Short title: Ubiquitin ligases in phytohormone signaling

Structural Aspects of Plant Hormone Signal Perception and Regulation by Ubiquitin Ligases

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One-sentence summary: An analysis of structural aspects of plant hormone sensing mechanisms by Ub ligases, and current understanding of the emerging field of strigolactone signaling.

Author contributions: All authors participated in writing the paper.
Summary
Hormonal cues regulate many aspects of plant growth and development, facilitating the plant’s ability to systemically respond to environmental changes. Elucidating the molecular mechanisms governing these signaling pathways is crucial to understanding how plants function. Structural and functional biology methods have been essential in decoding plant genetic findings and revealing precise molecular actions at the protein level. Past studies of plant hormone signaling have uncovered mechanisms that involve highly coordinated protein turnover to elicit immediate cellular responses. Many phytohormone signaling pathways rely on the ubiquitin (Ub) proteasome system, specifically E3 Ub ligases, for perception and initiation of signaling transduction. In this review, we highlight structural aspects of plant hormone-sensing mechanisms by Ub ligases and discuss our current understanding of the emerging field of strigolactone signaling.
Historically, the study of plants has greatly advanced human knowledge. Numerous scientific landmarks were first discovered in plants including the laws of genetic heredity, cytogenetics, RNA interference, transposable elements, and the identification of the first virus. (Mendel, 1865; Vines, 1880; Beijerinck, 1898; McClintock, 1984; van der Krol et al., 1990; Napoli et al., 1990)

Similarly, proteins extracted from plant tissues laid the foundations of protein crystallography. In 1926, J. B. Sumner used Jack beans (Canavalia ensiformis) to isolate and crystalize, for the first time, the protein Urease (Sumner, 1926). In addition to revealing the first protein crystals, Sumner’s work also provided the very first evidence that enzymes are proteins. In the era of x-ray crystallography and high-resolution single particle electron microscopy, determining three-dimensional protein structures in atomic detail has become the ultimate tool to decrypt the molecular mechanism of biological pathways. Despite the advances made in structural biology methodologies, the percentages of plant protein structures deposited in Protein Data Bank (PDB) has remained remarkably low compared to other kingdoms of life (Berman, 2000). Nevertheless, the past decade has witnessed groundbreaking structure-function studies in plants. These studies have had a significant impact on our understanding of fundamental biological processes, including photomorphogenesis, immune responses, and, in particular, phytohormone signaling pathways.

Plants maintain the ability to respond to environmental changes by altering growth patterns and varying developmental outcomes. This plasticity is attributed to the ability of plants to translate the environmental input into a systemic signal using a diverse range of molecular instruments, orchestrated by phytohormones. Many important genetic studies have identified the distinct key players of hormonal signaling cascades. The recent integration of structural biology with plant genetics has uncovered molecular mechanisms through which a small molecule can facilitate protein-protein interactions and trigger the transduction of a signal into a developmental outcome.

Phytohormones comprise a set of structurally unrelated small organic compounds. Notably, most phytohormone signaling pathways are tightly regulated by a highly coordinated intracellular protein degradation machine known as the ubiquitin-proteasome system (UPS, see Box. 1). The specificity of UPS is conferred by the action of a family of E3 ubiquitin ligase enzymes that target specific proteins for destruction in a timely manner (Hershko and Ciechanover, 1998; Zheng and Shabek, 2017). Plants have utilized this machinery multiple times.
across evolution to achieve time-dependent activation of a signaling pathway upon phytohormone perception. In this review, we focus on and outline the structural aspects of plant hormone perception by the UPS, and detail the contribution of these findings to our understanding of signaling at the molecular level. We also discuss the current view and recent advances in the emerging field of strigolactone (SL) signaling.

