as a negative regulator of cytokinin responses (Mähönen et al., 2006b). *APHP1* expression is induced by cytokinin and thus functions as part of a negative feedback loop to reduce the plants sensitivity to cytokinin, with APHP1 potentially interacting with the receiver domains of the cytokinin receptors to prevent phospho-transfer to bona-fide AHPs.

RESPONSE REGULATORS

There are 23 genes in the Arabidopsis genome encoding proteins predicted to be functional response regulators (Table 3, Figures 2 and 5). These authentic response regulators (ARRs) can be divided into three classes based on phylogenetic analysis and function: type-A type-B, and type-C response regulators (Imamura et al., 1999; Schaller et al., 2007). In addition, there are nine genes encoding response regulators that lack the conserved Asp for phosphorylation, and are called pseudo-response regulators (PRRs) (Makino et al., 2000).

Type-A response regulators

The type-A response regulators are relatively small, containing a receiver domain along with short N- and C-terminal extensions (Brandstatter and Kieber, 1998; Imamura et al., 1998; Urao et al., 1998). Members of the type-A family are transcriptionally induced to varying extents by cytokinin (Brandstatter and Kieber, 1998; Taniguchi et al., 1998; D'Agostino et al., 2000), and cytokinin also stabilizes some type-A ARR proteins in a phosphorylation-dependent manner (To et al., 2007). Genetic analyses indicate that *ARR3, 4, 5, 6, 7, 8, 9* and *15* function as negative regulators of cytokinin signaling, thus participating in a negative feedback loop to reduce the plant sensitivity to cytokinin (Kiba et al., 2003; To et al., 2004; Leibfried et al., 2005; Lee et al., 2007; To et al., 2007).

Some type-A ARRs are also implicated in other regulatory pathways. ARR4 interacts with phytochrome B to modulate its activity, allowing for cross-talk between the cytokinin and light signaling pathways (Sweere et al., 2001; Mira-Rodado et al., 2007). WUSCHEL, a regulator of stem cells in the shoot apical meristem, negatively regulates transcription of several type-A ARRs, revealing cross-talk between cytokinin signaling and a key meristem identity gene (Leibfried et al., 2005). *ARR3* and *ARR4* regulate the circadian period in a cytokinin-independent manner, with loss of these two genes resulting in a longer clock period (Salomé et al., 2006).

Type-B response regulators

The type-B ARRs differ from the type-A ARRs in that the type-B ARRs contain long C-terminal extensions with a Myb-like DNA binding domain referred to as the GARP domain (Imamura et al., 1999; Hosoda et al., 2002). Multiple lines of evidence support the role of the type-B ARRs as transcription factors (Sakai et al., 2000; Imamura et al., 2001; Lohrmann et al., 2001; Sakai et al., 2001;

