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Minireview

Roles of F-box Proteins in Plant Hormone Responses

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Abstract The F-box protein is an important component of the E3 ubiquitin ligase Skp1-Cullin-F-box protein complex. It binds specific substrates for ubiquitin-mediated proteolysis. The F-box proteins contain a signature F-box motif at their amino-terminus and some protein-protein interaction motifs at their carboxy-terminus, such as Trp-Asp repeats or leucine rich repeats. Many F-box proteins have been identified to be involved in plant hormone response as receptors or important medial components. These breakthrough findings shed light on our current understanding of the structure and function of the various F-box proteins, their related plant hormone signaling pathways, and their roles in regulating plant development.

Keywords F-box protein; plant hormone response; SCF complex; ubiquitin proteasome pathway

Plant hormones play pivotal roles in almost every aspect of plant development from embryogenesis to senescence. Plant hormone signaling pathways can be effectively controlled by modulation of positive and negative regulators during plant growth and development [1]. Recent research in plant hormone signaling pathways has shown that the ubiquitin (Ub) proteasome pathway is a central regulatory mechanism in the signal transduction pathways of different plant hormones [2,3]. Remarkably, approximately 1300 genes, or 5% of the *Arabidopsis* proteome genes have been thought to encode components in the Ub proteasome pathway, likely the most elaborate and crucial regulatory system in plants. Molecular genetic analysis has revealed that the Ub proteolytic system is involved in all aspects of plant biology, including embryogenesis, photomorphogenesis, circadian rhythms, senescence, disease resistance, and notably, hormone signaling [4]. The F-box protein is responsible for recruiting different substrates for ubiquitination in this pathway, and nearly 700 F-box proteins have been predicted in *Arabidopsis* [5].

The fact that F-box proteins act as important receptors and signaling components in plant hormone signaling pathways has emerged from physiological and molecular studies on a multitude of signaling mutants [6]. In this review, we focus on recent progresses on the structure and function of F-box proteins, and particularly, the roles of F-box proteins in plant hormonal responses.

F-box Proteins in the Ub Proteasome Pathway

Ub proteasome pathway and Skp1-Cullin-F-box protein (SCF) complex

The Ub proteasome system plays an important role through mediating degradation of some pivotal proteins in numerous cellular and organismal processes [7]. In this pathway, the highly conserved 76-amino acid protein Ub serves as a reusable tag for selective protein breakdown. The Ub conjugation cascade involves three enzyme families, an E1 Ub-activating enzyme, an E2 Ub-conjugating enzyme, and an E3 Ub ligase that ultimately ligates multiple Ubs to its substrates. In the initial reaction, E1 enzyme activates the Ub driven by ATP hydrolysis to form a high-energy thioester intermediate (E1-S~Ub), in which the C-terminal group of Ub is linked through a thiolester bond to the E1. Then, activated Ub is transferred to an E2 enzyme by transesterification. The transfer of Ub from E2-S~Ub to the target protein is mediated by an E3 enzyme. An

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isopeptide bond is formed between the C-terminal group of Ub and the ε-amino group of an internal lysine residue in the substrate. Subsequently, a polyubiquitin chain is synthesized by successively adding Ub moieties to the previously conjugated Ub molecule in which various Ub lysines (e.g., 29, 48, and 63 sites in Ub) as the sites for concatenating additional Ubs [8]. Finally, multi-ubiquitylated proteins are recognized by the 26S proteasome and proteolyzed into peptides, and Ub is recycled [9,10]. The current understanding on the general process of the Ub proteasome pathway is shown in **Fig. 1(A)**. The Ub proteasome system appears to be hierarchical, only two E1 enzymes, at least 45 E2 or E2-like proteins, and almost 1200 E3 components are encoded in the *Arabidopsis* genome [4].

