Mechanism of Auxin-Regulated Gene Expression in Plants

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Abstract

Plant hormones control most aspects of the plant life cycle by regulating genome expression. Expression of auxin-responsive genes involves interactions among auxin-responsive DNA sequence elements, transcription factors and *trans*-acting transcriptional repressors. Transcriptional output from these auxin signaling complexes is regulated by proteasome-mediated degradation that is triggered by interaction with auxin receptor-E3 ubiquitin ligases such SCF^{TIR1}. Auxin signaling components are conserved throughout land plant evolution and have proliferated and specialized to control specific developmental processes.

INTRODUCTION: HORMONES ACT BY REGULATING GENOME EXPRESSION

Hormone responses are fundamental to the development and plastic growth of plants. In general, plant hormones are small molecules with simple chemical structures (44). The list of plant hormones is growing and now includes indole-3-acetic acid (IAA or auxin), brassinosteroids (BR), cytokinin (CK), ethylene, gibberellins (GA), jasmonic acid (JA), salicylic acid, and the recently identified branching hormone strigolactone. Most hormones are involved in many distinct and/or overlapping processes throughout the life cycle of plants. For example, auxin and CK regulate cell elongation and cell division as well as establishment and maintenance of meristems; ethylene influences germination, etiolated growth, and fruit ripening; abscisic acid (ABA) controls seed dormancy and germination and stress responses. Studies of mutants, particularly in *Arabidopsis*, with defects in these and other processes have contributed substantially to our understanding of hormone perception and signal transduction (22, 74, 92, 133). Advances in transcript profiling methods have also stimulated the generation of catalogs of hormone-responsive transcripts (41). This body of work reveals that one major branch of hormone response is the hormone-mediated regulation of gene expression. An appealing model for hormone action is one in which the ultimate targets of signal transduction, the hormone response transcription factors, act at gene regulatory regions in a hormone-dependent manner to control gene expression.

To understand the mechanisms of hormone action in plants, we must elucidate the links between hormone perception, signal transduction, and hormone-responsive transcription as well as the downstream effects of differential gene expression. Which genes are targeted for hormone response? What promoter elements and transcriptional regulators confer hormone-responsiveness to these genes? How is the hormone response effected, and how is it controlled? In this review, we describe the systems controlling hormone-responsive gene expression in plants, focusing on auxin and incorporating aspects of other hormone pathways where relevant. We aim to illustrate the molecular mechanism of hormone action in plants by reviewing the genomic responses to auxin, the *cis*- and *trans*-acting factors regulating expression of auxin-responsive genes, and the mechanism by which auxin perception regulates the activity of these factors. We also briefly examine the evolution of auxin signaling, highlighting the proliferation of auxin-signaling components.

GENOMIC RESPONSES TO PLANT HORMONES

Treatment of plants with exogenous hormones rapidly and transiently alters genome-wide transcript profiles (41, 82). Overall, hormone-responsive gene sets include genes involved in many cellular processes, including hormone regulation, signal transduction, metabolism, transcription, cell expansion, and cell division. Genes regulated by specific hormones are involved in hormone homeostasis and distribution as well as negative transcriptional feedback. Sets of auxin-responsive genes also include transcription factors required for specific developmental outcomes as well as components of other hormone signaling pathways.

Genomic Responses Indicate Hormone-mediated Regulation of Many Cellular Processes

Studies designed to identify hormone-responsive genes have provided valuable insight into the range of outputs of hormone signal transduction. Although the precise catalog of differentially expressed genes varies with the experimental design, general trends can be observed. In *Arabidopsis*, hormone treatment for short periods (<1 h) alters expression of ~10–300 genes, with roughly equal numbers of genes repressed and activated (41, 82, 90). Not surprisingly, longer exposure to most hormones (1 h or more) alters expression of larger

numbers of genes. Ethylene appears to be exceptional in that changes in gene expression in response to ACC (the ethylene precursor) are strongly weighted toward gene repression, and longer treatments result in a reduction in the number of differentially expressed genes (41, 82).

Most cellular processes are represented in hormone-responsive gene sets, as determined by classification of the genes into gene ontology categories (6, 82). Genes involved in transcription and signaling are overrepresented among ABA, BR, auxin, CK, and JA responsive genes, but genes involved in cell wall modification, metabolism, and photosynthesis are also present. Interestingly, the transcriptional response to each hormone is relatively specific (82). This is surprising, when considering that similar growth responses induced by auxins, gibberellins, or brassinosteroids each occur within the time frames encompassed by transcriptional profiling experiments (16, 139, 144). An explanation offered by Nemhauser and associates (82) for this observation is that different hormones regulate different members of gene families involved in growth responses. For example, 14 members of the *Arabidopsis* expansin family are hormone regulated; however, eight of these are regulated by only one or two hormones. Thus, hormones that trigger similar growth responses may act through regulation of distinct gene sets with overlapping effects on growth (82).

