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REVIEW PAPER

Tuning the auxin transcriptional response

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Abstract

How does auxin provoke such a diverse array of responses? This long-standing question is further complicated by a remarkably short nuclear auxin signalling pathway. To crack the auxin code, several potential sources of specificity need to be evaluated. These include: specificity of interactions among the core auxin response components, specificity resulting from higher order complex dynamics, and specificity in interactions with global factors controlling protein turnover and transcriptional repression. Here, we review recent progress towards characterizing and quantifying these interactions and highlight key gaps that remain.

Key words: ARF, Aux/IAA, E3 ubiquitin ligase, phytohormones, TIR1, transcriptional repression.

Introduction

The central role of auxin in shaping plant form is made possible by context-specific responses. Cell type, developmental stage, and environment all contribute to striking differences in auxin responses, yet the many transcriptional effects of auxin rely on the same small repertoire of signalling components: receptors [TRANSPORT INHIBITOR RESPONSE1/AUXIN SIGNALING F-BOXES (TIR1/AFBs)], repressors [Auxin/INDOLE-3-ACETIC ACID (Aux/IAAs)], and transcription factors [AUXIN RESPONSE FACTORS (ARFs)]. The transmission of an auxin signal relies on interactions between these three components that comprise the core auxin signalling module. Formation of an ARF–Aux/IAA heterodimer results in repression of ARF target genes. This repression is relieved by the degradation of Aux/IAA following its auxin-induced association with a TIR1/AFB receptor. Given the large sizes of the protein families to which these components belong, it is tempting to speculate that particular combinations of signalling component family members confer auxin response specificity (Lokerse and Weijers, 2009; De Smet *et al.*, 2010; Stewart and Nemhauser, 2010; Rademacher *et al.*, 2012). For such a model to work, an auxin response module would need to be tuned to different auxin input properties and be able to deliver different transcriptional outputs. One likely source for varied input/output properties is differential interactions amongst the core auxin signalling components. Current models of auxin signalling are caught between the competing priorities of simplicity and capturing the most influential parameters. A key to improving these models, and to understanding the auxin code, will be the ability to rigorously quantify and rank the importance of each interaction within the auxin network. Here, we review what is currently known about differences between family members of the components that make up the auxin response complex, as well as areas of potential differences in their interactions outside of the core module (Fig. 1).

Abbreviations: APC/C, anaphase-promoting complex; ARFs, AUXIN RESPONSE FACTORS; Aux/IAAs, Auxin/INDOLE-3-ACETIC ACID; AXR1, AUXIN RESISTANT 1; CAND1, CULLIN-ASSOCIATED AND NEDDYLATION DISASSOCIATED 1; CSN, CONSTITUTIVE PHOTOMORPHOGENIC9 (COP9) SIGNALOSOME; CUL1, cullin-1; EAR, ethylene response factor-associated amphiphilic repression; ECR1, E1 C-terminal related 1; HDAC, histone deacetylase; IκB, nuclear factor-κB inhibitor; LUG, LEUNIG; NF-κB, nuclear factor-κB; NO, nitric oxide; RCE1, RUB1 CONJUGATING ENZYME 1; RUB, related to ubiquitin 1/neural precursor cell expressed developmentally down-regulated protein 8; SCF, Skp1-Cullin-F-box; TIR1/AFBs, TRANSPORT INHIBITOR RESPONSE1/AUXIN SIGNALING F-BOXES; TPR, TOPLESS-related protein; β-TrCP, β-transducin repeat-containing protein.