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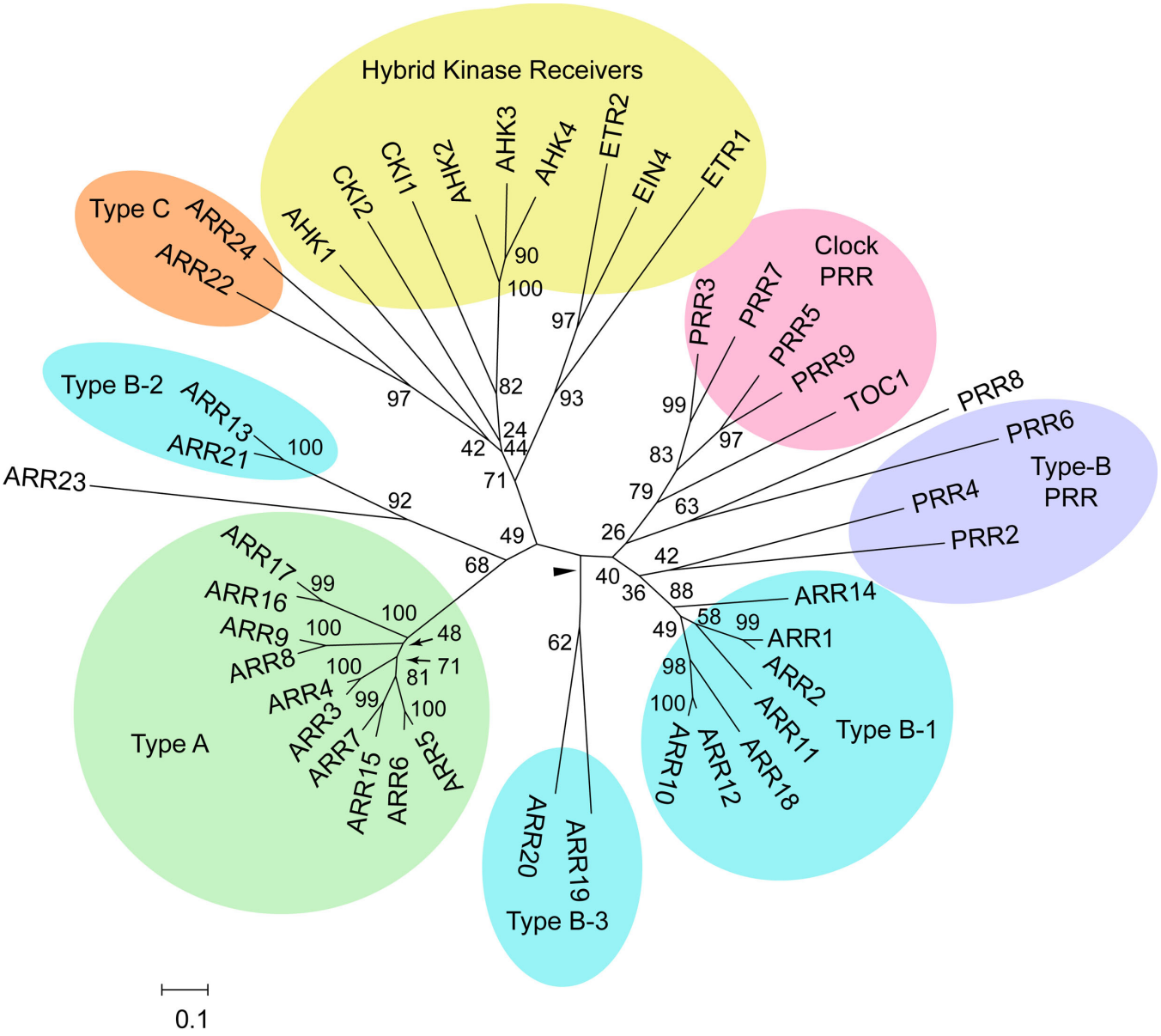

Figure 5. Phylogenetic Relationship of Receiver Domains from Response Regulators and Hybrid Kinases.

An unrooted bootstrapped tree is shown based on amino-acid alignment of receiver and pseudoreceiver domain sequences. The different families of receiver domains are highlighted, with subfamilies 1, 2 and 3 being indicated for the type-B ARRs. Note that the tree has some low bootstrap values indicating that regions of this tree should be considered to be simply radiations.

Hosoda et al., 2002; Imamura et al., 2003; Mason et al., 2004; Mason et al., 2005; Rashotte et al., 2006). Type-B ARRs are nuclear-localized in Arabidopsis and capable of transcriptional activation when expressed in yeast (Lohrmann et al., 1999; Sakai et al., 2000; Lohrmann et al., 2001). The ARR1, ARR2, and ARR10 type-B response regulators bind to a core DNA sequence 5'-(G/A)GAT(T/C)-3' (Sakai et al., 2000; Hosoda et al., 2002).