The Ub protein ligases (or E3 enzymes) are in charge of the substrate specificity and fall into different categories, such as HECT (homologous to E6-associated protein carboxyl terminus, which can form a covalent thiolester), APC (anaphase promoting complex), VBC-Cul2 (the von-Hippel Lindau-elongins B and C-Cul2 complex), Ring/U-box, and SCF [11,12]. A major type of E3 Ub ligases, the SCF complex is composed of four major components, Skp1, Cul1/Cdc53, Roc1/Rbx1/Hrt1, and an F-box protein [13,14]. The scaffold protein Cullin-1 interacts with Skp1 and the F-box protein at the amino-terminus and associates with the Ring-domain molecule Roc1/Rbx1/Hrt1 at the carboxyl-terminus, which associates with Ub-conjugated E2 enzyme [**Fig. 1(B)**]. Different substrates are recognized through the carboxyl-terminus of F-box protein and Ub is transferred to the substrate from E2 by mediation of E3 enzyme [12,15]. The *Arabidopsis* genome encodes 11 Cullin homologs, 2 Rbx1 homologs, 21 *Arabidopsis* Skp1 homologs and at least 700 putative F-box proteins [16,17].

Characteristics of F-box proteins

F-box proteins contain a conserved F-box domain (35–60 amino acids) in the amino-terminus and different substrate-binding domains in the carboxy-terminus [18]. The F-box domain was first described as a sequence motif found in human cyclin F by Bai *et al.* [19]. The F-box domain plays a role in mediating protein-protein interactions in a variety of processes, such as polyubiquitination, transcription elongation, centromere binding, and translation repression. In the Ub proteasome pathway, the F-box motif links the F-box protein to other components of the SCF complex by binding the core SCF component Skp1 or Skp1-like proteins. There are very few invariant positions in the F-box motif and it is difficult to spot the F-box motif by eye. In **Fig. 2**, we aligned the F-box motif sequences of several F-box proteins involved in plant hormonal responses. These proteins share some conserved positions, for example position 9 (in this position, the majority of plant F-box proteins have isoleucine or valine), 23 (serine or alanine), 25 (valine), 26 (serine or cysteine), 27 (lysine and arginine), and 29 (tyrosine). The carboxy-terminal part of F-box proteins has been shown to specifically bind to substrates. These regions of F-box proteins contain leucine-rich repeats (LRRs) and Trp-Asp repeats [20,21], but the majority of F-box proteins have unknown association motifs, and the functions of most of these proteins have not been defined yet. The diversity of protein-

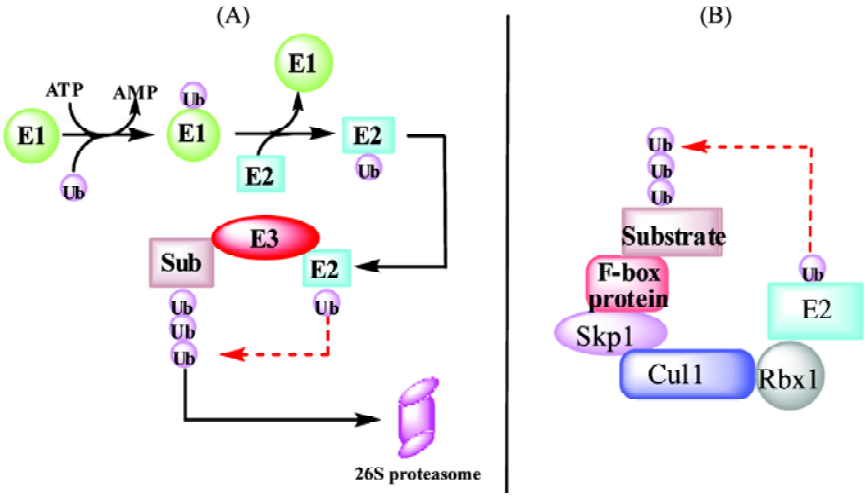

Fig. 1 Ubiquitin (Ub) proteasome pathway (A) and structure of Skp1-Cullin-F-box complex (B)
Red arrows indicate the process of Ub transfer from E2 Ub-conjugating enzyme to substrate (Sub). E1, Ub-activating enzyme; E3, Ub ligase.