Hormone-responsive Genes Are Involved in Hormone Homeostasis, Distribution, and Response

Genes that act to regulate hormone homeostasis, such as those involved in hormone synthesis and degradation, are frequently found among hormone-responsive genes. The gibberellin biosynthesis gene *GA4* is repressed by treatment with GA (82). *CKX6* and *CKX4* encode cytokinin oxidases that reduce cytokinin levels; these genes are induced by cytokinin treatment (82, 105). Hormone homeostasis and response are regulated by several groups of auxin-responsive genes, including members of the *GH3* family (111). Several GH3 proteins from *Arabidopsis*, such as DFL1/GH3–6, act as IAA-amido synthetases in the conjugation of various amino acids to IAA or JA. Amino acid conjugation is proposed to contribute to auxin homeostasis by facilitating hormone storage, protection, or transport (71, 111, 112). In the moss *Physcomitrella patens*, knock-out mutations in either of two *GH3* genes increase free auxin levels and sensitivity to exogenous auxin (72). This suggests that GH3 proteins act to regulate the auxin pool, effectively modulating auxin responses, and supports an evolutionarily conserved role for the *GH3* genes in hormone homeostasis.

Genes involved in controlling auxin distribution are also induced by auxin treatment, and in some cases, the function of this induction has been demonstrated. Members of the *PIN-FORMED* (*PIN*) gene family encode components of the auxin efflux machinery. *PIN1*, *PIN3*, and *PIN7* are induced by auxin treatment, particularly in root tissues (10, 14, 35, 65). PIN proteins control auxin distribution to establish and maintain auxin concentration gradients in various tissues in the plant (132, 141). During organogenesis, PIN proteins enable the formation of auxin maxima that trigger the establishment of new growth axes. Induction of *PIN* expression by auxin serves to reinforce auxin gradients, which is essential for accurate expression of stem cell specification genes such as *PLETHORA1* (*PLT1*) and *PLT2*. These genes encode AP2/EREBP transcription factors required for patterning of the root stem cell niche (4, 10, 14). Within the *LAX* family of auxin influx carriers, *AUX1*, *LAX2*, and *LAX3* are induced in roots by auxin treatment (90, 131). *LAX3* is expressed in cells overlying lateral root primordia and likely reinforces auxin influx into these tissues (114). This activates expression of several cell-wall-remodeling enzymes, and a model has been proposed in which auxin induction of *LAX3* around lateral root primordia triggers cell wall loosening to facilitate epidermal cell separation and subsequent emergence of lateral roots.

Aux/IAA: auxin/indole-3-acetic acid

SHY2: SHORT HYPOCOTYL2 or SUPPRESSOR OF HY2

A third group of auxin-induced genes, the *Aux/IAA* genes, encode transcriptional repressors of auxin response that are critical components of auxin signaling (discussed below) (74). *Aux/IAA* transcripts are rapidly and strongly induced by auxin treatment in peas, soybeans, and other plants (3) and have been used as marker genes for auxin-dependent transcription (41, 82). Aux/IAA proteins are short-lived nuclear proteins with half-lives ranging from ~10 min for *Arabidopsis* AXR2/IAA7 and AXR3/IAA17 to more than 60 min for IAA28 (142, 143). Application of auxin reduces the half-lives of the Aux/IAA proteins twofold or more (31). Indeed the auxin-sensitive nature of AXR3/IAA17 degradation led to its use as a quantitative and tissue-specific readout for perturbations in auxin signaling (47). Interestingly, the least stable of the *Arabidopsis* Aux/IAA proteins are encoded on transcripts that are among the most highly auxin induced (90). This suggests that rapid induction of *Aux/IAA* transcripts by auxin serves to replenish Aux/IAA protein pools, which then likely act to repress further transcriptional response. This negative-feedback role for Aux/IAA proteins is discussed in detail elsewhere (9). Regulation of expression of hormone signaling factors is a common theme in hormone-responsive transcription. The DELLA protein RGL2, a repressor of gibberellin responses, is induced by treatment of seedlings with gibberellic acid (82, 137). EIN2, an activator of ethylene responses, is repressed by treatment with the ethylene precursor ACC (5). Similar examples are seen in plants treated with abscisic acid, cytokinin, brassinosteroid, and methyl jasmonate (82).