**Perception and signaling by ubiquitin ligases**

The first line of phytohormone perception involves distinct intracellular protein receptors that evolved to sense and respond to extremely low concentrations of these naturally-occurring chemical signals. By leveraging the structurally diverse low molecular weight of these small molecules, phytohormones were proposed to facilitate selective protein-protein interaction and subsequently initiate a sequence of signaling cascades. Notably, Cullin-RING Ligases (CRLs), one of the prevalent E3 ligase superfamilies, were found to function as sensing centers in plant hormone perception and signaling (Vierstra, 2009; Shabek and Zheng, 2014). Cullin1, one of the CUL1–4 subtypes, serves as a large scaffold module with a C-terminal portion that interacts with the E2-recruiting RING domain (RBX1) and an N-terminal portion that binds the interchangeable substrate-receptor F-box protein via SKP1/ASK1 to form the functional ligase multi-subunit SCF (Skp1-Cullin1-F-box, see Box. 1 and Figure 1). To better illustrate the molecular basis of phytohormone signaling cascade, we divided the receptors into two main modes of actions: direct interaction enhancers (molecular glues) and allosteric effectors. The perception mechanism of auxin and jasmonates (JAs) operates as molecular glue as the presence of these phytohormones enhances the interactions between the F-box receptors and their target proteins. On the other hand, gibberellins (GAs) and SLs act as allosteric effectors by inducing conformational changes in their receptors to regulate downstream interactions with F-box proteins. This review focuses on the contribution of E3 ligases as direct or allosteric receptors; however, a dominant role of the UPS in downstream parts of the signaling cascade was documented for several other hormones, such as ethylene, cytokinin (CK) (Kim et al., 2013; Lee and Seo, 2015; Chen et al., 2018), and multiple components of abscisic acid (ABA) signaling, as reviewed in Yu et al. (2016).

**Auxins and JAs as “molecular glues”**
Auxin and JAs were the first hormones shown to be perceived by the F-box protein TIR1 (TRANSPORT INHIBITOR RESPONSE 1) (Ruegger et al., 1998; Dharmasiri et al., 2005; Kepinski and Leyser, 2005) and COI1 (CORONATINE INSENSITIVE1) (Feys et al., 1994; Xie et al., 1998; Katsir et al., 2008), respectively. Extensive genetic and biochemical studies prior to any structural insight on the pathways showed that auxin and JAs induce the rapid degradation of distinct families of co-repressors Aux/IAA (Auxin/INDOLE-3-ACETIC ACID) (Abel et al., 1994; Gray et al., 2001; Tiwari et al., 2001) and JAZ (JASMONATE ZIM DOMAIN) (Chini et al., 2007; Yan et al., 2007), which is followed by subsequent transcriptional activation of hormone-responsive genes.

The groundbreaking revelation of TIR1-Aux/IAA (Tan et al., 2007) and COI1-JAZ (Sheard et al., 2010) crystal structures illuminated the molecular basis for the perception of these phytohormones. These structural studies uncovered a new mechanism of ligand perception in which hormones act as “molecular glue” in macromolecular assembly. In the case of auxin, auxin docking to the bottom of TIR1 (via a side-chain carboxyl group and an indole ring) creates a modified surface that stabilizes its interaction with Aux/IAAs, leading to their polyubiquitination and degradation. TIR1 and COI1 are structurally similar to horseshoe-shaped LRR domains followed by F-box domain bound to ASK1 adaptor (Figure 1). The top surfaces of the TIR1- and COI1-LRR domains form a shallow pocket that binds both the hormone and the target substrate (Aux/IAA or JAZ). A short recognition motif (degron) within Aux/IAAs directly engages with auxin-loaded TIR1 and sandwiches auxin in the middle (Figure 1A). Similarly, JAZ degrons interact with COI1 to ensure high-affinity hormone binding. The JAZ degron covers the opening where JA-Ile binds and traps the hormone in the pocket (Figure 1B). Interestingly, both structures revealed the presence of secondary small molecule metabolites at the hormone perception site, inositol hexakisphosphate (InsP₆) in TIR1 and inositol pentakisphosphate (InspP₅) in COI1. These co-factors directly interact with the hormone-binding pocket and potentiate the hormone-receptor-substrate interaction.