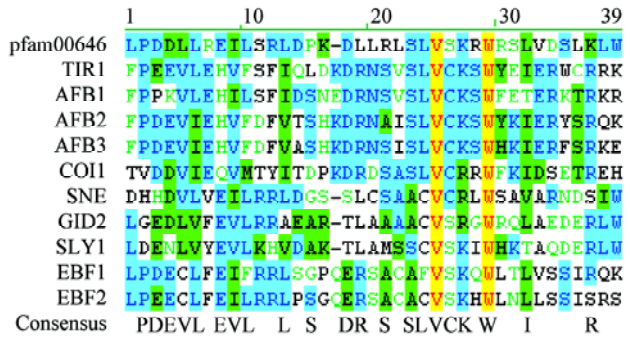

Fig. 2 Alignment of F-box motif sequences

Pfam00646 domain and F-box domains of 10 F-box proteins have been aligned and the single-letter amino acid code is used. Identities, similarities, and conservatives among the different proteins are highlighted in yellow, green, and blue, respectively. Consensus residues are denoted at the bottom of the alignment. Pfam00646 domain is taken from Pfam (http://www.ncbi.nlm.nih.gov/Class/Structure/pssm/pssm_viewer.cgi?cd=pfam00646&mode=Position). AFB, auxin-signaling F-box protein; COI, coronatine insensitive; EBF, ethylene insensitive 3-binding F-box protein; GID, gibberellin-insensitive dwarf; SLY, SLEEPY; SNE, SNEEZY; TIR, transport inhibitor response.

protein interaction domains of F-box proteins substantially increases the substrate repertoire.

F-box Proteins Involved in Plant Hormone Responses

F-box protein transport inhibitor response 1 (TIR1) is an auxin receptor

Auxin tightly regulates many plant growth and developmental processes throughout the life cycle [22], and its receptor has been found. The F-box protein TIR1 is an auxin receptor in *Arabidopsis thaliana* [23,24]. In addition, the auxin signaling F-box proteins 1, 2 and 3 (AFB 1–3) have displayed *in vitro* as auxin-dependent Aux/IAA proteins (Aux/IAAs) binding similar to TIR1 and contributed to auxin responsiveness *in vivo* [25]. TIR1 protein consists of an N-terminal F-box motif, a short spacer region of approximately 40 residues, 16 degenerate LRRs, and a C-terminal tail of approximately 70 residues [23].

In the auxin signaling pathway, two closely related protein families, Aux/IAAs and auxin response factors (ARFs), are key regulators in auxin-modulated gene expression [26]. The Aux/IAA genes encode short-lived, primary auxin response proteins [27], whereas ARFs are transcription factors that bind specifically to promoters of primary auxin response genes [28]. IAA proteins can form heterodimers with ARFs and negatively regulate the transcriptional activation activity of the ARF proteins through their potent repressor domains [29]. Auxin promotes Aux/IAAs ubiquitination by SCFTIR1, triggering their degradation by 26S proteosome, thereby releasing the ARFs from the repressive effects of the Aux/IAAs [3, 7]. ARF-ARF dimers are formed and mediate rapid auxin-induced gene expression [**Fig. 3(A)**].

