

Minireview

Signaling crosstalk between ethylene and other molecules

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Abstract In plants, growth and development are modulated in response to a number of signaling molecules. In past decades, many physiological studies suggested various antagonistic or synergistic effects by multiple signaling molecules in growth regulation of plants. Recent studies have highlighted the machinery for integration of signaling pathways. Here we summarize the findings on molecular mechanisms for crosstalk, focusing on crosstalk between ethylene and other signaling pathways in *Arabidopsis*.

Key words: Auxin, crosstalk of signaling, ethylene, glucose.

With their sessile nature, plants must be well-adapted to the environment to survive and to have progeny at the place where each plant has initially developed from a seed. Accordingly, both the primary condition of the place where a plant has germinated and fluctuation in a variety of environmental factors, including light intensity, temperature, nutrition and pathogen infection seriously influence the growth and development of the plant. Indeed, environmental fluctuations function as signals and trigger numerous cellular responses, including modification of gene expression patterns and metabolic regulation, leading to acclimatization of plants to a new condition and modulation of growth speed (Casal et al. 2003; Forde 2002; Iba 2002; Paul and Pellny 2003; Simpson and Dean 2002; Stitt et al. 2002; Thomashow 1999; Wang et al. 2003). Because some environmental signals promote growth of plants, whereas others repress it, plant growth must be determined on the basis of the sum total of positive and negative regulation by various environmental signals. Furthermore, because the life cycle of each plant is fundamentally based on its internal developmental program in which phytohormones play key roles (Bleecker and Kende 2000; Fleet and Sun 2005; Heyl and Schmülling 2003; Johnson and Ecker 1998; Nemhauser and Chory 2004; Woodward and Bartel 2005) and because some environmental signals are mediated by phytohormones (De Smet et al. 2003; Friml et al. 2002; Harper et al. 2000; Sakakibara 2003; Signora et al. 2001; Tatematsu et al. 2004; Xiong and Zhu 2003; Zhu 2002), the system

governing growth and development must also involve the machinery for integration of hormone and other signaling.

In past studies, it had been predicted that environmental signals and phytohormones function cooperatively, synergistically or antagonistically with one another, on the basis of observations of physiological responses of cells or of whole plant bodies (Addicott and Lyon 1969; Bao et al. 2004; Chory et al. 1994; Lieberman 1979; Murashige and Skoog 1962; Sachs and Thimann 1967). Precise evaluation of the intimate links between certain signaling pathways has also been carried out in molecular biological studies and studies using mutant plants (Casal 2002; Gazzarrini and McCourt 2001; Gazzarrini and McCourt 2003; Kunkel and Brooks 2002; Léon and Sheen 2003; Nemhauser and Chory 2004; Swarup et al. 2002). Despite the many past reports mentioning the presence of crosstalk between signaling pathways, only recently the mechanisms for crosstalk have been demonstrated. For example, a red light receptor, phytochrome B, has been found to directly interact with ARR4 protein, a component of the cytokinin signaling system in *Arabidopsis* (Brandstatter and Kieber 1998; Hwang and Sheen 2001; Sweere et al. 2001; To et al. 2004). Binding of ARR4 to phytochrome B led to stabilization of the active form of phytochrome B, offering the molecular basis of crosstalk between light and cytokinin signaling for development (e.g. Chory et al. 1994; Kusnetsov et al. 1999; Miller 1956; Sano and Youssefian 1994). The mechanism for the cooperative

action of two phytohormones, auxin and gibberellin, in promoting root growth has also been shown (Fu and Harberd 2003). Auxin transported from shoot to root promoted the degradation of DELLA proteins, negative regulators in the gibberellin signaling pathway, enhancing responses to gibberellin. Although only a limited number of studies to date have showed molecular mechanisms for crosstalk between signaling pathways, and each report has highlighted only pieces of the whole system regulating plant growth (Cólón-Carmona et al. 2000; Hass et al. 2004; Li et al. 2004; Moore et al. 2003; Spoel et al. 2003; Yanagisawa et al. 2003), it has become evident that the machinery integrating signaling pathways is critical in controlling growth and development in plants.

We introduce herein the molecular mechanisms for crosstalk between ethylene and other signaling. Because ethylene biosynthesis is activated by wounding, pathogen infection, winds and other stress signals (Yang and Hoffman 1984), ethylene is regarded as a stress hormone in plants. The interaction between ethylene signaling and sugar, light or auxin signaling provides us with an opportunity to realize that plant growth is strictly regulated under the operation of a highly sophisticated system.