The eleven type-B ARRs of Arabidopsis fall into three subfamilies based on phylogenetic analysis: subfamily 1 contains seven members (ARR1, ARR2, ARR10, ARR11, ARR12, ARR14, and ARR18); subfamily 2 contains two members (ARR13 and ARR21); and subfamily 3 is also comprised of two members (ARR19 and ARR20) (Mason et al., 2004). Genetic analyses indicate that at least five subfamily-1 members mediate cytokinin signaling, with ARR1, ARR10, and ARR12 appearing to play key roles (Mason et al., 2005; Yokoyama et al., 2007; Ishida et al., 2008). The cytokinin transcriptional response is substantially reduced in type-B mutant backgrounds, supporting a central role of the type-B ARRs

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in the cytokinin signaling pathway (Rashotte et al., 2006; Yokoyama et al., 2007). A number of primary response genes directly regulated by the type-B ARRs have been identified, including the type-A *ARR*s (Taniguchi et al., 2007). It has been proposed that the subfamily-1 member ARR2 may modulate ethylene signaling, but the effect is subtle and differing results have been obtained in the analysis of *arr2* mutants, perhaps due to differing growth conditions (Hass et al., 2004; Mason et al., 2005).

The functions of the subfamily-2 and subfamily-3 type-B ARRs are unclear. They are not as broadly expressed as the subfamily-1 *ARR*s (Mason et al., 2004; Tajima et al., 2004), and the only reported mutant phenotypes arise from overexpression of activated versions of the genes (Tajima et al., 2004; Kiba et al., 2005). Overexpression of activated *ARR21* (subfamily-2) results in seedlings in which cell proliferation is activated to form callus-like structures. Overexpression of activated *ARR20* (subfamily-

Table 3. Response Regulators of Arabidopsis

Gene Name	Synonyms	Chrom Locus[a]	Features[b]	Family	References
ARR3		At1g59940	Rec	Type A	Imamura et al. 1998
ARR4	IBC7, ATR1	At1g10470	Rec	Type A	Imamura et al. 1998, Brandstatter and Kieber 1998, Urao et al. 1998
ARR5	IBC6, ATR2	At3g48100	Rec	Type A	Imamura et al. 1998, Brandstatter and Kieber 1998, Urao et al. 1998
ARR6		At5g62920	Rec	Type A	Imamura et al. 1998
ARR7		At1g19050	Rec	Type A	Imamura et al. 1998
ARR8	ATRR3	At2g41310	Rec	Type A	Imamura et al. 1999, Urao et al. 1998
ARR9	ATRR4	At3g57040	Rec	Type A	Imamura et al. 1999, Urao et al. 1998
ARR15		At1g74890	Rec	Type A	D'Agostino et al. 2000
ARR16		At2g40670	Rec	Type A	D'Agostino et al. 2000
ARR17		At3g56380	Rec	Type A	D'Agostino et al. 2000
ARR1		At3g16857	Rec, Myb	Type B	Sakai et al. 1998a
ARR2		At4g16110	Rec, Myb	Type B	Sakai et al. 1998a
ARR10	ARLP2	At4g31920	Rec, Myb	Type B	Imamura et al. 1999, Lohrmann et al. 1999
ARR11	ARLP1	At1g67710	Rec, Myb	Type B	Imamura et al. 1999, Lohrmann et al. 1999
ARR12		At2g25180	Rec, Myb	Type B	Imamura et al. 1999
ARR13		At2g27070	Rec, Myb	Type B	Imamura et al. 1999
ARR14		At2g01760	Rec, Myb	Type B	Imamura et al. 1999
ARR18		At5g58080	Rec, Myb	Type B	Schaller et al. 2002, Mason et al. 2004, Tajima et al. 2004
ARR19		At1g49190	Rec, Myb	Type B	Schaller et al. 2002, Mason et al. 2004, Tajima et al. 2004
ARR20		At3g62670	Rec, Myb	Type B	Schaller et al. 2002, Mason et al. 2004, Tajima et al. 2004
ARR21		At5g07210	Rec, Myb	Type B	Schaller et al. 2002, Mason et al. 2004, Tajima et al. 2004
ARR22		At3g04280	Rec	Type C	Schaller et al. 2002, Kiba et al, 2004
ARR23		At5g62120	missing 5' end		Schaller et al. 2002
ARR24		At5g26594	Rec	Type C	Gattolin et al., 2006
TOC1	PRR1, APRR1	At5g61380	Pseudo-Rec, CCT	Clock	Makino et al. 2000, Strayer et al. 2000
PRR3	APRR3	At5g60100	Pseudo-Rec, CCT	Clock	Matsushika et al. 2000
PRR5	APRR5	At5g24470	Pseudo-Rec, CCT	Clock	Matsushika et al. 2000
PRR7	APRR7	At5g02810	Pseudo-Rec, CCT	Clock	Matsushika et al. 2000
PRR9	APRR9	At2g46790	Pseudo-Rec, CCT	Clock	Matsushika et al. 2000
PRR2	APRR2	At4g18020	Pseudo-Rec, Myb		Makino et al. 2000
PRR4	APRR4	At5g49240	Pseudo-Rec, Myb		Schaller et al. 2002
PRR6	APRR6	At1g68210	Pseudo-Rec, Myb		Schaller et al. 2002
PRR8	APRR8	At4g00760	Pseudo		Schaller et al. 2002