Two research groups have revealed that an auxin receptor co-purifies with TIR1 by immunoprecipitation of TIR1, and by using a protein pull-down assay with tagged Aux/IAAs, that the interaction between SCF^{TIR1} and Aux/IAAs involves direct auxin binding [23,24]. They proved that tritiated IAA ([^{3}H]IAA) binds to the SCF^{TIR1} complex rather than to Aux/IAAs, using the radiolabeled method, and the apparent dissociation constant Kd should be within the range of 20–80 nM. To testify the fact that TIR1 binds auxin directly, the *TIR1* gene from *Arabidopsis* was expressed in *Xenopus laevis* oocytes and insect cells, then the TIR1 reacted to [^{3}H]IAA and the interaction curve of TIR1 and [^{3}H]IAA accorded with the characteristics of receptor-ligand association. Afterward, the Myc-tagged TIR1 protein was treated with auxin and mixed with GST-tagged Aux/IAA protein. It proved that the TIR1-Aux/IAAs interaction depended on auxin and the ability of interaction was enhanced with the increased dosage of IAA in a limited concentration range. Recently, the crystal structure of TIR1 has been presented and shows that the LRR domain of TIR1 contains an unexpected inositol hexakisphosphate co-factor and recognizes auxin and the Aux/IAAs polypeptide substrate through a single surface pocket. By filling in a hydrophobic cavity at the protein interface, auxin enhances the TIR1-substrate interactions by acting as a "molecular glue" [30].

F-box proteins involved in gibberellin signaling

Gibberellins are tetracyclic diterpenoid hormones that induce a wide range of plant growth responses including seed germination, hypocotyl elongation, stem elongation, leaf expansion, pollen maturation, and induction of flowering [31]. The F-box proteins SLEEPY1 (SLY1) and SNEEZY (SNE) can regulate the gibberellin signaling pathway in *Arabidopsis* [32–34] and gibberellin-insensitive dwarf 2 (GID2) in *Oryza sativa* [35]. Mutations in both the *SLY1* gene in *Arabidopsis* (*AtSLY1*) and the *GID2* gene in *O. sativa* (*OsGID2*) result in a recessive, gibberellin-insensitive dwarfed phenotype and the accumulation of DELLA proteins. AtSLY1 and OsGID2 amino acid sequences are 36.8% identical and 56% similar to each other. The high levels of homology and correspondence of function between dicot and monocot species indicate

