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CURRENT PERSPECTIVE ESSAY

A Receptor for Auxin

A long-sought hormone receptor has been found. Two recent *Nature* articles reveal that the F-box protein TRANSPORT INHIBITOR RESPONSE1 (TIR1) binds auxin and responds to the phytohormone even when heterologously expressed in animal systems (Dharmasiri et al., 2005a; Kepinski and Leyser, 2005). The road to the identification of an auxin receptor has been long and circuitous, leading down dark and sometimes blind alleys before arriving back at a protein known for nearly a decade.

Auxin is a vital hormone that regulates many aspects of plant development. Experiments conducted in the late 1800s examining growth responses to light and gravity led to the hypothesis that these tropisms are regulated by an endogenous substance later termed auxin. The responsible molecule was identified as indole-3-acetic acid (IAA) in the 1930s (reviewed in Woodward and Bartel, 2005). Since then, a fundamental goal of auxin research has been the identification of an auxin receptor.

BIOCHEMICAL SEARCH FOR THE RECEPTOR

The direct approach to receptor identification was biochemical. In the 1980s, isolation of auxin binding plant proteins revealed receptor candidates including Auxin Binding Protein1 (ABP1), which influences certain cellular responses to auxin (reviewed in Jones et al., 1998). Furthermore, ABP1 is essential for early embryonic development (Chen et al., 2001), reflecting an importance to the plant that one might expect of an auxin receptor. However, the molecular activity of ABP1 has remained elusive, and proteins interacting with ABP1 have not been identified, making it difficult to classify ABP1 definitively as a receptor.

RAPID TRANSCRIPTIONAL RESPONSES TO AUXIN

Meanwhile, molecular biologists were studying transcriptional responses to auxin. Levels of certain transcripts are dramatically induced only minutes after auxin application (Walker and Key, 1982; Hagen et al., 1984; Theologis et al., 1985), suggesting that whatever the identity of the receptor, one of its primary tasks would be to regulate specific transcriptional targets. A conserved auxin-responsive element was identified in the promoter region of many auxin-induced genes (reviewed in Hagen and Guilfoyle, 2002), paving the way to the identification of the proteins that proximally mediate these transcriptional responses to auxin.

Indeed, a family of AUXIN RESPONSE FACTOR (ARF) proteins was found to interact with an auxin-responsive promoter sequence (Ulmasov et al., 1997a). ARF proteins either promote or inhibit target gene expression (Ulmasov et al., 1999). Closing the transcriptional loop, a class of auxin-induced genes encodes Auxin/IAA (Aux/IAA) proteins that can directly bind activating ARF proteins (Kim et al., 1997) and thereby inhibit transcription of ARF-induced genes (Ulmasov et al., 1997b; Tiwari et al., 2001, 2004). These Aux/IAA inhibitors are short-lived proteins (Abel et al., 1994), and the Aux/IAA degradation rate is increased by auxin (Gray et al., 2001; Zenser et al., 2001).

GENETIC SEARCH FOR THE RECEPTOR

With the advent of facile genetic screens and positional cloning in *Arabidopsis*, geneticists joined in the hunt for the auxin receptor. It was reasonable to expect that receptor defects might be found among mutants with reduced response to a phytohormone. For example, one of the first characterized ethylene response mutants, *etr1* (Bleeker et al., 1988), defined an ethylene receptor (Chang et al., 1993; Schaller and Bleecker, 1995), validating the genetic receptor hunt.

In the 1980s, genetic screens to identify players in auxin response by isolating *Arabidopsis* mutants resistant to the inhibitory effects of auxin or auxin analogs on root elongation were initiated (Maher and Martindale, 1980; Estelle and Somerville, 1987). However, the first such gene cloned, *AUXIN RESISTANT1* (*AXR1*), encoded not an auxin receptor, but rather a protein related to ubiquitin activating enzymes (Leyser et al., 1993), suggesting that proteolysis might play a prominent role in auxin responses. Other auxin response mutants were defective in potential auxin signaling mediators that were proteolytic targets. For example, both *axr2* and *axr3* carried gain-of-function mutations in *Aux/IAA* genes (Rouse et al., 1998; Nagpal et al., 2000), which typically encode unstable proteins (Abel et al., 1994). This type of dominant mutation was found to stabilize the Aux/IAA auxin response repressors (Worley et al., 2000; Ramos et al., 2001).

A role for TIR1 in auxin response was first described nearly a decade ago. As the name *transport inhibitor response* suggests, *tir1* was isolated in a screen for mutants resistant to compounds that inhibit polar auxin transport, rather than direct auxin resistance (Ruegger et al., 1997). However, subsequent phenotypic analysis revealed reduced lateral root proliferation and resistance to root elongation inhibition by the synthetic auxin-like molecule 2,4-D, indicating generally compromised auxin responses (Ruegger et al., 1998).