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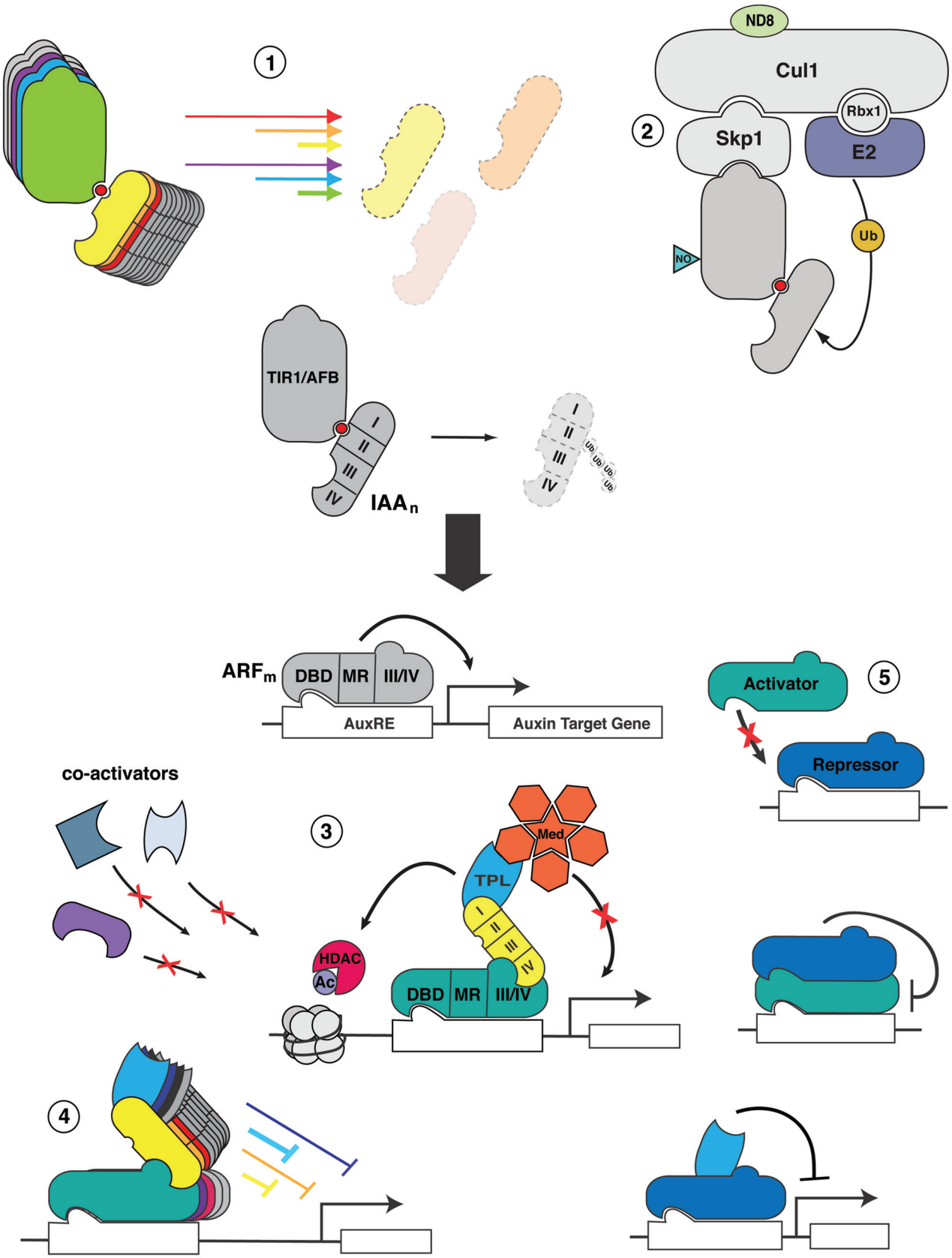

Fig. 1. Tuning the auxin response module. The activity of the auxin response module is governed by interactions between a core set of proteins: auxin receptors (TIR1/AFBs), repressors (Aux/IAAs), and transcription factors (ARFs). The basic mechanism of auxin signalling is depicted centrally in grey: the Aux/IAAs interact with the TIR1/AFBs in an auxin-dependent manner, leading to the ubiquitination and subsequent degradation of the Aux/IAA, which promotes the activity of the ARF transcription factors on auxin target genes. Modulation

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The TIR1/AFB receptor family

In *Arabidopsis thaliana*, there are three ancient lineages within the AFB family of auxin receptors. Each lineage is represented by pairs of genes: TIR1 and AFB1; AFB2 and AFB3; and AFB4 and AFB5 (a fourth lineage found in angiosperms was lost in *Brassicaceae* and *Poaceae*) (Parry *et al*., 2009). Genetic studies have revealed that the two dominant auxin receptors in plants are TIR1 and AFB2, although they are not functionally equivalent (Dharmasiri *et al*., 2005b; Parry *et al*., 2009). Biochemical studies have demonstrated auxin-induced, dose-dependent interactions of AFB2 and TIR1 with several Aux/IAAs (Gray *et al*., 2001; Dharmasiri *et al*., 2005a; Kepinski and Leyser, 2005; Parry *et al*., 2009; Calderón Villalobos *et al*., 2012). Both proteins have highly similar auxin-binding and Aux/IAA interaction domains (Tan *et al*., 2007). Despite this high degree of similarity, AFB2 degrades Aux/IAAs faster than TIR1 in a yeast degradation assay (Havens *et al*., 2012).