The structural studies of the auxin and JA pathways were instrumental in improving our understanding of hormonal cues and transcriptional regulation. Aux/IAAs and JAZs participate in transcriptional repressive complexes containing transcription factors like ARFs (AUXIN RESPONSE FACTOR) for auxin and MYC for JA, adaptor proteins like NINJA (NOVEL...
INTERACTOR OF JAZ) for JAs, and corepressors like TOPELESS (TPL) for both phytohormones (Lorenzo et al., 2004; Szemenyei et al., 2008; Pauwels et al., 2010). Crystal data of the NINJA-TPL interaction uncovered the molecular basis of protein interactions with TPL through their ethylene response factor-associated amphiphilic repression (EAR) motifs (Ke et al., 2015). Crystallographic data of ARFs alone (Boer et al., 2014) or complexed with Aux/IAAs (Nanao et al., 2014) revealed the structural foundations of oligomerization of auxin transcriptional repressors, whereas the structure of MYC3 (Zhang et al., 2015) was the first illustration of non-complexed MYC transcription activation domain. These are selected examples that illustrate the value of adding crystallographic data to the fields of plant development and physiology. Efforts to understand transcriptional repressive complexes at the biochemical and structural level of other hormones are necessary to gain a full appreciation of the complexity of hormone-dependent transcriptional regulation.

GAs and SLs as allosteric activators

Unlike TIR1 and COI1, the GA and SL receptors are not F-box proteins themselves. The GA receptor GID1 (GIBBERELLIN INSENSITIVE DWARF 1) and the SL receptor D14 (DWARF 14) are α/β hydrolases that associate with F-box proteins in a hormone-dependent manner to recognize substrate proteins for ubiquitination and degradation. In contrast to the “molecular glue” mechanism, GAs and SLs induce conformational changes in their receptors that enable them to interact with their respective F-box proteins (Figure 2). GID1 is a soluble protein (Ueguchi-Tanaka et al., 2005) that has structural similarity to hormone-sensitive lipases (HSLs) involved in lipid metabolism in animals (Yeaman, 2004). Perception of GA by GID1 induces conformational changes in the enzyme that enable it to interact with the SCF-type E3 Ub ligase AtSLEEPY1 (SLY1)/AtSNEEZY (SNZ)/OsGID2 (SCF<sub>GID2/SLY1</sub>) to ubiquitinate and degrade DELLA transcriptional regulators, including GIBBERELLIN INSENSITIVE (GAI1) (Peng et al., 1997; Fu et al., 2002; McGinnis et al., 2003; Sasaki et al., 2003; Ueguchi-Tanaka et al., 2007).

The mechanism by which GA is recognized by GID1 was elucidated by the crystal structures of GA-bound GID1 in both free and DELLA-associated forms (Murase et al., 2008; Shimada et al., 2008). GAI1 is a monomeric protein composed of one α/β core hydrolase (albeit with a
nonfunctional catalytic triad) (Ueguchi-Tanaka et al., 2005) and a unique N-terminal extension that folds back over the GA-bound pocket upon hormone perception and covers it like a lid (Figure 2A). This process creates binding surfaces for the N-terminal DELLA domain of GAI1. Binding of this region to GID1 induces its coil-to-helix conformational transition, which in turn affects the structure of the C-terminal GRAS domain of the same protein. Mediated by the GRAS domain, the GID1-GA-DELLA complex is then recognized by the SCF$^{\text{GID2/SLY1}}$ for ubiquitination and degradation of the DELLAs by the UPS. The structure of a GRAS domain has been recently solved in the non-DELLA protein SCARECROW-LIKE 7 (SCL7) (Li et al., 2016). However, determining the structure of the GID1-GA-DELLA complex with SCF$^{\text{GID2/SLY1}}$ will further our understanding of the GA signaling core regulatory mechanism.