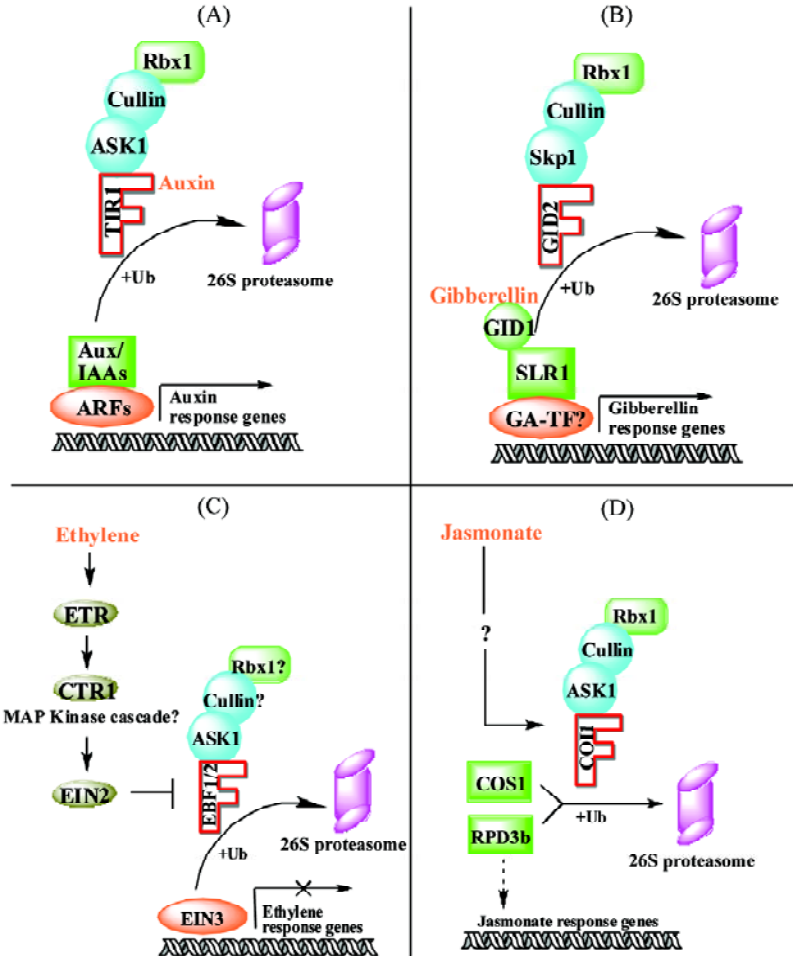

Fig. 3 Roles of F-box proteins in plant hormone response

(A) Transport inhibitor response 1 (TIR1) in auxin (Aux) signaling response. (B) Gibberellin-insensitive dwarf 2 (GID2) in gibberellin signaling response. (C) Ethylene insensitive 3 (EIN3)-binding F-box protein (EBF)1/2 in ethylene signaling response. (D) Coronatine insensitive 1 (COI1) in jasmonate signaling response. ARF, auxin response factor; ASK, *Arabidopsis* SKP1-LIKE; COS1, COI1 suppressor 1; CTR1, CONSTITUTIVE TIPLE RESPONSE 1; ETR, ethylene response; IAA, indole-3-acetic acid; MAP, mitogen-activated protein; RPD3b, histone deacetylase; Skp1, S-phase kinase-associated protein 1; SLR1, SLENDER RICE1; Ub, ubiquitin.

that the role of the $SCF^{AtSLY1/OsGID2}$ complex is highly conserved in the plant kingdom [36].

Significant progress has been made in understanding the gibberellin signaling pathway in rice and many components have been identified, for example, the receptor GID1 (a soluble receptor for gibberellin) [37], GID2 (an F-box protein) [36], and the negative regulator SLR1 (a DELLA protein) [38]. DELLA proteins negatively function in the gibberellin signaling cascade as pivotal regulators [39,40]. GID1 physically interacts with SLR1 in a gibberellin-dependent manner and induces phosphorylation of SLR1 [41]. The F-box protein GID2 directly interacts with the phosphorylated SLR1, bringing it to the SCF^{GID2} complex for ubiquitination, and subsequent degradation through the 26S proteasome [35]. But recent results suggested that phosphorylation of SLR1 was not needed when GID1 triggered association of active SLR1 with the SCF^{GID2} complex in a gibberellin-dependent manner [42]. Disappearance of the DELLA protein releases its suppression of gibberellin signaling and promotes transcription of the gibberellin response genes [**Fig. 3(B)**]. In *Arabidopsis*, the DELLA family has five members (GAI, RGA, RGL1, RGL2, and RGL3) [41]. Similar to GID2 in rice, SLY1 interacts with DELLA proteins for controlling gibberellin response in *Arabidopsis* [34]. There is an interesting parallel between the auxin and gibberellin response because both appear to induce rapid degradation of the negative regulator by interaction with the SCF complex.

Both OsGID2 and AtSLY1 contain three conserved

domains, the F-box, GGF, and LSL domains. In addition to these domains, GID2 has a unique N-terminal variable region (VR1) [32]. All the conserved domains are essential for the function of GID2 except the VR1. Gomi *et al*. carried out a yeast two-hybrid screen and revealed that GID2 associated with rice OsSkp15 and OsCul1 to assemble the SCF complex. RNA gel blot analysis and reverse transcription-polymerase chain reaction assay of the *GID2* gene in different rice organs revealed that *GID2* was expressed in all organs examined, with higher levels in elongation stem, shoot apex, and unopened flower, and lower levels in the leaf blade, leaf sheath, root, and rachis. This expression pattern coincided with the locations in which gibberellin is actively produced. An *in vitro* binding assay showed that GID2 specifically interacted with the phosphorylated SLR1 protein but not with the unphosphorylated one [41].