The role of the other AFB family members in the auxin response is less clear. Single *afb1* or *afb3* loss-of-function mutants have only subtle phenotypes, although they can enhance phenotypes of *tir1* and *afb2* mutants (Dharmasiri *et al*., 2005*b*; Parry *et al*., 2009). This is consistent with the weaker interactions observed between AFB1 or AFB3 and Aux/IAAs in yeast two-hybrid or *in vitro* pull-down assays (Parry *et al*., 2009; Calderón Villalobos *et al*., 2012). *afb4* and *afb5* mutants were identified in screens for resistance to the synthetic auxin herbicide picloram (Walsh *et al*., 2006), and later shown to function as auxin receptors *in vitro* (Greenham *et al*., 2011). AFB5 binds picloram with much higher affinity than TIR1, probably as a result of amino acid substitutions within the auxin-binding pocket (Calderón Villalobos *et al*., 2012). Initial AFB4 loss-of-function studies revealed growth defects consistent with auxin hypersensitivity, leading the authors to hypothesize that AFB4 might act as a negative regulator of auxin signalling (Greenham *et al*., 2011). However, more recent studies indicate that AFB4 acts similarly to other AFB family members (Hu *et al*., 2012). Future experiments are needed to determine whether any differences in biochemical properties among AFBs contribute to specificity in auxin binding or response dynamics.

Post-translational modification of TIR1, as well as other components of the larger SCF (Skp1-Cullin-F-box) E3 ubiquitin ligase complex, is a potential additional layer of regulation. Recently, TIR1 has been shown to undergo *S*-nitrosylation, a nitric oxide (NO)-mediated protein modification (Terrile *et al*., 2012). *S*-Nitrosylation enhanced TIR1 association with Aux/IAAs, and a mutant TIR1 protein lacking a putative *S*-nitrosylation site was unable to restore auxin sensitivity when expressed in a *tir1* mutant. Additionally, SCF complex assembly and activity can be regulated through ubiquitin-related protein RUB/NEDD8 post-translational modification of the CUL1 scaffold protein (reviewed in Duda *et al*., 2011; Hua and Vierstra, 2011). In plants, mutants in several proteins involved in RUB/NEDD8 conjugation (e.g. AXR1, ECR1, and RCE1) show strong auxin resistance phenotypes (Cheng *et al*., 2004; Mockaitis and Estelle, 2008). NEDD8 modification of CUL1 is further regulated by the complex interplay of de-neddylation by the CSN [CONSTITUTIVE PHOTOMORPHOGENIC9 (COP9) SIGNALOSOME] and the inhibitory protein CAND1 (CULLIN-ASSOCIATED AND NEDDYLATION DISASSOCIATED 1); however, *csn* and *cand1* mutant plants display more subtle and complex auxin phenotypes (Gusmaroli *et al*., 2007; Stuttmann *et al*., 2009; Dohmann *et al*., 2010). While CSN and CAND1 are required for proper SCF–TIR1 function, the molecular basis of this regulation remains to be firmly established. Recent *in vitro* experiments have suggested that the F-box identity and substrate binding can also impact neddylation of the SCF (Emberley *et al*., 2012; Enchev *et al*., 2012). Together, these data suggest that the SCF complex can be regulated by post-translational modification at several levels that can influence the efficacy of F-box function and, in turn, the transmission of an auxin signal.

The Aux/IAA co-repressor family

The diversity of Aux/IAA-related phenotypes and the size of the family suggest that Aux/IAAs are excellent candidates for providing specificity in auxin responses (Lokerse and Weijers, 2009). Most Aux/IAAs have four domains thought to act modularly to confer: auxin-induced degradation through interaction with TIR1/AFBs (DII), dimerization with the ARFs and other IAAs (DIII and DIV), and transcriptional repression through the recruitment of co-repressors (DI). The interactions at each of these domains

