

PERSPECTIVE

F-box proteins regulate ethylene signaling and more

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Ethylene regulates several aspects of plant development, such as fruit ripening. In this issue of *Genes & Development*, Qiao and colleagues (pp. 512–521) report that the stability of the ethylene signaling protein EIN2 is modulated by two F-box proteins ETP1/2, reminiscent of the finding that another regulator of ethylene response, EIN3, is also targeted by the F-box proteins EBF1/2. ETP1/2 and EBF1/2 show distinct phylogenetic patterns, suggesting that they have different evolutionary constraints.

Ethylene is a gaseous molecule that regulates many aspects of plant development and physiology, including seedling development, leaf and flower senescence, fruit ripening, floral sex determination, root hair development, and biotic and abiotic stress responses (Guo and Ecker 2004; Kendrick and Chang 2008; Zhu and Guo 2008). In dark grown *Arabidopsis* seedlings, ethylene induces a characteristic morphological syndrome called triple response, with a shortened and thickened seedling stem called a hypocotyl and an exaggerated apical hook. This morphology allows the seedlings that develop in the soil and without light exposure to overcome the pressure of soil and emerge to the surface. In addition, many fruits, such as bananas and tomatoes, become softened in the presence of ethylene; this property of fruit ripening has been exploited such that fruits can be harvested and transported prior to maturity and then artificially “ripened” near the retailing locations. In cucumber and other members of the melon family, male and female flowers develop from the same immature flowers with primordia for both male and female reproductive organs, the stamens and pistil. Under the influence of ethylene, bisexual immature cucumber flowers undergo programmed cell death in the stamens, resulting in the formation of

female flowers with a functional mature pistil, whereas male flowers form in the absence of ethylene (Trebith et al. 1997; Hao et al. 2003).

Genetic studies have identified a number of key components of the ethylene signaling pathway, including membrane-localized ethylene receptors, a Raf-like protein kinase, MAP kinases (MAPKs) and MAPK kinases (MAPKKs), and transcriptional regulators (Fig. 1; Guo and Ecker 2004; Kendrick and Chang 2008; Zhu and Guo 2008). It has been shown that ethylene inactivates ethylene receptors, such as ETR1 and ETR2, which are redundant negative regulators of ethylene responses (Kendrick and Chang 2008). Dominant mutations in these genes prevent receptors from binding to ethylene, allowing the receptors to function even in the presence of ethylene, whereas recessive loss-of-function mutations in a single receptor gene do not cause obvious defects because of functional redundancy. Plants with recessive mutations in multiple receptor genes exhibit a constitutive ethylene response, indicating that the receptors are indeed negative regulators of the ethylene response. Downstream from the ethylene receptors is the Raf homolog CTR1, which also negatively regulates ethylene response. Recessive mutations in *CTR1* cause a constitutive triple response, and are epistatic to the dominant ethylene-insensitive mutations in the receptor genes. Multiple genes are known to encode MAPKs and MAPKKs in *Arabidopsis* and other plants, and molecular genetic studies support their role in ethylene response, at least in some physiological processes.

Furthermore, early mutant screens uncovered recessive *ein2* and *ein3* mutants, both are insensitive to ethylene (Chao et al. 1997). Both *ein2* and *ein3* mutations are epistatic to the *ctr1* mutation, suggesting that *EIN2* and *EIN3* act downstream from *CTR1* and are important positive regulators of the ethylene response. *EIN3* encodes a transcription factor and has been shown to bind to the primary ethylene response element (ERE) in the promoter region of the ethylene early responsive gene *ERF1* (Solano et al. 1998). *ERF1* and its paralogs are members of the AP2 family of DNA-binding proteins that were initially identified as proteins that bind to the

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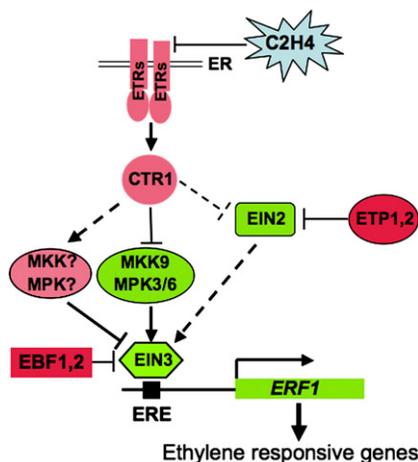


Figure 1. The ethylene signaling pathway and the regulation of its components by F-box proteins. Ethylene is perceived at the endoplasmic reticulum membrane by a family of ethylene receptors (ETRs, including ETR1 and ERS1). In the absence of ethylene, the ethylene receptors activate the RAF-like MAPKK kinase CTR1, which represses ethylene signaling by inhibiting the activity of MKK9-MPK3/6 module and the membrane localized EIN2. In addition, another unknown MAPK module may be activated by CTR1 and phosphorylate the T592 site of EIN3, leading to the degradation of EIN3 mediated through the two F-box proteins EBF1 and EBF2. Ethylene binding to its receptors inhibits the activity of receptors and CTR1, and leads to the activation of the MKK9-MPK3/6 module, which phosphorylates EIN3 on T174, leading to the stabilization and accumulation of EIN3. Then EIN3 enhances the expression of ERF1 through binding to the ERE element of the promoter region of ERF1, which further regulates the expression of ethylene-responsive genes. In the presence of ethylene, EIN2 is activated and promotes ethylene-induced responses through EIN3 using an unknown mechanism. The stability of EIN2 is negatively regulated by the two newly discovered F-box proteins ETP1 and ETP2.