Roles of F-box proteins in ethylene signaling

The phytohormone ethylene is a gaseous hydrocarbon molecule that can trigger a wide range of physiological and morphological responses, including inhibition of cell expansion, promotion of leaf and flower senescence, induction of fruit ripening and abscission, and adaptation to external stress factors [43]. In the signaling pathway of ethylene, two *Arabidopsis* F-box proteins, ethylene insensitive 3 (EIN3)-binding F-box protein 1 (EBF1) and EBF2, target the transcriptional activator EIN3 for degradation [44–46]. Mutation in either gene shows enhanced ethylene response by stabilizing EIN3, whereas *efb1* and *efb2* double mutants show constitutive ethylene phenotypes. Plants overexpressing either F-box gene display ethylene insensitivity and destabilization of EIN3 protein. These results indicate that the Ub proteasome pathway negatively regulates ethylene responses by targeting EIN3 for degradation [44].

Genetic studies have identified several components of the ethylene signaling pathway, including the receptor family ETR1 (ETHYLENE RESPONSE), ETR2, ERS1 (ETHYLENE RESPONSE SENSOR), ERS2, and EIN4, and other components CTR1 (CONSTITUTIVE TRIPLE RESPONSE 1), EIN2, and EIN3 [47]. *Arabidopsis* EIN3 protein is a key transcription factor that modulates ethylene-regulated gene expression and morphological responses [48], which is expressed constitutively and acts on its target promoters only upon perception of ethylene. In the absence of ethylene, EIN3 is ubiquitinated by the SCFEBF1/2 complex, and degraded by the 26S proteasome [**Fig. 3(C)**]. In the presence of ethylene, EIN2 prevents EIN3 from being ubiquitinated by SCFEBF1/2, leading to EIN3 accumulation and the activation of ethylene-response gene expression [44,45]. It is worth noting that EIN3 is degraded in ethylene signaling as a transcription activator, differing from Aux/IAA and DELLA proteins in responses to auxin and gibberellin as repressors.

Coronatine insensitive 1 (COI1): pivotal regulator in jasmonate signaling

Jasmonates (JAs), including jasmonic acid and its cyclopentanone derivatives, are essential plant hormones that are involved in the regulation of many physiological and developmental processes, including root growth, fruit ripening, senescence, pollen development, and adaptation to environmental stresses [49,50]. The F-box protein COI1 is a pivotal factor in the JA signal response [**Fig. 3(D)**] and is required for all JA-dependent responses in *Arabidopsis* [19,51]. The *coi1* mutant is male sterile, less resistant to insect attack, and less responsive to wounding damage [52]. The COI1 protein has an F-box motif and 16 LRRs that selectively recruit regulators of JA response for polyubiquination and proteolysis [19]. COI1 has been shown to form a functional E3-type Ub ligase complex. Moreover, plants that are deficient in other components of SCF complexes also show impaired JA responses [16, 53]. Thus, SCF^{COI1} is a central component of all JA-dependent responses, the activity of which is presumably modulated by several Ub proteasome pathway genes (e. g., *AXR1*, *SGT1b*, and *CSN*) that are also involved in the modulation of other SCF complexes [54]. It has been suggested that SCF^{COI1} is associated with the COP9 signalosome *in vivo* to mediate JA responses together [55].

Putative targets of COI1 have been identified and their functional analysis will be instrumental to furthering our understanding of the molecular mechanisms that regulate JA responses [56,57]. Using a two-hybrid strategy, researchers have identified RPD3b, a histone deacetylase, as a COI1 target [56]. Because histone deacetylation is believed to decrease the accessibility of chromatin to the transcription machinery [58], COI1-dependent proteasome degradation of RPD3b would be a probable mechanism for derepression of JA-dependent transcription. Another putative target of COI1 is COS1. The mutant *cos1* has been identified as a suppressor of *coi1* mutant, restoring some JA-regulated responses, such as root growth, senescence, and defense [57]. COS1 encodes lumazine synthase, and lumazine is a key component of the riboflavin pathway, which suggests the involvement of this pathway in the modulation of JA signaling. By analogy, COI1, the closest F-box protein to TIR1 in the *Arabidopsis* genome, could be the JA receptor. Certainly, further research on

JA signaling responses will clarify this point and extend our understanding of the JA signaling response.