of these interactions has the potential to fine-tune the output of the auxin response. (1) The timing and degree of auxin-induced Aux/IAA degradation can be influenced by the particular combination of TIR1/AFBs and Aux/IAAs present in a cell. (2) The auxin co-receptor is part of a larger E3 ubiquitin ligase complex whose activity can be regulated by several post-translational modifications and by interaction with E2 ubiquitin-conjugating enzymes. (3) When auxin levels are low, activator ARFs dimerize with Aux/IAAs, which in turn recruit the TOPLESS (TPL) co-repressors to inhibit transcriptional activity of the target gene. Though the mechanism of TPL repression is largely unknown, TPL probably recruits HDACs to remodel chromatin at auxin target genes and/or blocks recruitment of co-activators and the Mediator complex. (4) Differential and specific interactions between the various members of the ARF, Aux/IAA, and TPL families may also contribute to the dynamics of auxin transcriptional responses. (5) Much less is known about how repressor ARFs function, though it is speculated that they may block binding of activator ARFs, dimerize with and inhibit activator ARFs, and/or directly recruit co-repressors to target genes. ND8, NEDD8; Cul1, cullin 1; Rbx1, RING-box protein 1; Ub, ubiquitin; NO, nitric oxide; DBD, DNA-binding domain; MR, middle region; HDAC, histone deacetylase; Ac, acetyl group; Med, Mediator complex.

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may act as tuning knobs to specify the output properties for a given auxin signal.

Degradation (DII)

Degradation rates differ among Aux/IAAs. Aux/IAA–reporter fusions with diverse DII sequences show a range of degradation rates when expressed in *Arabidopsis* or yeast (Dreher *et al*., 2006; Havens *et al*., 2012). These and other approaches showed that 13 amino acids within DII are both necessary and sufficient for auxin-induced degradation (Ramos *et al*., 2001; Dharmasiri *et al*., 2005a; Kepinski and Leyser, 2005). Structural studies revealed that the DII from IAA7 directly contacts both auxin and TIR1 (Tan *et al*., 2007). Interestingly, efficient auxin binding *in vitro* requires both TIR1 and a member of the Aux/IAA family, suggesting that the complex behaves as an auxin co-receptor (Calderón Villalobos *et al*., 2012). Pairs of AFBs and Aux/IAAs exhibit wide variation in auxin binding affinities, suggesting that different pairs may be tuned to different ranges of auxin concentrations. In addition, different auxin binding affinities were observed when the TIR1/IAA7 co-receptor was exposed to several auxin variants (Calderón Villalobos *et al*., 2012), suggesting that co-receptor pairs may also vary in their sensitivity to the type of auxin present.

How auxin affinity relates to Aux/IAA turnover rates is still unclear, although recently reported Aux/IAA degradation rates in yeast (Havens *et al*., 2012) were not strongly correlated with measured dissociation constants of purified complex components (Calderón Villalobos *et al*., 2012). Several studies indicate that sequences outside of DII play a role in regulating both complex association and Aux/IAA degradation rates (Dreher *et al*., 2006; Calderón Villalobos *et al*., 2012; Havens *et al*., 2012). Sequences outside of the TIR1–auxin–Aux/IAA interaction surfaces may also contribute to differences in the Aux/IAA degradation rate, possibly by facilitating transfer of ubiquitin from the E2 ubiquitin-conjugating enzyme. Several substrates of the E3 anaphase-promoting complex (APC/C) share conserved sequences termed 'initiation motifs' that act in this way to accelerate substrate degradation (Williamson *et al*., 2011).

In identifying informative parameters for models of auxin signalling, it may be useful to look at how the degradation rate impacts other signalling systems. For example, the mammalian nuclear factor (NF)-κB pathway is among the best-studied degradation-triggered signalling pathways. Similar to the auxin signalling pathway, ubiquitination of several NF-κB inhibitor (IκB) repressor proteins by the β-TrCP (β-transducin repeat-containing protein) SCF E3 ligase immediately follows pathway activation (Kanarek and Ben-neriah, 2012). This facilitates de-repression of NF-κB transcription factors allowing them to activate expression of a host of genes, including the IκBs. Under prolonged or repeated exposure to the activating stimulus, this negative feedback can generate strong oscillations in NF-κB transcriptional activity that play a significant role in determining the timing and intensity of the transcriptional response (Tian *et al*., 2005; Kearns *et al*., 2006; Ashall *et al*., 2009; Sung *et al*., 2009). Much like the Aux/IAAs, the IκBs are each degraded with different kinetics (from 5 min for IκBα to 60–90 min for IκBβ and IκBε). In particular, the presence of slow degrading IκBs that are turned over out of phase with the faster IκBα can act to dampen transcriptional oscillations. It is conceivable that Aux/IAAs behave similarly to tune the intensity and duration of downstream auxin transcriptional responses.