Mechanism connecting ethylene and glucose signaling

Because both the ethylene signaling and glucose signaling pathways are complex due to many components involved, we will at first summarize the pathways in brief and then describe the mechanism for crosstalk between these pathways.

Ethylene signaling pathway

Gaseous hormone ethylene plays a variety of roles in plant growth and development, acting in stress response, in fruit ripening and in senescence as well as in seedling development (Lieberman 1979; Pratt and Goeschl 1969). Several components of the ethylene signaling pathway have been identified by molecular genetics approaches with *Arabidopsis*. A model for the ethylene signaling pathway, which is currently accepted in general, has been well-documented in Wang et al. (2002). In this model, ethylene is perceived by a family of ethylene receptors, ETR1/2, EIN4 and ERS1/2, which negatively regulate a Raf-like protein kinase, CTR1. CTR1 negatively regulates the action of a key transcription factor, ETHYLENE INSENSITIVE3 (EIN3) and its related proteins (EILs), which directly activate a part of ethylene-responsive gene expression. EIN3 and EILs also appear to directly activate expression of a downstream transcription factor, ERF1, because EIN3 binds the promoter of the *ERF1* gene (Solano et al.

1998). ERF1 binds to a *cis*-element called GCC-box and activates transcription from several ethylene-responsive gene promoters (Solano et al. 1998). Despite many intensive studies, the pathway between CTR1 and EIN3 is largely unknown (Ecker 2004; Guo and Ecker 2004).

Glucose signaling pathway

Sugar is a carbon and energy source in all living organisms. In plants, sugar is synthesized endogenously by photosynthesis in source organs (mature leaves) and transported to sink organs. It is known that sugar acts as a signaling molecule in plants as well as in yeast, and in mammals (Rolland et al. 2002). In general, sugar reduces source function and elevates sink function. The role of glucose as a signaling molecule is separable from its role as metabolizable carbon source because nonmetabolizable glucose analogs as well as glucose can also trigger the suppression of expression of photosynthetic genes (Jang and Sheen 1994). Using *Arabidopsis* mutants, a key component in glucose signaling has been identified. A highly concentrated glucose causes inhibition of seedling development in wild-type *Arabidopsis*. However, an *Arabidopsis* line having a mutation in a hexokinase gene, *AtHXX1/GIN2*, did not show glucose-induced arrest of seedling development, suggesting that the *gin2* mutant is hyposensitive to glucose. Based on this result and further characterization of *AtHXX1*, *AtHXX1* is proposed to be a glucose sensor responsible for glucose signaling in *Arabidopsis* (Jang et al. 1997; Moore et al. 2003). The HXK-dependent glucose signaling pathway appears to be a major route for sugar-signaling, but other routes have also been suggested (Gibson 2000; Gibson 2005; Sheen et al. 1999; Smeekens 2000).

Crosstalk between sugar and hormone signaling

The crosstalk between sugar and hormone signaling has been suggested based on the use of *Arabidopsis* mutants. Because the mutations in abscisic acid (ABA) biosynthesis or signaling genes caused defects in glucose response, the ABA pathway could be an important constituent of glucose signaling (Léon and Sheen 2003). In addition, another phytohormone, ethylene, has also been implicated in glucose signaling (Gazzarrini and McCourt 2001; Gibson et al. 2001; Léon and Sheen 2003; Zhou et al. 1998). The addition of ethylene alleviated the glucose-induced inhibition of seedling development. Ethylene-insensitive mutants showed a more severe phenotype of glucose-induced growth arrest, whereas a constitutive ethylene response mutant, *ctr1*, and ethylene-overproducing mutants were insensitive to glucose. Conversely, glucose-insensitive mutants exhibited in part, phenotypes similar to that of the *ctr1* mutant, such as darker green leaves. Therefore, sugar indicating the internal nutrition condition appears to

cooperatively regulate growth and development together with phytohormones.