[a]Chromosome loci are given by the MIPS designation.

[b]Features include receiver domain (Rec), pseudo-receiver domain lacking the phosphorylatable Asp (Pseudo-Rec), Myb-like DNA binding domain (Myb), CCT motif found in clock proteins, and whether the gene is missing essential coding sequence for a receiver.

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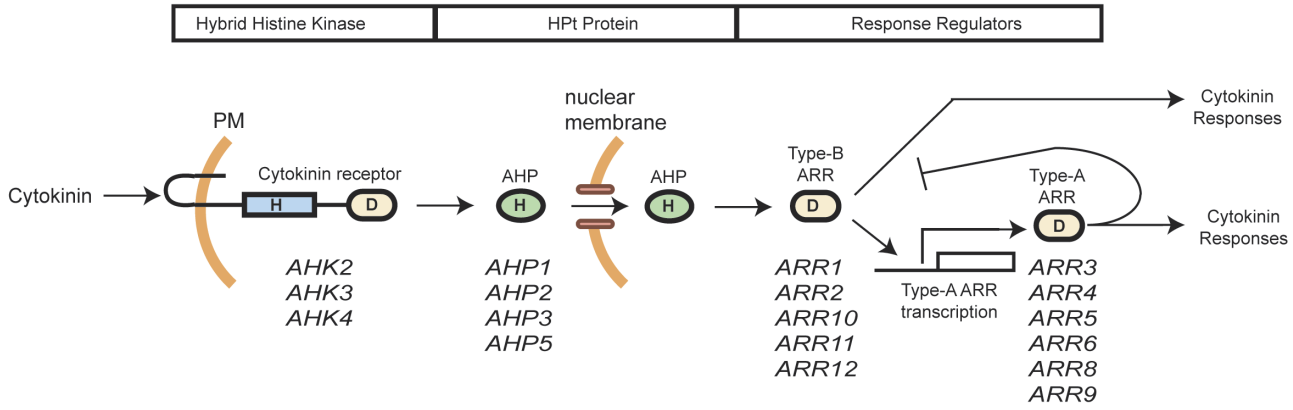

Figure 6. Cytokinin Signal Transduction Occurs Through a Multi-Step Phosphorelay.

Cytokinin receptors, AHPs, and type-B ARRs function as a positive regulatory circuit to relay the cytokinin signal from plasma membrane to nucleus. Type-B ARRs act as transcription factors, one target being genes encoding type-A ARRs. The type-A ARRs feed back to inhibit their own transcription and may also mediate other cytokinin responses. The roles of the listed cytokinin receptors, AHPs, type-B response regulators, and type-A response regulators in cytokinin signal transduction have each been confirmed by the analysis of T-DNA insertion mutations.

3) results in plants that develop small flowers and abnormal siliques with reduced fertility.