The most recently identified phytohormone, SL, represents yet another new perception and signaling paradigm wherein both the F-box protein, namely MAX2/D3 (MORE AXILLARY BRANCHES2 / DWARF3), and the SL receptor $\alpha/\beta$-hydrolase, namely D14 (DWARF14), have multiple functional states. Similar to GA perception, SL does not function as molecular glue in the interface between the receptor and the E3 ligase. Unlike GID1, the D14 is an active hydrolase that slowly metabolizes SL into non-bioactive products. Here, D14 forms a SL-dependent complex with SCF-MAX2/D3 and recruits D53 (DWARF53, rice; Oryza sativa) or SMXL6/7/8 (SUPPRESSOR OF MAX2 LIKE, Arabidopsis) for ubiquitination and rapid proteasomal degradation. The dynamic state of SL perception, hydrolysis, and signaling is biologically intriguing yet perplexing. The following part of this review will discuss our current understanding of SL perception and regulation.

**SL perception by the UPS and downstream signaling**

SLs were first identified as germination stimulants of the parasitic witchweed *Striga hermonthica*, following their isolation from cotton (*Gossypium hirsutum*) root exudates in 1966 (Cook et al., 1966). Since 1966, researchers have characterized a variety of SLs as well as a diversity of functions of the SL molecule(s). SLs function exogenously to initiate symbiosis with mycorrhizal fungi and incidentally stimulate germination of parasitic plants (Akiyama et al., 2005). Whereas SLs function endogenously and regulate many aspects of growth and development, they are notoriously known to inhibit shoot branching (Gomez-Roldan et al., 2008;
Umehara et al., 2008). Before the SL receptor was identified, MAX2 was first recognized as a protein involved in SL-related pathways (Stirnberg et al., 2002; Stirnberg et al., 2007; Gomez-Roldan et al., 2008). Mutant max2 plants presented phenotypes similar to SL synthesis mutants (Stirnberg et al., 2002; Booker et al., 2005; Ishikawa et al., 2005; Gomez-Roldan et al., 2008); however, unlike these mutants, max2 phenotypes could not be rescued with SL treatment, pointing to MAX2 involvement in SL signaling (Umehara et al., 2008). MAX2 encodes an F-box E3 ubiquitin ligase that targets its substrates for selective protein degradation. Thus, at the birth of the field it was apparent that like auxin, JA, SA, and GA signaling pathways, the SL signaling cascade was dependent on regulated turnover via the UPS.

Later, the SL receptor protein was first identified via its mutant characterized by an increased shoot branching phenotype (Arite et al., 2009). Multiple groups provided evidence that an α/β hydrolase such as D14 was responsible, and in fact later showed that D14 is the receptor of SL (Arite et al., 2009; Hamiaux et al., 2012; Waters et al., 2012; de Saint Germain et al., 2016). The SL receptor is remarkable because it serves as both a receptor as well as an enzyme, capable of hydrolyzing its ligand SL (Hamiaux et al., 2012; Waters et al., 2012; Zhao et al., 2013; Abe et al., 2014; Waters et al., 2015; de Saint Germain et al., 2016; Shahul Hameed et al., 2018; Yao et al., 2018; Bürger et al., 2019). The sought-after degradation targets of the MAX2-D14 complex were characterized in 2013 using the rice mutant d53 that shows increased branching and SL-insensitivity phenotypes. D53 encodes a protein that shares a similar secondary structure composition to proteins of the class I Clp ATPase family (Jiang et al., 2013; Zhou et al., 2013). D53/SMXLs contain a transcriptional repressor EAR motif and are rapidly degraded in response to D14-MAX2-dependent SL treatment (Zhou et al., 2013; Soundappan et al., 2015; Wang et al., 2015; Liang et al., 2016). Unlike in other phytohormone signaling cascades, the exact function and the specific transcriptional targets of D53/SMXLs remain largely unknown (Song et al., 2017).