Mechanism underlying crosstalk between ethylene and glucose signaling

A clue to reveal the mechanism of crosstalk between ethylene and glucose signaling was provided through functional analysis of EIN3 with protoplasts (Yanagisawa et al. 2003). The EIN3-dependent activation of transcription was suppressed by application of glucose to protoplasts. Subsequently, it was shown that this phenomenon reflected enhancement of EIN3 degradation by glucose. In addition, co-expression of AtHXXK1 led to suppression of the EIN3-dependent transcriptional activation in the presence of a lower concentration of glucose, while co-expression of yeast hexokinase did not, suggesting that the AtHXXK1-dependent pathway is involved in the regulation of EIN3 activity. Because AtHXXK1 but not yeast hexokinase was associated with nuclei in plant cells and the AtHXXK1 lacking its enzymatic activity could also promote degradation of EIN3, the glucose sensor activity but not metabolic enzyme activity of AtHXXK1 is essential in mediating glucose signal into nuclei and triggering nuclear events including the promotion of EIN3 degradation. On the other hand, application of 1-aminocyclopropane-1-carboxylic acid (ACC), a biosynthetic precursor of ethylene, conferred an opposite effect, the stabilization of EIN3 protein. These results suggested that glucose and ethylene signaling differently regulate degradation of the EIN3 transcription factor, thereby producing antagonistic effects (Figure 1; Yanagisawa et al. 2003).

The linkage between the accumulation of EIN3 protein and the sensitivities of plants to glucose and ethylene was also investigated. The transgenic *Arabidopsis* overexpressing EIN3 was hyposensitive to glucose but hypersensitive to ethylene while the *ein3* mutant was hypersensitive to glucose but insensitive to ethylene, indicating that the differential regulation of EIN3 stability by glucose and ethylene are physiologically relevant *in planta*.

Ubiquitin-dependent degradation of EIN3

There are several systems for protein degradation in eukaryotic cells. Because inhibitors of 26S proteasome repressed the degradation of EIN3 protein both *in vitro* and *in planta*, the 26S proteasome system was suggested to have major responsibility for degradation of EIN3 protein (Yanagisawa et al. 2003).

In eukaryotic cells, 26S proteasome degrades polyubiquitinated proteins. Ubiquitin is covalently attached to substrate protein by sequential reactions of E1 ubiquitin-activating enzyme, E2 ubiquitin-conjugating enzyme and E3 ubiquitin ligase. E3 ubiquitin ligases, which recognize substrate and recruit E2, are classified

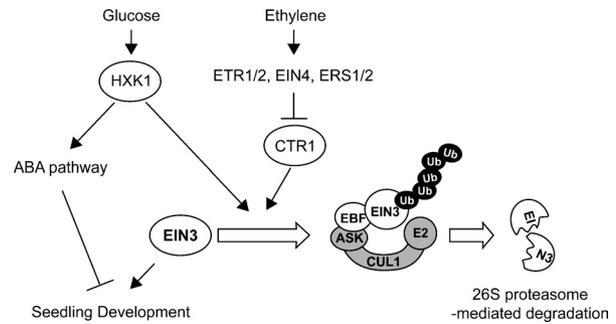


Figure 1. Model for the regulation of EIN3 stability by glucose and ethylene. The EIN3 protein is ubiquitinated by SCF^{EBF} E3 ligase and then degraded by 26S proteasome. Glucose signaling by HXXK promotes the degradation. In the absence of ethylene, CTR1 promotes the degradation of EIN3. Ethylene gas is perceived by a family of ethylene receptors (ETR1/2, EIN4 and ERS1/2), which negatively regulate CTR1 activity.

into several types. SCF complex is a type of E3 and consists of Skp1, CULLIN1, RING domain protein Rbx1 and an F-box protein. F-box protein determines the substrate specificity of each SCF complex (Deshaies 1999; Hochstrasser 1996; Smalle and Vierstra 2004). *Arabidopsis* is proposed to have approximately seven hundred F-box proteins, based on *Arabidopsis* genome data, and several *Arabidopsis* F-box proteins including TIR1 and COI1 are known to be involved in phytohormone signaling (Gagne et al. 2002; Smalle and Vierstra 2004).

The implication that degradation of EIN3 might be mediated by 26S proteasome was verified by identification of *Arabidopsis* F-box proteins that could bind EIN3 (Gagne et al. 2004; Guo and Ecker 2003; Potuschak et al. 2003). The two related F-box proteins, EBF1 and EBF2, interacted with EIN3 and EIL1 through their leucine-rich repeat domain and also associated with E3 components, CUL1 and ASK1 (an *Arabidopsis* Skp1 homologue). In double mutants of the two F-box genes, EIN3 protein accumulated at a high level that was comparable to that in the *ctr1* mutant, and the double mutant showed constitutive ethylene-response phenotype. On the other hand, overexpression of the F-box proteins in transgenic *Arabidopsis* resulted in a reduction in EIN3 protein level and these plants exhibited ethylene-insensitive phenotype (Gagne et al. 2004; Guo and Ecker 2003; Potuschak et al. 2003). The results indicated that these F-box proteins are involved in the degradation of EIN3.