TIR1 contains an F-box domain, suggesting involvement in ubiquitin-mediated protein degradation (Ruegger et al., 1998). F-box proteins determine substrate specificity of Skp1/Cullin/F-box (SCF) complexes that ubiquitinate target proteins, marking them as substrates for proteasomal degradation. F-box proteins are found throughout eukaryotes, and *Arabidopsis* contains almost 700 of these proteins (Gagne et al., 2002). The F-box domain mediates interaction with the SCF complex via the SKP1/ASK subunit. Proteins bearing an F-box motif often have one of many

CURRENT PERSPECTIVE ESSAY

categories of other conserved domains, often implicated in protein–protein interactions (Gagne et al., 2002); presumably, some of these motifs mediate substrate interaction. Thus, F-box proteins tether condemned proteins to the SCF to allow ubiquitination and ultimately, degradation.

By the turn of the century, an outline was coming into focus: auxin promotes Aux/IAA ubiquitination by SCF^{TIR1}, triggering Aux/IAA proteasomal degradation, thereby freeing activating ARFs from the repressive effects of the Aux/IAA proteins and allowing them to promote the transcription of auxin-induced genes (Figure 1). But what connected auxin, the Aux/IAA repressors, and SCF^{TIR1}, and where was the receptor?

BACK TO BIOCHEMISTRY

Because the Aux/IAA repressors are degraded in response to auxin and the F-box motif implicated TIR1 in ubiquitination, the geneticists turned to biochemistry to uncover any direct linkage between TIR1 and Aux/IAA proteins. Indeed, TIR1 binds to Aux/IAA proteins in cell-free extracts (Gray et al., 2001). Most remarkably, auxin promotes the TIR1–Aux/IAA interaction (Gray et al., 2001). Moreover, domain II, one of four regions conserved among Aux/IAA proteins, is sufficient to confer auxin-accelerated degradation to an artificial fusion protein in vivo (Zenser et al., 2001). This same region is mutated in gain-of-function *Aux/IAA* mutations that confer auxin resistance (Rouse et al., 1998; Nagpal et al., 2000; Rogg et al., 2001; Fukaki et al., 2002), and these mutations disrupt in vitro TIR1–Aux/IAA interaction (Gray et al., 2001). As proper degradation of Aux/IAA proteins was necessary for auxin response, and this in vivo degradation was correlated with TIR1 binding to Aux/IAA proteins in vitro, auxin-dependent TIR1 binding to Aux/IAA proteins became the proxy for auxin response in the hunt for the receptor (Dharmasiri et al., 2003). The auxin receptor was alive and well in the test tube; all that remained was to find it.

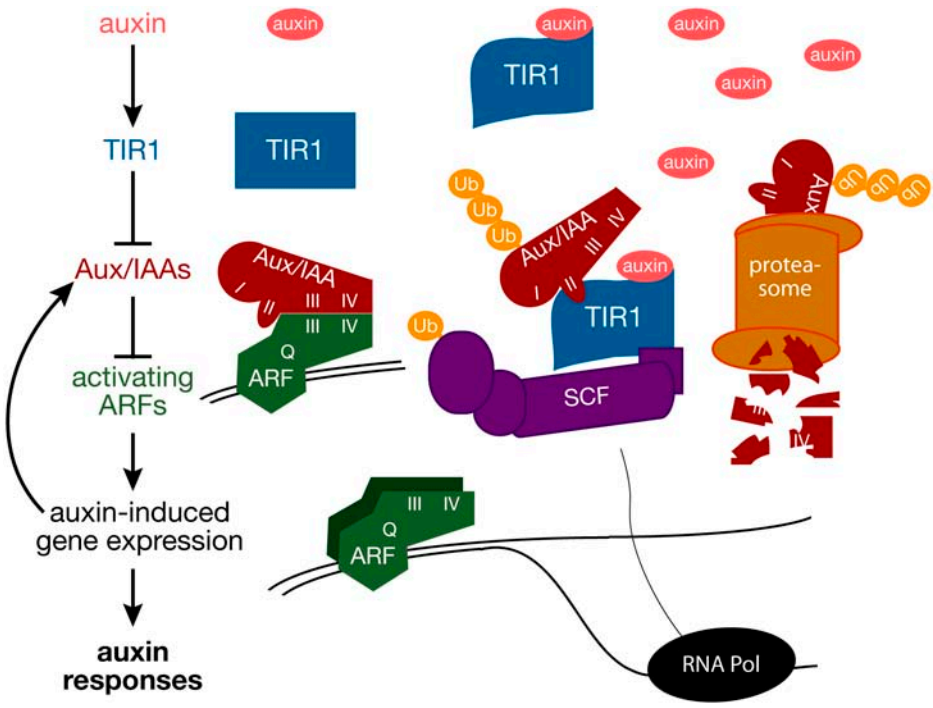

Figure 1. A Model for Auxin Response through the TIR1 Auxin Receptor Pathway.

