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Sci. STKE **2007** (407), cm5. [DOI: 10.1126/stke.4072007cm5]

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(Published 9 October 2007)

Cytokinins are essential plant hormones that control cell division, shoot meristem initiation, leaf and root differentiation, vasculature patterning, chloroplast biogenesis, photomorphogenesis, fertility, seed development, senescence, and stress tolerance. The *Arabidopsis* cytokinin signal transduction pathway involves hybrid histidine protein kinases [AHK2, AHK3, and AHK4 (also known as CRE1or WOL)] as cytokinin receptors, histidine phosphotransfer proteins (AHPs), and nuclear response regulators (ARRs) that serve as transcriptional regulators. There are four major steps in the cytokinin phosphorelay: (i) AHK sensing and signaling, (ii) AHP nuclear translocation, (iii) ARR-dependent transcriptional activation, and (iv) a negative-feedback loop through cytokinin-inducible ARR gene products. Each step is executed by components encoded by multigene families. The effects of cytokinin depend on cell type, environment, and developmental stage. The response is frequently the outcome of interactions with other plant signaling pathways.

Description

This record contains information specific to the Arabidopsis Cytokinin Signaling Pathway.

In *Arabidopsis thaliana*, cytokinin signaling has been implicated in control of the stem cell pool in the shoot meristem, leaf and root differentiation, vasculature patterning, chloroplast biogenesis, photomorphogenesis, apical dominance, gravitropism, fertility, seed development, senescence, and stress tolerance (*1*–*6*). Thus, cytokinins are important regulators of plant growth and development in multiple tissues and under diverse environmental conditions.

Cytokinin signaling is mediated by a multistep two-component circuitry through histidine (His) and aspartate (Asp) phosphorelay [see the canonical Cytokinin Signaling Pathway (http://stke.sciencemag.org/cgi/cm/stkecm;CMP_9724) for details about multistep, two-component relay in cytokinin signaling]. In *Arabidopsis*, hybrid histidine protein kinases (AHKs) serve as cytokinin receptors; histidine phosphotransfer proteins (AHPs) relay the phosphate to the nuclear response regulators (ARRs), which regulate a transcriptional network to control plant responses. There are four major steps in the cytokinin phosphorelay: (i) cytokinin sensing and initiation of signaling by AHKs; (ii) transfer of a phosphoryl group to AHPs and nuclear translocation of the "activated" AHPs; (iii) phosphotransfer to nuclear B-type ARRs that activate transcription; and (iv) negative feedback through cytokinin-inducible A-type ARR gene products, that is, the A-type ARR genes are transcriptionally induced by B-type ARRs (Fig. 1).

Cytokinins are a family of ligands synthesized enzymatically from adenine (*7*, *8*). Ligand binding to the CHASE (cyclase- and histidine kinase–associated sensing extracellular) domain of the AHK receptors triggers autophosphorylation of the receptors at a conserved His residue. In cytokinin signaling, the phosphoryl group is first transferred to a conserved Asp residue in the receptor's receiver domain. The phosphoryl group is then transferred to an AHP that translocates to the nucleus, where the phosphoryl group gets passed over to a conserved Asp residue in the receiver domain of an ARR protein. There are two types of ARRs: A-type and B-type. A-type ARRs include ARR3, 4, 5, 6, 7, 8, 9, 15, 16, and 17. B-type ARRs include ARR1, 2, 10, 11, 12, 13, 14, 18, 19, 20, and 21. Both types of ARRs have a conserved receiver domain at their N terminus; however, their C-terminal domains diverge, and their functions are opposite. B-type ARRs bind to DNA and activate transcription. In contrast, A-type ARRs have a short, poorly defined C-terminal domain, and they inhibit cytokinin signaling. Because the genes A-type ARRs also represent immediate-early transcriptional targets, they establish a negative-feedback loop in the pathway (*1*–*5*). Interestingly, two *Arabidopsis* RRs (ARR22 and ARR24) that are specifically expressed in reproductive organs have a receiver domain similar to the one found in HKs. Structurally and functionally however, ARR22 and ARR24 are similar to A-type RRs, except that their expression is not induced by cytokinin (*9*, *10*).