F-box proteins in other plant responses

So far we have discussed F-box proteins involved in plant hormone response and their related signal transduction pathways individually. Many F-box proteins have also been identified in plants that are involved in other cellular and organismal processes. These F-box proteins include: the proteins regulating lateral root formation, such as MAX2 [59], ARABIDILLO-1/2 [60], and CEGENDUO [61]; in light signaling, such as EMPFINDLICHER IM DUNKELROTEN LICHT (EID1) [62], ATTENUATED FAR-RED RESPONSE (AFR) [63]; in the circadian system, such as ZEITLUPE (ZTL) [64], LOV KELCH PROTEIN2 (LKP2), FLAVIN-BINDING, KELCH-REPEAT, F-box1 (FKF1) [65]; influencing self-incompatibility, such as AhSLF-S2 [66]; and controlling floral development, such as UNUSUAL FLORAL ORGANS (UFO) and FIMBRIATA (FIM) [67]. F-box proteins might also participate in stress response and regulation of leaf senescence ORE9 [68] in plants. Given the large number of F-box proteins in the plant kingdom, we can envision that more F-box proteins will be found involved in other plant processes.

Conclusions and Prospects

Recent research in plant hormone responses has enhanced our two major understandings. First, plant hormone signaling pathways are a series of complex networks and these networks often cross-talk with each other. Second, Ub-mediated protein degradation is a central regulatory mechanism involving many different hormonal pathways. F-box proteins play crucial roles in the ubiquitination system by specifically recruiting target regulatory proteins to the Ub complex. Although considerable progresses have been made in understanding the roles of F-box proteins in plant hormone responses, great challenges remain in deciphering the mechanisms of each F-box protein that regulates plant hormone responses. We are of the opinion that the following questions regarding F-box proteins and plant hormone signaling transduction should be taken into account in the future and will be resolved gradually.

Genomic analysis has indicated a large number of uncharacterized F-box proteins in plants, and there are many questions about these proteins. For example, how can we obtain and characterize the corresponding mutants of unknown F-box proteins? What are the target substrates for the putative F-box proteins in plants? What are the biological functions of these predicted plant F-box proteins? These questions remain to be intriguing issues within the field of protein degradation. On the encouraging side, methods of genetic mutant and reversed genetics are available for studying these genes. Different screens can be used for physiological and molecular characterization of mutants. The related genes can be cloned using Map-based cloning or insertion of T-DNA. The functions of the genes can be analyzed by combining techniques of functional genomics and proteomics. Microarray technique can help us comprehend the change in genes after transcription and identify the unknown genes. New high-throughput gene expression analysis techniques and system-wide approaches will also be important in investigating these questions.

In the SCF complex, the F-box motif binds to Skp1 or Skp1-like proteins, however, so far there is no evidence of F-box proteins binding to other types of proteins. Whether there are other F-box-binding proteins remains as an interesting question.

The F-box protein family is the largest protein superfamily. Much research has focused on the model plants *A. thaliana* or *O. sativa* that help us best understand the processes involved in hormonal perception. F-box protein research on other plant species is relatively weak. Our laboratory is currently studying F-box proteins in *Gossypium hirsutum* and we believe that many important F-box proteins involved in hormone signaling responses in cotton will be identified in the near future.

Overall, we are still far from having an integrated picture of F-box protein functional repertory. Searching the new F-box proteins in the plant kingdom and determining the functions of these uncharacterized F-box proteins will prove to be an important area of future research.

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