Dimerization (DIII/IV)

Aux/IAAs modulate ARF transcriptional activity through binding at the conserved DIII and DIV domains at the C-terminus of both families (Guilfoyle *et al*., 1998; Tiwari *et al*., 2003). Expression of ARFs without DIII/DIV can lead to constitutive reporter activation in protoplast transfection assays (Tiwari *et al*., 2003; Wang *et al*., 2005), and a similarly truncated version of ARF5 acts as a gain-of-function allele in plants (Krogan *et al*., 2012). Different ARF–Aux/IAA interactions may allow for distinct auxin responses, but the degree of interaction specificity and its molecular basis have yet to be uncovered. Interaction studies suggest that Aux/IAAs can interact with one another almost non-discriminately and most Aux/IAAs can interact with a number of ARFs (Kim *et al*., 1997; Vernoux *et al*., 2011). Functional modules of ARF–Aux/IAA pairs may be generated by their shared location in time, space, and developmental context (Weijers *et al*., 2005; Walsh *et al*., 2006; Muto *et al*., 2007; Rademacher *et al*., 2012). However, the expression pattern alone cannot fully explain different functions within the Aux/IAA family, as stabilized Aux/IAAs provoke different phenotypes even when expressed from the same promoter (Weijers *et al*., 2005; Muto *et al*., 2007).

In addition, multiple ARFs and Aux/IAAs can be naturally expressed in the same cell yet generate different mutant phenotypes (Rademacher *et al*., 2011; Vernoux *et al*., 2011). For example, genetic studies suggest that IAA12–ARF5 and IAA14–ARF7/19 make up distinct functional modules despite all being expressed in lateral root founder cells (De Smet *et al*., 2010). How modules are distinguished within a cell, to what extent known Aux/IAA–ARF pairs interact with or influence one another, and how the induction of Aux/IAAs by auxin may alter Aux/IAA–ARF interactions are all open questions. Auxin-induced expression of specific Aux/IAAs may act to alter the cell's response to the next auxin cue. Such a scenario could explain the observations of a temporal offset of the IAA12 and IAA14 modules in the root (De Smet *et al*., 2010).

Dimerization within the Aux/IAA family may also contribute to the repertoire of auxin response modules, though few assays or computational models have addressed this possibility. The high degree of interaction between the Aux/IAAs observed in yeast two-hybrid assays prompted Vernoux and colleagues to include degradation of Aux/IAA dimers in their mathematical model of auxin signalling in the shoot apical meristem (Vernoux *et al*., 2011). If naturally auxin-resistant Aux/IAAs form heterodimers with auxin-degradable Aux/IAAs, they might act to fine-tune auxin transcriptional responses. Indeed, yeast interaction studies demonstrate that

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these combinations are possible (Vernoux *et al*., 2011) and they could have large impacts on transcriptional dynamics in a given cell. For example, an Aux/IAA without a degron sequence could shield its partner from the SCF machinery and thereby delay activation of an ARF.

Repression (DI)

Aux/IAAs inhibit activity of ARFs by recruiting the co-repressor TOPLESS (TPL) and related proteins (TPRs) through an ethylene response factor-associated amphiphilic repression (EAR) motif in domain I (Szemenyei *et al*., 2008). This interaction can also be found in the moss *Physcomitrella patens* (Causier *et al*., 2012b), suggesting that this mechanism may be largely conserved among land plants. TPL has been shown to interact with transcriptional regulators in a number of pathways and may be recruited by diverse repression domains (Causier *et al*., 2012a). Almost all Aux/IAAs have an EAR motif, but there is some diversity in its composition (Lokerse and Weijers, 2009). Site-directed mutagenesis of EAR motifs has shown that the same mutation in different Aux/IAAs results in a range of auxin-related phenotypes (Li *et al*., 2011). This result suggests that variation in the specificity or strength of TPL/TPR recruitment may be another source of functional diversity within the Aux/IAA repressor family.