Transcriptionally activating ARFs (green) with Gln-rich (Q) middle regions are bound to auxin-responsive promoter elements but are counteracted (blunt arrows) by heterodimerization with Aux/IAA transcriptional repressors (dark red) via two domains (III and IV) conserved between ARF and Aux/IAA proteins. Auxin (pink) binds to TIR1 (blue) or a TIR1-Aux/IAA complex to promote or stabilize TIR1-Aux/IAA domain II interaction. TIR1 tethers the Aux/IAA protein to an SCF complex (purple) that is thought to catalyze attachment of multiple ubiquitin (Ub) moieties to the Aux/IAA target protein. The ubiquitinated Aux/IAA protein is then degraded by the 26S proteasome (orange). Increased Aux/IAA degradation in response to auxin frees the activating ARF proteins from repression, allowing auxin-responsive transcription. Among the auxin-induced transcripts are those encoding the Aux/IAA repressors themselves, creating a negative feedback regulatory system. See text for references.

Various signals can alter SCF-mediated degradation of target proteins, classically by introducing or removing a modification, such as phosphorylation, to render targets more or less susceptible to SCF interaction (Deshaies, 1999). Thus, one hypothesis to be tested was that auxin led to Aux/IAA phosphorylation or other modification, which promoted affinity of these proteins for TIR1. However, Aux/IAA domain II remains unstable even when lacking phosphorylatable esidues (Ramos et al., 2001). In fact, Aux/IAA domain II is not covalently modified in response to auxin in any detectable way (Kepinski and Leyser, 2004). These data suggested that auxin acts by a novel mechanism. The simplest explanation would be that auxin directly or indirectly modulates TIR1 instead of a TIR1 substrate.

Finally, the last piece snapped into place with the demonstration that the TIR1-Aux/IAA complex itself appears to bind auxin directly (Dharmasiri et al., 2005a; Kepinski and Leyser, 2005). Because TIR1 is the only plant-derived component necessary for auxin-induced interaction with an Aux/IAA protein in two different metazoan systems, it seems that TIR1 is an auxin receptor (Dharmasiri et al., 2005a; Kepinski and Leyser, 2005). Moreover, radiolabeled IAA is pulled down with the SCF^{TIR1}-Aux/IAA complex formed in plant extracts (Dharmasiri et al., 2005a). In fact, radiolabeled IAA is pulled down with the TIR1-Aux/IAA domain II complex even when TIR1 is expressed in a heterologous metazoan system (Kepinski and Leyser, 2005). Because residual auxin binding to the Aux/IAA protein alone is

nonspecific (Dharmasiri et al., 2005a; Kepinski and Leyser, 2005), and because TIR1 and the Aux/IAA protein are the only plant-derived proteins in the heterologous systems, TIR1 itself is likely to be responsible for auxin binding (Figure 1). Indeed, auxin pretreatment of TIR1, but not an Aux/IAA protein alone, enhances subsequent TIR1-Aux/IAA interaction in vitro (Kepinski and Leyser, 2004). However, it is possible that auxin binds to the TIR1-Aux/IAA interface, or that domain II of the Aux/IAA protein achieves specificity for auxin binding only when complexed with TIR1. It remains to be demonstrated whether TIR1 can bind auxin in the absence of Aux/IAA proteins.

If TIR1 is an auxin receptor, then why is the *tir1* phenotype so weak? Although auxin responses are muted in *tir1* (Ruegger et al., 1998), they are certainly not abolished and do not approach those of certain gain-of-function *Aux/IAA* mutants or loss-of-function *ARF* mutants (reviewed in Woodward and Bartel, 2005). It appears that genetic redundancy is the answer. TIR1 is one of six closely related F-box proteins, and a quadruple *tir1 afb1 afb2 afb3* mutant has less auxin binding capacity than *tir1* alone (Dharmasiri et al., 2005a). Moreover, the AUXIN SIGNALING F-BOX (AFB) proteins display in vitro auxin-dependent Aux/IAA binding similar to TIR1 and contribute to auxin responsiveness in vivo (Dharmasiri et al., 2005b). Progressive inactivation of the four genes progressively diminishes auxin responses; the quadruple mutant displays a range of phenotypes indicative of reduced auxin responses. Growth of the most severely affected individuals arrests after germination with a single cotyledon and no root (Dharmasiri et al., 2005b), phenocopying *monopteros*, a loss-of-function *ARF* mutant (Berleth and Jürgens, 1993), and *bodenlos*, a gain-of-function *Aux/IAA* mutant (Hamann et al., 2002). Less severely affected *tir1 afb1 afb2 afb3* individuals develop into extremely stunted plants with multiple developmental defects that almost completely lack transcriptional and bioassay auxin responses (Dharmasiri et al., 2005b). Thus, TIR1, AFB1, AFB2, and AFB3 appear to function as auxin receptors that together are necessary for many *Arabidopsis* auxin responses; two additional AFB-like F-box proteins remain to be characterized.