The first evidence that cytokinin is transduced by a phosphorelay system came in 1996 when *Arabidopsis* cytokinin independent 1 (CKI1) was identified as a transmembrane hybrid histidine kinase (HK) (*11*). Overexpression of CKI1 induced cytokinin responses independent of cytokinin in culture (*11*), protoplasts, and whole plants (*12*). Endogenous CKI1 function is expressed and required during female gametophyte development (*13*, *14*). In a tissue culture assay, *cre1* (*cytokinin response1*) was isolated on the basis of reduced responses to cytokinins and was determined to be a missense mutation in *AHK4* (*15*). AHK4 (also known as CRE1or WOL) binds cytokinin (*16*) and complements yeast and bacteria HK mutants in a cytokinin-dependent manner (*15*, *17*). Survey of the *Arabidopsis* genome identified two AHK4 homologs, AHK2 and AHK3 (*16*). Although the three receptors share a CHASE domain for cytokinin binding, they differ in their number of transmembrane segments at their N terminus. Transient expression in protoplasts of any of these three receptors, in particular AHK4, increases sensitivity to cytokinin (*12*). Endogenous expression of the three receptors seems to largely overlap and to support partially redundant functions (*18*–*20*). There may be specific functions for each receptor as well. For example, in addition to its kinase functions, AHK4 harbors a phosphatase that is activated in the absence of a ligand and that removes phosphoryl groups from interacting AHPs. This observation suggests that AHK4 may act as a negative regulator without cytokinin, in addition to its positive role in the presence of cytokinin (*21*). AHK3 may have unique functions in leaf senescence that

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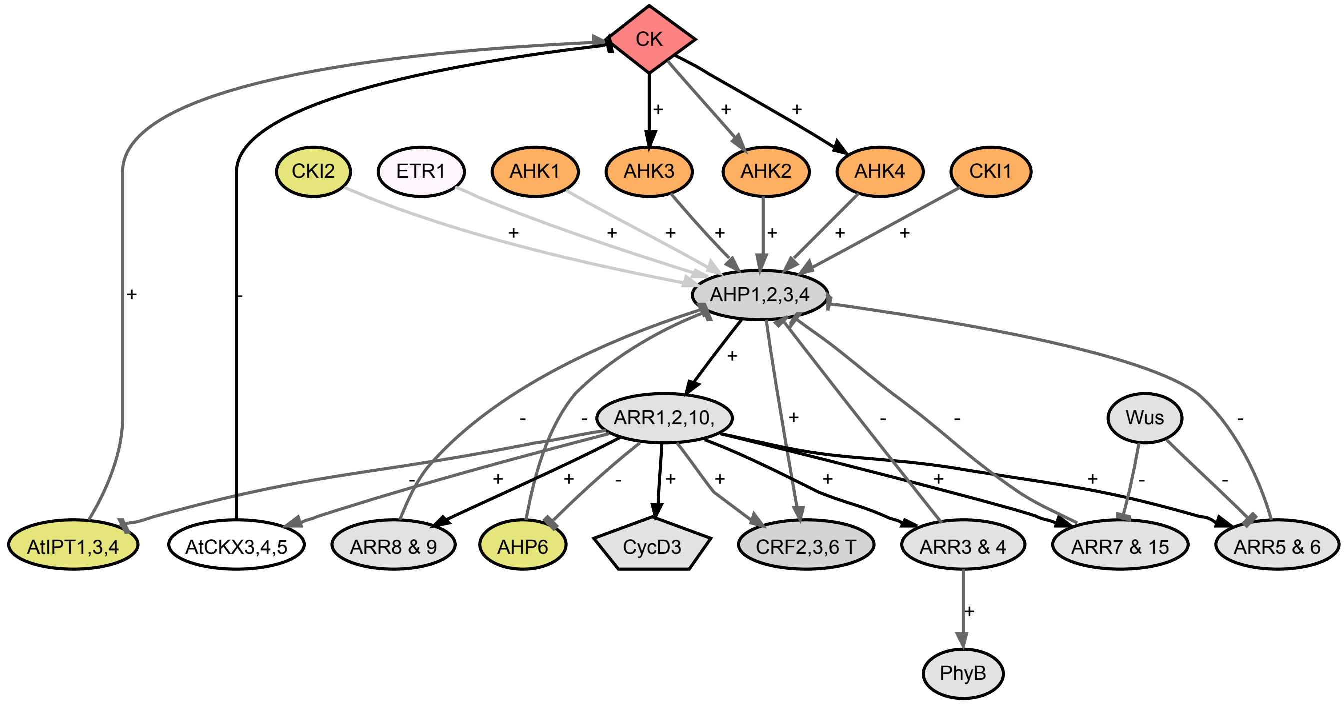

Fig. 1. Pathway image captured from the dynamic graphical display of the information in the Connections Maps available 13 September 2007. In this updated version of the pathway, components defined by mutational and genomic analyses have been added. The pathway illustrates the highly redundant and interconnected nature of cytokinin signaling. For a key to the colors and symbols and to access the underlying data, please visit the pathway (http://stke.sciencemag.org/cgi/cm/stkecm; CMP_10021).

cannot be replaced by AHK2 and AHK4 (*20*, *22*). Also, when expressed in *Escherichia coli*, different receptors seem to prefer different versions of cytokinin (*8*, *16*, *17*, *23–25*). More specialized tasks of individual cytokinin receptors may emerge in the future.