**SL perception and hydrolysis by D14**

Structural biology has become a promising tool in understanding the function, specificity, and complexity of the D14-SL perception mechanism. The crystal structures of D14 have been determined for Arabidopsis, rice (Kagiyama et al., 2013; Zhao et al., 2013), striga (Xu et al.,
2018), and petunia (*Petunia hybrida*; Hamiaux et al., 2012). These structures reveal a common
α/β hydrolase fold with a deep pocket that is formed by a V-shaped lid composed of four α-
helices. The D14 pocket contains a canonical serine catalytic triad that is conserved across plant
species, indicating that the protein hydrolase activity was maintained throughout evolution
(Bythell-Douglas et al., 2017). Notably, the pocket is widely open to solvent, and several crystal
structures have claimed to capture synthetic SL analogs or byproducts bound to D14 (Jiang et al.,
2013; Nakamura et al., 2013; Zhao et al., 2013; Zhao et al., 2015; Takeuchi et al., 2018).
Whereas it has been biochemically demonstrated that the binding pocket can accommodate SL
for hydrolysis, it is less clear whether any of the D14 structures are able to capture the ligand at
atomic resolution. Because of the low occupancy and poor electron density of SL analogs in all
D14 crystal structures, the precise position and topography of SL has remained considerably
elusive (Carlsson et al., 2018).

One of the major questions in the SL field is centered on SL hydrolysis and its necessity to
propagate SL signaling. Much of the consensus was driven by the idea that hydrolysis of SL
conferred a conformational change in D14, thus providing an interfacing ability with SCF-
MAX2 Ub ligase (de Saint Germain et al., 2016; Yao et al., 2016). However, the requirement of
hydrolysis was challenged by a recent study showing that D14 catalysis mutants are able to bind
SL, but not hydrolyze it, and rescue the d14 mutant phenotype in a SL-dependent manner. This
implies that SL binding (not hydrolysis) is necessary for initiating the signaling cascade (Seto et
al., 2019). Additionally, the distinct states of intact SL binding and SL hydrolysis may confer
different signals. In this model, one state is important for D14-MAX2 to create an interface for
SMXLs, and another for the release or degradation of D14 and/or deactivation of the SL
molecule. Nonetheless, in all these cases, it is the Ub ligase MAX2 that directs the rate of SL
hydrolysis, the interactions, and the proteasomal degradation of D14 and SMXLs.

*SL regulation by the Ub ligase SCF-MAX2/D3*

Protein structures containing the complex of D14-D3 (D3, rice ortholog of MAX2) indicate an
even more intriguing level of complexity and regulation at the level of the Ub ligase. It was
shown that D14 undergoes a great conformational change when complexed with D3, presumably
post SL hydrolysis (Yao et al., 2016). This finding was strongly supported by the identification
of a SL-hydrolysis covalently linked intermediate molecule (CLIM), and by the fact that D14 is a single turnover enzyme (or very slowly releases SL products in vitro) (de Saint Germain et al., 2016; Yao et al., 2016). Given that D14 is also targeted for degradation by MAX2 (Chevalier et al., 2014), it is unclear whether the D14_{CLIM}-D3 complex recapitulates the effective interface to recruit SMXLs or simply targets the receptor to reset signaling.

A recent study reported another mode of action that is centered around the conformational state of the Ub ligase (Shabek et al., 2018). It has been shown that MAX2/D3 exists in multiple functional states highlighted by a flexible, highly conserved C-terminal alpha helix domain (CTH). The CTH, which is the last LRR repeat within the horseshoe structure, can be either open (dislodged) or closed (engaged). The dislodged D3-CTH can directly bind D14-SL, and this interaction results in allosteric inhibition of SL hydrolysis (Figure 2B). It was also proposed that the dislodged form provides an interface to enable the recruitment of D53/SMXLs and their subsequent ubiquitination and degradation (Shabek et al., 2018). Before D53/SMXLs are released to the proteasome, the transient interaction with D3 alters D14 inhibition and slowly restores SL hydrolysis. The restored activity can successively reset the SL signal by both depleting SL and degrading the D14 receptor until the next environmental cue. Taken together, the mode of perception and signaling cascade of SL is likely dynamic and complex and may differ molecularly from other characterized phytohormone signaling pathways.