Type-C response regulators

Arabidopsis also contains two additional response regulators (ARR22 and 24). These lack long C-terminal extensions, like the type-A ARRs, but are not closely related to the type-A ARRs based on phylogenetic analysis (Figure 5) (Kiba et al., 2004; Schaller et al., 2007). The type-C ARRs are also not transcriptionally regulated by cytokinin. The type-C ARR sequences are more similar to the hybrid-kinase receiver domains than to other response regulators (Figure 5), raising the possibility that a histidine kinase, rather than an HPt protein, could serve as their phosphodonor. *ARR22* and *ARR24* are predominantly expressed in flowers and siliques (Kiba et al., 2004; Gattolin et al., 2006). Single and double loss-of-function mutants grow similarly to wild-type (Gattolin et al., 2006). Overexpression of *ARR22* inhibits cytokinin signaling based on the transgenic lines having reduced shoot growth, poor root development, reduced cytokinin-responsive gene induction, and insensitivity to cytokinin under conditions for callus production (Kiba et al., 2004; Kiba et al., 2005; Gattolin et al., 2006). Whether the type-C ARRs normally antagonize the cytokinin signaling pathway is not known.

Pseudo-response regulators

Arabidopsis contains nine pseudo-response regulators termed PRRs (Table 3, Figures 2 and 5). These contain complete receiver domains but are missing essential residues required for activity (Makino et al., 2000). In particular, the aspartate that serves as a site for phosphorylation is missing, in many cases being replaced by a glutamate residue that may mimic the phosphorylated form. These also contain C-terminal extensions, some members with a CCT-motif (PRR1/TOC1, PPR3, PRR5, PRR7, and PRR9) and others with the Myb-like motif found in the type-B response regulators (PRR2, PRR4, and PRR6).

The pseudoresponse-regulators with the CCT motif are involved in the regulation of circadian rhythms and participate in multiple regulatory feedback loops in recent models for the Arabidopsis clock (Mizuno, 2005; Gardner et al., 2006; McClung, 2006). *PRR1/TOC1* was identified in a forward genetic screen due to a semi-dominant mutation (*timing of cab expression 1-1*) that had shortened circadian periods for leaf movement, stomatal conductance, and several molecular markers (Millar et al., 1995; Somers et al., 1998; Strayer et al., 2000). PRR1/TOC1 participates in a feedback loop involving the other well-known clock components, CCA1 and LHY (Alabadi et al., 2001). Evidence that all the CCT-motif PRRs participate in the clock came from the discovery that their expression varies in a circadian manner (Matsushika et al., 2000; Makino et al., 2001) and that loss-of-function mutants have altered circadian periods (Kaczorowski and Quail, 2003; Michael et al., 2003; Farré et al., 2005; Nakamichi et al., 2005b; Nakamichi et al., 2005a; Salomé and McClung, 2005; Ito et al., 2008). The current model places PRR5, PRR7, and PRR9 in a feedback loop that also involves CCA1 and LHY. Recent work indicates that protein stability of TOC1, PRR5, PRR7, and PRR9 is post-translationally regulated (Farré and Kay, 2007; Ito et al., 2007; Kiba et al., 2007; Para et al., 2007). Additionally, PRR7 is phosphorylated, presumably on serine/threonine residues since it lacks the canonical phospho-acceptor aspartate, which may serve as a means to regulate its stability and/or function (Farré and Kay, 2007).

Potential Pseudogenes

Arabidopsis also contains the predicted sequence for a response regulator (ARR23) that, although containing the phosphorylated

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aspartate, is predicted to lack the N-terminal domain of the receiver; no EST is reported and *ARR23* could be a pseudogene. The gene product of At3g04270 also shows homology to receiver domains but is missing what would be its C-terminal end.

SIGNALING THROUGH PHOSPHORELAYS

A multi-step phosphorelay, rather than a simple two-component system, appears to be the major His-Asp signaling circuit employed by Arabidopsis. This possibility was initially raised by analysis of the Arabidopsis genome, which revealed a preponderance of hybrid kinases in Arabidopsis along with the presence of HPt proteins (Schaller et al., 2002). Subsequent analyses of protein-protein interactions using the yeast two-hybrid system supports interactions among the hybrid kinases with HPt proteins, and of the HPt proteins with both type-A and type-B response regulators, consistent with what would be expected in a multi-step phosphorelay (Imamura et al., 1999; Urao et al., 2000; Dortay et al., 2007). Finally, as described below, analysis of the cytokinin signaling pathway supports use of the multi-step phosphorelay *in planta.*