The *ahk2*, *ahk3*, *ahk4* triple mutant plants are insensitive to exogenously applied cytokinins (*18*, *19*). They also have severe developmental defects, such as strongly reduced shoot and root growth, decreased lateral root formation, defects in vasculature differentiation, accelerated leaf aging, and increased seed size. Except root protoxylem specification, no obvious pattern defects in root or shoot were found in triple-mutant plants (*18–21*). This was surprising because ectopic activation of the cytokinin signaling pathway can induce ectopic shoots (*11*, *12*). One possible explanation is signaling input that is independent of the known receptors (*18*, *19*). Although no more CHASE domain–containing proteins exist in the genome, there are five more genes with conserved HK domains: CKI1, AHK1, CKI2 (*11*, *26*), ETR1, and ERS1 (*27*). Potentially, the proteins they encode are able to transfer phosphoryl groups to AHPs. Interestingly, AHK1, CKI1, and ETR1 interact with AHP's in a yeast two-hybrid assay (*26*). The roles of those HKs in phosphorelay signaling deserve further analysis.

Six *AHP* genes are encoded in the *Arabidopsis* genome. AHP1 and AHP2 translocate to the nucleus after cytokinin treatment (*12*). AHP interaction with AHKs and ARRs seems largely promiscuous, at least in vitro and in yeast two-hybrid assays (*26*, *28*). Phenotypes resulting from reduced cytokinin signaling become most apparent with a quintuple *ahp1*, *2*, *3*, *4*, *5* mutant, which suggests functional redundancy (*29*). AHP6 is called a pseudo-AHP because an inert Asn residue is found where AHP1 to AHP5 have a conserved His for phosphorelay. AHP6 has been shown to impair phosphotransfer from AHKs to AHP1 through 5, most likely by directly competing with functional AHPs for interaction with AHKs (*21*). Interestingly, AHP6 is restricted to specific cell types in root vascular tissues, and the gene encoding AHP6 is repressed by cytokinin (*21*). Therefore, the presence of AHP6 may limit the number of cytokinin signaling cells and contribute to sharpening and defining cell differentiation boundaries.

After accepting the phosphoryl group, nuclear B-type ARR proteins bind DNA and activate target gene transcription. The unphosphorylated N-terminal receiver domain that predominates in the absence of a signal has been proposed to inhibit B-type ARR function (*22*, *30*, *31*). The *Arabidopsis* genome comprises 11 members. They are broadly expressed, mostly in overlapping domains, with the exception of some members that are specific to reproductive organs (*32*, *33*). Besides their N-terminal receiver domain, they all share a conserved DNA binding domain of about 60 amino acids, called the GARP domain, that optimally binds to the core sequence 5′-(A/G)GAT(T/C)-3′ in vitro (*30*, *34*, *35*). Such short sequence motifs are enriched in primary cytokinin target genes and are therefore likely important in vivo as well (*36*). Support for the notion of extensive redundancy among B-type ARRs was provided by extensive mutational analysis (*31*, *37*). Higher-order mutants revealed progressively decreased sensitivity to cytokinin (*37*). Nevertheless, there seem to be unique functions as well, exemplified by specific expression profiles and distinct overexpression phenotypes (*12*, *33*).

Among the immediate-early gene targets are the genes encoding A-type ARRs, which constitute 10 individual members

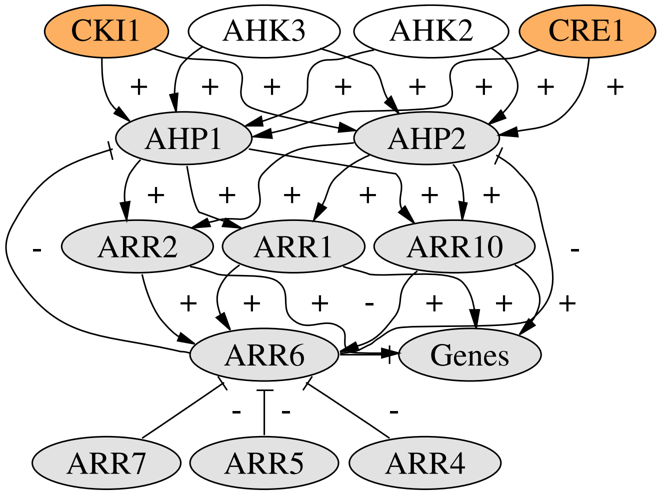

Fig. 2. Historic pathway image captured from the dynamic graphical display of the information in the Connections Maps available 24 July 2006. For a key to the colors and symbols and to view the most current information, please visit the pathway (http://stke.sciencemag.org/cgi/cm/stkecm;CMP_10021).