ERE motifs found in promoters of ethylene-induced genes and activate these genes. Therefore, EIN3 and ERFs represent two levels in a transcriptional network for ethylene response.

The *EIN2* gene encodes a membrane protein whose N-terminal region has limited sequence similarity to mammalian metal transporters called NRAMPs (Alonso et al. 1999). The C-terminal region of the EIN2 protein is well conserved in flowering plants and contains ~850 amino acid residues; this region was found to confer constitutive ethylene response in transgenic *Arabidopsis* plants (Varma Penmetsa et al. 2008). Although genetic studies clearly indicated that EIN2 is an important component of the ethylene signaling pathway, it has been unclear how ethylene regulates its activity. In this issue of *Genes & Development*, Qiao et al. (2009) describe results from a comprehensive study that sheds new light on the regulation of EIN2 and ethylene signaling.

Because ethylene regulates the expression of many genes, including *ERFs*, it was reasonable to hypothesize that ethylene might activate *EIN2* transcription. However, Alonso et al. (1999) showed previously that *EIN2*

mRNA levels were not affected by ethylene, suggesting that transcriptional control was not a major mechanism for regulating EIN2. How, then, is ethylene connected to EIN2 activity? Qiao et al. (2009) show that EIN2 is regulated by ethylene at the level of protein stability; EIN2 was found to be unstable and its stability was enhanced by proteasome inhibitors and by ethylene. The amount of EIN2 protein was increased in the *ctr1* mutant, but reduced in the *etr1* mutant, suggesting that EIN2 stability is regulated by known components of the ethylene signaling pathway.

How is the stability of the EIN2 protein controlled? To address this question, Qiao et al. (2009) used the yeast two-hybrid method to search for proteins that interact with EIN2 using its conserved C-terminal region. They found an EIN2-interacting protein (ETP1) that contains an F-box domain; in addition, they showed that a paralog of ETP1, ETP2, also can interact with EIN2. A number of F-box proteins are known to be components of protein ubiquitin ligases called SCF complexes and are important for specifying specific substrates. This suggests that ETP1 and ETP2 might facilitate the ubiquitination of EIN2, thereby regulating its degradation by the proteasome. To test this idea, Qiao et al. (2009) used plants that had altered the function of ETP1 and ETP2, and found that EIN2 accumulated to abnormally high levels in plants with reduced ETP1/2 function and was hardly detectable in plants with elevated ETP1/2 function. Moreover, over-expression of *ETP1* or *ETP2* resulted in a decrease in response to ethylene, whereas reduced ETP1/2 function caused changes in plant morphology and gene expression similar to those induced by ethylene treatment. They also showed that ethylene could induce a reduction of ETP1 and ETP2 protein levels, but had no detectable effect on *ETP1/2* mRNA, suggesting that *ETP1/2* themselves are regulated post-transcriptionally.

In short, Qiao et al. (2009) provided strong genetic and biochemical evidence that the F-box proteins ETP1/2 are important for modulating ethylene signaling, and that they likely regulate EIN2 protein levels by facilitating its ubiquitination. In fact, EIN2 is not the first key mediator of ethylene signaling that is regulated at the level of protein stability and ETP1/2 are not the first F-box proteins found to be important for this process. Previous studies showed that the level of the EIN3 protein, but not EIN3 mRNA, increased following ethylene treatment, indicating that ethylene can stabilize the EIN3 protein (Guo and Ecker 2003). In addition, inhibition of proteasome leads to the accumulation of EIN3, suggesting that EIN3 is degraded by the proteasome (Guo and Ecker 2003). Using the yeast two hybrid method, two EIN3-binding proteins (EBF1 and EBF2) were identified and found to be F-box proteins (Guo and Ecker 2003; Potuschak et al. 2003); moreover, EBF1 and EBF2 can interact with putative SCF subunits ASKs, suggesting that EBF1 and EBF2 are indeed components of SCF complexes (Guo and Ecker 2003; Potuschak et al. 2003; Gagne et al. 2004). Mutations in *EBF1* and *EBF2* lead to accumulation of the EIN3 protein and enhanced ethylene responses (Guo and Ecker 2003; Potuschak et al. 2003; Gagne et al. 2004).

clades include members from *Arabidopsis*, poplar and rice, suggesting that both clades each originated from an ancestral gene in the most recent common ancestor of these three species. Furthermore, the *ETP1/2* clade contains several *Arabidopsis* genes that are closely related to *ETP1/2*, suggesting that they might also play a role in regulating EIN2 stability. The topology of the *ETP1/2* clade also indicates that there have been recent duplications, suggesting that they have evolved more rapidly than the *EBF1/2* genes. At the same time, the putative *ETP1/2* homologous F-box proteins in rice and poplar might be involved in targeting the EIN2 homologs in these plants.