**Concluding remarks**

The study of phytohormone perception and signaling cascades illustrates the importance of complementary genetic and structural biology methods. Integration of data from both disciplines overcomes their individual limitations and leads to a holistic understanding of molecular processes. In this review, we described various structural studies outlining how plants utilize the UPS to perceive hormonal triggers and activate signaling cascades. Hormone perception followed by protein complex formation is a dynamic, multifaceted process, and an x-ray crystallography approach may recapitulate a single energetically favored state of the protein machinery. Thus, comprehensive understanding of the molecular action of Ub ligase complexes in plant hormone biology remains a great challenge that is technically difficult to recapitulate at atomic resolution. For example, considering the gaseous phytohormone ethylene, the structure
function of its perception mechanism is currently unresolved although its signaling components are well known. The contribution of structural biology to plant biology has been immense and likely to provide answers to many unresolved questions (see Outstanding Questions). Whereas x-ray crystallography has remained the favorable approach to determine Ub ligase function in hormone signaling, this method relies heavily on minimum protein flexibility and maximum ability to be organized in a rigid and specific pattern. This notion can explain why most published structures were recapitulated using only portion of the complex components (AUX/IAA, JAZ, SLY). The emerging method of single particle cryo-electron microscopy holds promise to resolve the long-standing challenges of dynamic full-length complete protein complexes in plant hormone biology.

Acknowledgements
N.S is supported by UC Davis College of Biological Sciences Start-Up Funds. L.T is supported by BARD, the United States - Israel Binational Agricultural Research and Development Fund, Vaadia-BARD Postdoctoral Fellowship Award FI-559-2017. We apologize to those colleagues whose work was not cited due to space constraints.

Figure legends

Figure 1. Structural models of direct phytohormone perception and target recognition by E3 Ub ligase receptors. SCF\textsuperscript{TIR1} (A), and SCF\textsuperscript{COI} (B) mediating AUX/IAA and JAZ ubiquitination and degradation, respectively. Auxin and Ja-Ile (Jasmonic Acid – Isoleucine) are directly perceived by F-box receptors (TIR1 and COI1, respectively) and this results in an altered interface that recruits substrate for ubiquitination and degradation. In the SCF (SKP1-CUL1-F-box) complex, Cullin1 serves as a scaffold that binds RBX1 (RING protein, required for E2-Ub recruitment) \textit{via} its C-terminal, and ASK1/SKP1 (F-box adaptor protein) \textit{via} its N-terminal. (i) Molecular surface of TIR1 (PDB: 2P1Q) and COI1 (PDB: 3OGL) crystal structures are modeled with CUL1-RBX1 (PDB: 1LDK). (ii) Phytohormone recognition interface between F-box LRR (Leucine Rich Repeat) and the target substrate recognition element (degron). Detailed amino acid side chain interactions with auxin (A) and JA (B) are shown in the small framed windows.
(iii) Model of phytohormone signaling mechanism. All colored texts are consistent with colored structural elements. Ubiquitination is denoted U.