As summarized here, recent data suggest that binding of ethylene to its receptors negatively regulates a Raf-like kinase, CTR1, which positively regulates EBF-mediated degradation of the EIN3 transcription factor (Figure 1). The question remains, however, as to which step in the degradation of EIN3 proteins is regulated by ethylene. Similarly, how glucose signal regulates the degradation of EIN3 has not yet been determined. It is

even unknown whether ethylene and glucose signaling regulate the same step in EIN3 degradation. There are several possible processes that the signaling pathways could regulate, as it is already known that modification of target proteins for the recognition by SCF complex (Deshaies 1999), enhancement of SCF assembly (Li and Johnston 1997; Tao et al. 2005) and modulation of E3 activity through neddylation/deneylation of the CULLIN subunit (Serino and Deng 2003; Wee et al. 2005; Wei and Deng 2003) are involved in the regulation in some 26S proteasome-mediated protein degradation. In addition, it has recently been reported that auxin enhances the interaction between an F-box protein, TIR1, and its substrate, IAA7, probably by direct binding of auxin to TIR1 (Dharmasiri et al. 2005; Kepinski and Leyser 2005), suggesting that small signaling molecules could directly modulate the association of F-box protein with substrate protein. The question as to which process glucose and ethylene signaling regulate in the degradation of EIN3 will be answered by future analyses. The structural similarity between EBFs and Grr1, a yeast F-box protein involved in yeast glucose signaling (Xiao and Jang 2000; Potuschak et al. 2003; Gagne et al. 2004) might provide a cue because glucose promoted association of Skp1 and Grr1 *in vivo* (Li and Johnston 1997).

Mechanism of crosstalk among ethylene, auxin and light signaling

Roles of ethylene, auxin and light in apical hook maintenance

Dark-grown seedlings form an apical hook, a bending of hypocotyls below the cotyledons (see Figure 2). This structure protects the apical meristem of seedlings during their penetration through the soil. Differential cell growth on the inner and outer sides of the hook region is responsible for the hook maintenance (Silk and Erickson 1978). Two phytohormones, ethylene and auxin are likely implicated in this process, because application of ethylene to dark-grown seedling exaggerates the curvature of the apical hook (Figure 2; Guzmán and Ecker 1990) and disturbance of auxin polar transport or over-accumulation of auxin in the seedling abolishes the apical hook structure (Boerjan et al. 1995; King et al. 1995; Lehman et al. 1996; Zhao et al. 2001). Furthermore, when dark-grown seedlings are exposed to light, the apical hook opens. Therefore, apical hook maintenance is differently regulated by distinct signaling pathways mediating ethylene, auxin or light.

HOOKLESS1 regulation of ARF2

HOOKLESS1 (HLS1) is a protein required for apical hook maintenance because *hls1* mutants do not form an apical hook in the dark (Guzmán and Ecker 1990;



Figure 2. Apical hook of dark-grown *Arabidopsis* seedling. Dark-grown seedlings form an apical hook. ACC, a precursor of ethylene, treatment results in exaggerated curvature of the apical hook. From Yanagisawa et al. (2003), by permission from Nature, copyright 2003, Macmillan Publishers Ltd.

Lehman et al. 1996). Several observations have suggested that HLS1 might be a key component of crosstalk between ethylene and auxin signaling: (1) *hls1* mutants are insensitive to ethylene with regard to apical hook maintenance; (2) the steady-state level of *HLS1* transcript increased upon ethylene treatment; (3) the expression of primary auxin-responsive genes was altered in the *hls1* mutants (Lehman et al. 1996; Figure 3).

Recently, two suppressor loci of the *hls1* mutation (*hss*) have been identified by genetic screening (Li et al. 2004). One of them, *HSS1*, encodes ARF2, which is a member of the auxin response factor family (ARFs). It is known that ARFs bind auxin-response elements found in the promoters of primary auxin-response genes (Ulmasov et al. 1999a) and that ARF2 and its closely related protein, ARF1, act as repressors of auxin-dependent transcription when they were transiently expressed in carrot protoplasts (Tiwari et al. 2003; Ulmasov et al. 1999b). In *arf2* mutants, the expression of auxin-responsive *DR5-GUS* reporter gene in the apical hook region was stronger than that in wild-type *Arabidopsis* when they were grown in the presence of ACC in the dark (Li et al. 2004). In addition, the *arf1 arf2* double mutants exhibited exaggerated apical hooks, similar to the *Arabidopsis* plants overexpressing HLS1 (Li et al. 2004). These findings suggested that ARF2, along with ARF1, is a repressor of auxin action in apical hook maintenance (Li et al. 2004; Figure 3).