In addition to *EBF1/2* and *ETP1/2*, several other F-box proteins also have been found to control the degradation of key components in other hormonal pathways. In the auxin signaling pathway, a small family of F-box proteins, TIR1 (Transport Inhibitor Response 1) and its paralogs, AFBs (Auxin signaling F-Box proteins), facilitates ubiquitination of key transcription repressors, the AUX/IAA proteins, in an auxin-dependent manner (Dharmasiri et al. 2005a,b; Kepinski and Leyser 2005; Tan et al. 2007), causing their rapid degradation by the proteasome. This releases the inhibitory effect of AUX/IAA on the auxin response factors (ARFs) to promote the expression of auxin-responsive genes (Leyser et al. 1993; Abel et al. 1994; Gray et al. 2001; Guilfoyle and Hagen 2007). Similarly, the receptor COI1 (Coronatine-Insensitive 1) for the plant defense hormone, jasmonic acid (JA) is also an F-box protein (Xie et al. 1998; for review, see Browse 2008). Genetic and biochemical data indicate that jasmonoyl-isoleucine (JA-Ile), the active form of JA, induces the binding of COI1 to the JAZ (Jasmonate ZIM domain) transcriptional repressors, leading to the degradation of the JAZ proteins by the proteasome (Chini et al. 2007; Thines et al. 2007; Katsir et al. 2008). Therefore, both auxin and JA directly bind to F-box proteins and regulate their ability to bind to their substrates, which are repressors of the respective hormone-induced genes.

In the case of the signaling pathway for the hormone gibberellic acid (GA), the regulation is slightly more complex. GA response also involves transcriptional activation, and requires GA-induced degradation of a class of DELLA proteins, which represses GA-activated genes (Schwechheimer 2008), similar to the proteasome-mediated degradation of AUX/IAA and JAZ proteins in the auxin and JA pathways, respectively. The degradation of DELLA proteins is also facilitated by F-box proteins called SLEEPY1 (SLY1) in *Arabidopsis* (McGinnis et al. 2003; Dill et al. 2004) and GID2 in rice (Sasaki et al. 2003). However, the GA hormone does not bind to the F-box proteins directly. Instead, the GA receptor, GID1 is a novel soluble protein (Ueguchi-Tanaka et al. 2005, 2007). The binding of GA to GID1 dramatically enhances the interaction of the F-box protein GID2/SLY1 with DELLA proteins (Griffiths et al. 2006), providing a mechanism for GA induction of DELLA protein degradation. Thus, acting via the GA receptor GID1, GA activates the function of SCF^{SLY1/GID2} to target DELLA proteins for ubiquitin-mediated proteolysis.

The levels of key components of the brassinosteroid signaling pathway, the transcription factors BES1/BZR1—especially the phosphorylated form—are also regulated by the proteasome (He et al. 2002; Wang et al. 2002; Yin et al. 2002). It was reported recently that a negative regulator Brassinosteroid-Insensitive 2 (BIN2) of the brassinosteroid signaling pathway is also regulated by protein degradation (Peng et al. 2008). However, the specific ubiquitin ligases responsible for the degradation of either BES1/ZBR1 or BIN2 have not been identified. Recently, F-box proteins or other ubiquitin ligases have been found to mediate signaling of other hormones, including abscisic acid (Zhang et al. 2005; Stone et al. 2006) and a recently discovered hormone regulating plant branching (Mouchel and Leyser 2007).

Qiao et al. (2009) report new results that demonstrate an important function for F-box proteins in regulating ethylene responses. This represents the latest chapter in a series of discoveries concerning the crucial roles that F-box proteins and the proteasome play in several plant hormonal signaling pathways. From these studies, it is amply clear that regulated protein degradation is a highly effective mechanism for the regulation of signal transduction pathways. In animals, hormonal signaling and transduction of neural transmitters are often mediated by transmembrane receptors and protein kinases, which catalyze reversible changes of proteins, allowing protein activities to be controlled in a transient fashion. This is probably important for rapid animal reactions that are important in a predator and prey relationship. In contrast, plants cannot move and respond to much slower environmental changes by altering developmental programs. It is possible that protein degradation is an effective and stable means of regulating plant signaling processes, which often cause morphological changes over a period of time.

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