The cytokinin signaling pathway gives us our clearest picture of how two-component signaling elements have been adapted to signaling in plants (Hwang and Sheen, 2001; Haberer and Kieber, 2002; Heyl and Schmülling, 2003; Kakimoto, 2003; To and Kieber, 2008). Genetic analyses using loss-of-function mutations indicate that the primary cytokinin signaling pathway is a positive regulatory circuit that requires hybrid histidine kinases (AHK2, AHK3, and AHK4) (Inoue et al., 2001; Suzuki et al., 2001; Ueguchi et al., 2001; Yamada et al., 2001; Kakimoto, 2003; Kim et al., 2006), HPt proteins (AHP1, AHP2, AHP3, AHP5) (Hutchison et al., 2006), and type-B response regulators (ARR1, ARR2, ARR10, ARR11, and ARR12) (Sakai et al., 2001; Mason et al., 2005; Yokoyama et al., 2007; Ishida et al., 2008) (Figure 6). The function of type-B ARRs as transcription factors indicates that signals may move from histidine kinase to the nucleus solely through elements of a two-component system, the same type of signaling circuit employed by many prokaryotes. The mobile element of this signaling circuit are the AHPs, which relocate from cytosol to nucleus in response to cytokinin (Hwang and Sheen, 2001; Yamada et al., 2004). It should be noted that additional two-component signaling elements (such as other type-B ARRs) may also contribute to this cytokinin signaling circuit but this has not yet been confirmed genetically.

Several negative regulatory circuits are also employed in cytokinin signaling. First, AHK4, like some bacterial histidine kinases, has both kinase and phosphatase activities (Mähönen et al., 2006a). In the absence of cytokinin, AHK4 acts as a phosphatase to dephosphorylate AHPs, thereby decreasing signaling through the phosphorelay. Upon cytokinin binding, AHK4 switches to act as a histidine kinase to initiate the multi-step phosphorelay, resulting in phosphorylation of AHPs and downstream response regulators. Second, one of the initial transcriptional responses mediated by the type-B ARRs in response to cytokinin is to induce the expression of the type-A ARRs (Brandstatter and Kieber, 1998; Imamura et al., 1998; D'Agostino et al., 2000; Mason et al., 2005; Rashotte et al., 2006; Taniguchi et al., 2007; Yokoyama et al., 2007). The type-A ARRs then negatively regulate cytokinin signaling, potentially by competing with the type-B ARRs for phosphorylation by the AHPs (Kiba et al., 2003; To et al., 2004; Leibfried et al., 2005; Lee et al., 2007; To et al., 2007). Furthermore, multiple type-A proteins are stabilized by cytokinin, further increasing this negative feedback loop (To et al., 2007). Third, the pseudo-HPt, *APHP1,* is induced by cytokinin and acts as a negative regulator of cytokinin responses (Mähönen et al., 2006b).

The presence of additional hybrid histidine-kinases in Arabidopsis, such as ETR1, AHK1, CKI1, and CKI2, suggests that multi-step phosphorelays function in relaying signals other than cytokinin. This raises the question as to which downstream components are involved in relaying the additional signals, given that a majority of the two-component signaling elements have already been implicated in cytokinin signaling. While there exists a formal possibility for unique combinations of signaling elements, it is far more likely that downstream signaling elements are shared among the receptors. In some cases, different input signals may be channeled into the same downstream signaling pathway to regulate a common response. Alternatively, a response tailored to a specific signal input could still be obtained even with shared signaling elements. One way to accomplish this would be to have varying affinities between the receptors and the AHPs, and between the AHPs and the response regulators, such that each signal would differentially activate the downstream components. Yeast two-hybrid analysis does suggest some specificity to the interactions between receptors and the AHPs (Urao et al., 2000), but the physiological relevance of these differences has not been determined. An alternative possibility would be for specificity of the downstream signaling elements to be modified by covalent modification or protein-protein interaction in ways unique to the signal input. It is also possible that protein subsets are sequestered in unique signaling complexes by scaffold proteins. Genetic, molecular, and proteomic approaches should clarify how this network of interactions functions in plants.

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