**Figure 2. Structural models of allosteric regulation of phytohormone perception and signaling by E3 Ub ligases.** (A) Crystal structure of gibberellin (GA) perception complex (based on PDB: 2ZSI) contains GA3, GID1A, and the DELLA domain of GAI. (i) Molecular surface of GID1A N-terminal extension (N-Ex, labeled in violet) and its core (labeled in blue). Helices of GAI DELLA (labeled green) are represented as cylinders. (ii) Recognition interface between GID1-GA and DELLA, shown in detail by ribbon representation. Small framed window represents detailed amino acid side chain interfaces. (iii) Model for GA perception and signaling. GA binding induces a conformational change in the N-Ex of GID1 and promotes an interaction with the DELLA domain. Subsequently, GID1-GA-DELLA can be recognized and ubiquitinated (U) by SCF\textsuperscript{SLY}. (B) (i–ii) Molecular surface representation of ASK1-D3 complex and C-terminal helix (CTH, light blue) dislodged. D14, the SL receptor (labeled in green; SL in magenta), is bound to D3-CTH (light blue) in an open conformation and can perceive SL. Crystals structures are modified from Shabek et al. (2018) (based on PDB: 6BRO and 6BRT). (iii–iv) Molecular surface representation of ASK1-D3-D14 complex in a closed conformation (modified from Yao et al. (2016); based on PDB: 5HZG). (C) Model of SL signaling. (i) D3/MAX2 binds D14, the SL receptor, via D3’s CTH. (ii) This interaction results in an allosteric inhibition of SL hydrolysis, allowing sufficient time to recruit and ubiquitinate (U) D53/SMXL’s transcriptional repressors. (iii) Targeting of D53 through SCF\textsuperscript{D3} triggers a conformational change in D3 and D14 that results in SL hydrolysis by D14 and a butenolide-bound intermediate (CLIM, small magenta triangle). D14 is subsequently ubiquitinated by D3 and recycled and/or degraded to reset the signal.
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BOX 1. The Ubiquitin Proteasome System (UPS)

The UPS plays a crucial role in virtually every aspect of plant growth and development including the cell-cycle, defense, environmental responses, and hormone signaling. In this pathway, ubiquitin (Ub) is covalently attached to target proteins through the action of three enzymes: E1 (Ub-activating enzyme), E2 (Ub-carrier enzyme), and E3 (Ub ligase) (Hershko and Ciechanover, 1998). The result of Ub modification depends on the type and/or extent of polyubiquitination that either regulates substrate function or targets them for destruction by the 26S proteasome (Zheng and Shabek, 2017). In the Arabidopsis genome, over 1,000 genes encode components related to the UPS. Most of these genes are E3 ligases that provide specificity by directly facilitating the transfer of Ub to the target substrate. The diversity of plant E3 Ub ligases can be classified into various families according to their distinct complex composition and modes of action. One of the largest gene families in Arabidopsis encodes the F-box subunits of multi-subunit Skp1-Cullin1-F-box (SCF) E3s, which are considerably more abundant in plants compared to mammals (Vierstra, 2009; Shabek and Zheng, 2014).
ADVANCES

- Structural biology has provided important contributions to our understanding of the molecular mechanisms that control plant hormone perception and signaling.
- The last decade has revealed that the ubiquitin proteasome system, and E3 Ub ligases in particular, play central roles in the regulation of various plant signaling pathways.
- The growing field of strigolactone (SL) signaling has been greatly advanced by biochemical and structural biology studies, in particular by elucidating the intriguing complexity of SL perception mechanism.
OUTSTANDING QUESTIONS

• What are the mechanisms, structure, and function of the Ub system in the perception and downstream signaling cascades for all phytohormones?
• What is the sequence of events of strigolactone (SL) perception and signaling, in particular how exactly does the Ub ligase MAX2/D3 target its substrate D53/SMXLs, and how is the complex assembly coordinated with SL perception and hydrolysis by D14?
• How does the perception machinery distinguish among structurally diverse SL molecules and propagate a specific physiological response?
• How is D3/MAX2 Ub ligase activated? What are the specific biological conditions that trigger its conformational change?
• What are the transcriptional outputs elicited by degradation of D53/SMXLs?
• SL is a known facilitator of plant-mycorrhizal symbiosis; what are the identities and structure of fungi SL receptors?
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