of the *Arabidopsis* genome. Together with the B-type ARRs, they share a receiver domain with conserved Asp residues. Their short C-terminal region, however, is variable, with poorly defined motifs (*1–5*). When expressed in mesophyll protoplasts, the induction of a cytokinin-specific reporter gene is strongly impaired. A-type ARRs have thus been proposed to act in a negative-feedback loop (*12*). Consistent with such a model, plants mutated in several A-type ARRs exhibit higher sensitivity to cytokinin (*38*), whereas plants overexpressing A-type ARRs show phenotypes reminiscent of impaired cytokinin output (*9*).

Changes of the transcriptome profile after adding cytokinin have been measured in various contexts (*9*, *36*, *39–41*). Genes encoding A-type ARRs are transcriptionally induced in all experiments. Two immediate-early target genes encode transcription factors that belong to the AP2/ERF superfamily (*36*, *42*). They belong to a small group of closely related AP2/ERF genes that have been renamed as cytokinin-response factors (CRF1 to 6). Interestingly, fusion proteins of CRF and green fluorescent protein (GFP) enter the nucleus through a mechanism that is dependent on cytokinin, AHK, and AHP. CRFs control a subset of cytokinin responses, but not A-type ARR genes (*42*). Cyclin D3 is an important early signaling target that is involved in promoting cytokinin-induced proliferation (*43*). Cytokinin early signaling triggers another negative-feedback loop by activating genes encoding cytokinin oxidase (CKX), which degrades cytokinin (*44*), and repressing genes encoding isopentenyl transferases (IPTs), which are involved in cytokinin synthesis (*25*).

The effects of cytokinin depend on cell type, environment, and developmental stage. The response is frequently the outcome of interactions with other plant signaling pathways. For example, the ratio of auxin to cytokinin defines the type of de novo organ formation in cultured tissue. Even though this now-classic interaction with auxin was first described in 1957 (*45*), its relevance for the normal plant development is not established. Cross-talk between cytokinin and the light signal transduction pathways is mediated by a specific interaction between phosphorylated A-type ARR4 and the physiologically active form of phytochrome B. The interaction stabilizes phytochrome B, making the cells more sensitive to red light (*46*). Cytokinin signaling by AHK4 represses response genes induced by phosphate starvation (*47*). Cytokinin also seems to be involved in relaying the nitrogen nutritional status from roots to leaves (*23*, *48*). WUSCHEL (WUS), a homeobox protein important for shoot meristem maintenance, directly represses transcription of the A-type ARRs. Consequently, cells in which WUS is present will be more sensitive to cytokinin (*49*).

There has been a lot of progress in the field during the past 5 years. In the initial Connections Maps for the pathway dating from 2002, only a handful of potential signaling components had been associated with cytokinin signaling (Fig. 2). Now, the general logic of phosphorelay signaling as proposed earlier (*12*, *50*) has been confirmed, and the participants in the pathway have been elucidated by thorough genetic analysis of higher-order mutants and other approaches (*1–5*) (Fig. 1). The future challenges lie in explaining the molecular mechanisms of signaling and interactions with other plant regulatory pathways in detail. For example, how do A-type ARRs inhibit signaling? How can B-type ARRs activate specific target genes, given such a short DNA recognition motif? How is context-dependent specificity of signaling output achieved? High-resolution analysis of the cytokinin signaling pathway activity in different cell types during development will be essential for learning more about their physiological functions. With the increased availability of plant genome sequences and functional analysis systems, it will be interesting to compare the role of phosphorelay signaling among different plant species.

Pathway Details

URL: http://stke.sciencemag.org/cgi/cm/stkecm;CMP_10021
Scope: Specific
Organism: plants: *Arabidopsis thaliana*
Tissue and cell: plant structures: seedling
Canonical Pathway: Cytokinin Signaling Pathway (http://stke.sciencemag.org/cgi/cm/stkecm;CMP_9724)

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Citation: B. Müller, J. Sheen, *Arabidopsis* cytokinin signaling pathway. *Sci. STKE* 2007, cm5 (2007).