The level of ARF2 protein was higher in the *hls1* mutant, but lower in the *Arabidopsis* overexpressing HLS1, as compared with the level in wild-type *Arabidopsis*. In contrast, the level and distribution of the *ARF2* transcript were similar in the *hls1* mutant and in wild-type *Arabidopsis*, indicating that HLS1 negatively regulates accumulation of the ARF2 protein. As ethylene elevated the levels of *HLS1* transcript and the corresponding protein, it decreased the amount of ARF2. Since application of 26S proteasome inhibitor

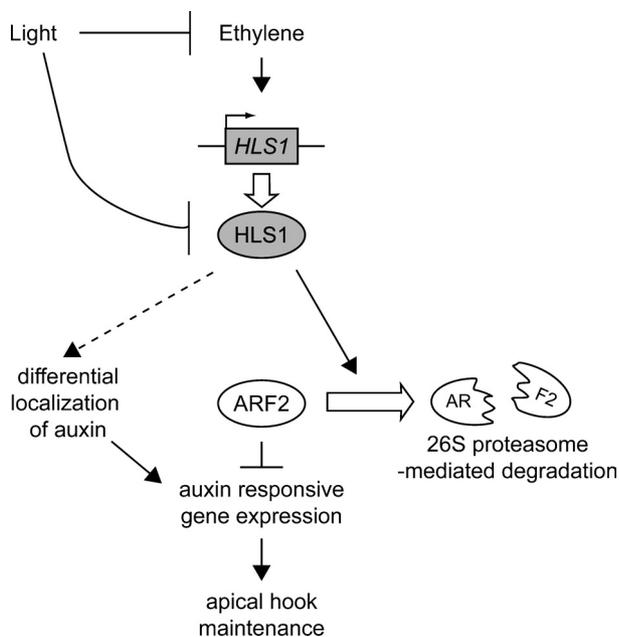


Figure 3. Model for ethylene and light regulation of apical hook maintenance through HLS1. Ethylene upregulates expression of the *HLS1* gene. Light decreases HLS1 protein level directly and/or indirectly. HLS1 promotes the 26S proteasome-mediated degradation of the ARF2 protein, which is a repressor of the auxin-mediated gene expression required for apical hook maintenance. HLS1 may also affect the differential localization of auxin, as expression patterns of some auxin-responsive reporter genes were altered in the *hls1* mutants (Lehman et al. 1996).

suppressed the ethylene-stimulated decrease of ARF2, HLS1 has been suggested to be required for 26S proteasome-dependent degradation of ARF2 protein (Li et al. 2004; Figure 3).

Control of *HLS1* abundance by light

When dark-grown seedlings were exposed to the light, a decrease in HLS1 protein and an increase in ARF2 protein were observed in parallel with the opening of apical hook (Li et al. 2004). It is currently obscure how light regulates the abundance of HLS1, although regulation of transcription and/or modulation of protein is possibly regulated by light. The suppression of ethylene production by light (Goeschl et al. 1967; Kang et al. 1967) is one explanation, but it does not completely account for the observation that HLS1 overexpressed by the use of the 35S promoter was also decreased by light, and for the observation that application of ACC did not alleviate the decrease of HLS1 caused by light (Li et al. 2004; Figure 3). There might be several steps at which light exerts its control over HLS1. Although further analysis is necessary for the conclusion, the HLS1 protein, whose function is regulated by ethylene and light, is likely a key component in apical hook maintenance and controls the degradation of ARF2 protein, altering the auxin response in the apical hook (Figure 3).

Perspective

Several molecular mechanisms for crosstalk between signaling pathways are emerging. As reviewed here, the mechanisms of crosstalk appear to be highly sophisticated. Plants probably have needed to evolve complex machinery integrating various signaling pathways to optimize their responses to the environment.

Most of the previously suggested mechanisms for crosstalk remain elusive. In addition, further investigation would identify new examples of crosstalk. In fact, two-component signaling network that integrates both cytokinin and ethylene signals has recently been reported (Hass et al. 2004). Elaborate analyses including complete identification of components in each signaling pathway and dissection of the processes in signaling would be necessary. The analyses also need to include spatial and temporal analyses of crosstalk, as it is unlikely that every type of crosstalk occurs in all types of cells and at all stages of the life cycle. Unraveling the molecular basis for crosstalk between signaling pathways will better our understandings of the complicated process of growth regulation in plants.

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