TPL belongs to the Groucho/TUP1 co-repressor family, broadly conserved across eukaryotes. How TPL confers repression is not well understood, although genetic studies connect TPL function to histone deacteylases (HDACs) (Long, 2006; Liu and Karmarkar, 2008). Another plant member of the Groucho/TUP1 family, LEUNIG (LUG), interacts both with HDACs and with components of the Mediator complex (Gonzalez *et al*., 2007). The yeast TUP1 co-repressor utilizes several repression mechanisms: HDAC recruitment, displacing Mediator interactions with activators, and nucleosome repositioning (Liu and Karmarkar, 2008). A recent study has proposed that TUP1 functions primarily by blocking recruitment of co-activators (and the Mediator complex), thereby allowing rapid transitions between on and off states in stress responses (Wong and Struhl, 2011). The identification of a similar repression mechanism for TPL would explain the rapid relief of repression upon the degradation of the Aux/IAAs. The efficiency of both short- and long-term repression mechanisms may differ across the Aux/IAA family, providing potential additional control points in auxin signalling.

The ARF transcription factor family

The auxin sensitivity of ARF transcription factors is mediated by their interaction with the Aux/IAA co-repressors (Guilfoyle *et al*., 1998; Tiwari *et al*., 2003; Wong and Struhl, 2011). Yet of the 23 ARFs in *Arabidopsis*, only five are classified as transcriptional activators. This classification is based in large part on their effect upon an auxin-inducible reporter in protoplast transfection assays (Guilfoyle *et al*., 1998; Ulmasov *et al*., 1999a; Tiwari *et al*., 2003). The other ARFs tested in these assays conferred repression, and the remaining ARFs were classified as repressors based on the shared absence of glutamine enrichment in their middle regions (Tiwari *et al*., 2003). This distinction appears to be quite ancient, as activator and repressor ARFs belong to distinct clades, with at least one clade of each class dating back to the origin of land plants (Finet *et al*., 2013). There is little evidence that repressor ARFs interact with Aux/IAAs, and it is not understood how such an interaction might mediate auxin sensitivity. Thus, repressor ARF–Aux/IAA interactions are commonly left out of models of auxin response. This fundamental difference between activators and repressors implies functional diversification of their respective DIII/DIV domains (reviewed in Guilfoyle and Hagen, 2012).

The ARF repression mechanism is not well understood, although there is evidence to support at least two distinct mechanisms. First, repressor ARFs may act through a direct repression mechanism where they inhibit activator ARF activity by dimerization or by independently conferring repression to auxin-responsive promoters. The latter scenario is supported by evidence that ARF2 can repress a yeast reporter when fused to a heterologous DNA-binding domain (Vert *et al*., 2008). In addition, several repressor ARFs have been pulled out of screens for interactions with TPL/TPR co-repressors (Causier *et al*., 2012a) and contain EAR domains in their middle regions. Repression via TPL recruitment may be evolutionarily conserved as putative repressor ARFs identified in moss can interact with moss TPL proteins (Causier *et al*., 2012b). Several ARFs contain predicted interaction domains for LUG (Lokerse and Weijers, 2009), providing additional mechanisms for blocking transcriptional activation. The dimerization scenario is based on early studies that demonstrated that some ARFs could bind DNA as either dimers or monomers, and that dimerization could enhance DNA binding (Ulmasov *et al*., 1999b). One argument against dimerization is that very few ARF–ARF interactions were detected in a recent large-scale interactome study, although for most ARFs only DIII/DIV were used (Vernoux *et al*., 2011). Little is known yet about the formation of ARF dimers *in vivo* and any partner preferences that shape which complexes may form.

An alternative means of repression is indirect. In this scenario, repressor ARFs inhibit activator ARF activity by competing for access to the same promoter elements. While many ARFs bind the same synthetic promoters (Ulmasov *et al*., 1999a; Tiwari *et al*., 2003; Lokerse and Weijers, 2009), it is unclear whether activator and repressor ARFs bind to the same *cis*-elements under natural conditions. A recent mathematical model for auxin signalling incorporates a competition between repressor and activator ARFs, largely based on their extensive co-expression (Vernoux *et al*., 2011). This model predicts that the balance of repressor and activator ARF levels maintains a constant transcriptional response even in the presence of fluctuating auxin signals.

Conclusion

The small molecule auxin accomplishes a vast array of biological tasks using a deceptively simple three-protein signal

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perception and transduction module (TIR1/AFB, Aux/IAA, ARF). While much progress has been made in understanding the molecular mechanisms underlying this diversity, many questions remain. New technologies and higher precision characterization of known components can hopefully help untangle the auxin response network, and lead to a clear picture of how the auxin signal is so exquisitely fine-tuned in time and space.

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