TIR1: ONE OF MANY?

Plant research has revealed a new type of receptor, the F-box protein, that allows an appealingly short signal transduction chain from stimulus to response. Intriguingly, another clade of plant F-box proteins may include photon receptors. The *Arabidopsis* flavin binding kelch-repeat F-box protein FKF1 and the related ZEITLUPE protein (Nelson et al., 2000; Somers et al., 2000) mediate circadian degradation of clock-controlled proteins in response to light (Imaizumi et al., 2003, 2005; Más et al., 2003). Like TIR1, these proteins could act as receptors, in this case directly sensing light and causing SCF-mediated degradation of target proteins.

The F-box protein class may include currently unrecognized receptors for other ligands, both orphan and undiscovered. Of immediate interest are, of course, other hormones that lack established receptors but for which F-box proteins have been genetically implicated in hormone responsiveness. For example, the CORONATINE INSENSITIVE1 (COI1) F-box protein is necessary for response to the plant hormone jasmonic acid (Xie et al., 1998). It is particularly intriguing that COI1 is closely related to TIR1 and the AFB proteins. Because jasmonic acid is a carboxylic acid structurally similar to auxin, and COI1 is structurally similar to auxin receptors, it is tempting to speculate that COI1 might serve as a jasmonic acid receptor. Future research will doubtless test the ability of COI1 to bind jasmonic acid and may be facilitated by identification of presumed COI1 target proteins.

Another receptorless hormone is gibberellin. The related F-box proteins SLEEPY and SNEEZY mediate responses to gibberellin by targeting DELLA repressors for degradation (McGinnis et al., 2003; Strader et al., 2004). Although SLEEPY and SNEEZY are in a different clade and lack the Leu-rich repeats present in TIR1 and COI1, it will be interesting to learn how close these gibberellin signaling F-box proteins are to a gibberellin receptor. Moreover, as F-box proteins are found outside the plant lineage, it is possible that F-box protein receptors await discovery in other eukaryotes.

FUTURE PROSPECTS

An auxin receptor has been found, but many critical questions remain unanswered. First, what are the molecular details of auxin binding—where is the binding site and how does the structure change upon hormone binding to facilitate Aux/IAA interaction? Furthermore, how have TIR1 and the AFB proteins divided the labor of targeting various Aux/IAA proteins and binding to different auxins in different tissues? How are these receptors transcriptionally and posttranscriptionally regulated? The promoters of these genes are active in most or all cells (Dharmasiri et al., 2005b), but the functional expression domains may be constrained by miR393, a microRNA that negatively regulates *TIR1* and the *AFB* transcripts (Jones-Rhoades and Bartel, 2004; Sunkar and Zhu, 2004).

Of course, TIR1 and the AFB proteins may not be the only auxin receptors. Other auxin binding proteins, such as ABP1, might mediate certain cellular responses to auxin. Some changes occur too quickly following auxin exposure to result from a transcriptional mechanism such as that manipulated by SCF^{TIR1}. Any auxin responses remaining in plants lacking functional *TIR1* and *AFB* genes would indicate the presence of additional auxin receptors. More generally, what aspects of the cellular environment does auxin modulate to achieve diverse developmental effects? Furthermore, auxin metabolism is complex, apparently involving layered redundancy that is only beginning to be explored (reviewed in Woodward and Bartel, 2005), and the in vitro auxin receptor assay will allow more definitive discrimination of potentially active auxins from auxin precursors and catabolites. In the continuing quest for fuller understanding of auxin action, future vistas will be enhanced by the recognition of an auxin receptor in the landscape.

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CURRENT PERSPECTIVE ESSAY

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Andrew W. Woodward
Department of Biochemistry and Cell Biology
Rice University
Houston, TX 77005

Bonnie Bartel
Department of Biochemistry and Cell Biology
Rice University
Houston, TX 77005
bartel@rice.edu

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