Auxin-responsive Genes Include Transcription Factors Implicated in Development and Hormone Cross-Talk

Transcriptional regulators form one of the largest groups of hormone-responsive genes (82, 95). Auxin-induced transcription factors include members of the HD-Zip superfamily, AP2/EREBP-type transcription factors, AS2-like (LBD) and MYB-like transcription factors, zinc finger-like transcription factors, and others (42, 82, 90, 104). In general, the roles of these factors in specific developmental processes are poorly understood. Exceptions are the genes *LATERAL ORGAN BOUNDARIES-DOMAIN16/ASYMMETRIC LEAVES2-LIKE18 (LBD16/ASL18)* and *LBD29/ASL16*, which are expressed in root vasculature and lateral root primordia in *Arabidopsis* and are required for initiation of lateral roots (85, 87). A related auxin-responsive *LBD/ASL* gene in rice, *CROWN ROOTLESS1*, has been similarly characterized and is associated with formation of crown roots and lateral roots (57, 69). Additional studies are needed to understand the specific roles of the many hormone-responsive transcription factors in development.

An interesting feature of hormone-responsive data sets is the frequent occurrence of genes associated with other hormone signaling pathways. For example, several *ACS* genes, which encode enzymes involved in ethylene biosynthesis, are induced by auxin (87, 124). Auxin also regulates several genes in the GA biosynthesis pathway (34). The role of cross-talk among these three hormones (auxin, ethylene, and GA) is not yet fully understood, but they are proposed to act interdependently in some conditions and independently in others (19, 130). In root meristems, the antagonism between auxin and cytokinin has an essential developmental function. Auxin activates *ARR7* and *ARR15*, which encode repressors of cytokinin signaling (76, 78). Repression of cytokinin activity is essential in the developing meristem for specification of root stem cells. Interestingly, an inverse auxin-cytokinin antagonism acts in the elongation-differentiation zone of the root, where repression of auxin activity enables differentiation of root cells (17, 23). This is done through cytokinin induction of *SHY2*, a repressor of auxin signaling (**Figure 1**).

CIS-ACTING SEQUENCES REGULATE AUXIN-RESPONSIVE GENES

Expression of hormone-responsive genes involves interactions between *cis*-acting DNA sequence elements and *trans*-acting transcriptional regulators. Promoters of hormone-responsive genes contain constitutive elements required for basal expression as well as sequences associated with hormone responsiveness. Auxin-responsive domains such as the auxin-responsive element (*AuxRE*) contain DNA motifs recognized and bound by transcription factors.

Much of the initial characterization of *cis*-acting sequences in auxin-responsive promoters was done with the *IAA4/5* gene from *Pisum* and the *GH3* gene from soybean (**Table 1**) (7, 8). Analysis of *PS-IAA4/5* revealed a major auxin-responsive region located between nucleotides −150 and −325, relative to the transcription start site. Within this region, two domains conferring auxin inducibility were identified. Domain A contains the sequence 5′- (T/G)GTCCAT-3′, the position and orientation of which are important for auxin inducibility. Domain B is located upstream of domain A and contains the sequence 5′-ACATGGN-3′ upstream of the sequence 5′-TGTCTC-3′. Auxin inducibility is less affected by perturbations in the position and orientation of this element. Interestingly, the TGTCTC motif was also identified in two auxin-responsive regions of the soybean *GH3* promoter (70). The soybean *SAUR15A* promoter also contains the TGTCTC motif, which is preceded in *SAUR15A* and *PS-IAA4/5* by the sequence 5′-GGTCCCAT-3′ (1, 8, 67).

The two small auxin-responsive regions of the *GH3* promoter that contain the motif TGTCTC were each found to confer auxin inducibility to a heterologous minimal promoter (70, 128). Analyses of native and synthetic promoters containing this element demonstrated that in the absence of auxin, the sequence acts to repress adjacent constitutive elements (128, 129). Although TGTCTC alone is not sufficient to promote gene expression in an auxin-dependent manner, promoters containing this sequence are activated following auxin treatment (88, 128). This observation led to the definition of TGTCTC as the *AuxRE* and to the construction of a number of synthetic auxin-responsive promoters such as *DR5* and *BA*, which contain multimers of the TGTCTC sequence fused to a constitutive promoter element (88, 129, 136) (**Table 1**). These synthetic promoters are now widely used as experimental readouts for auxin response and/or auxin levels in planta.

The *AuxRE* is widely distributed in authentic auxin-responsive promoters (42, 83, 95), and

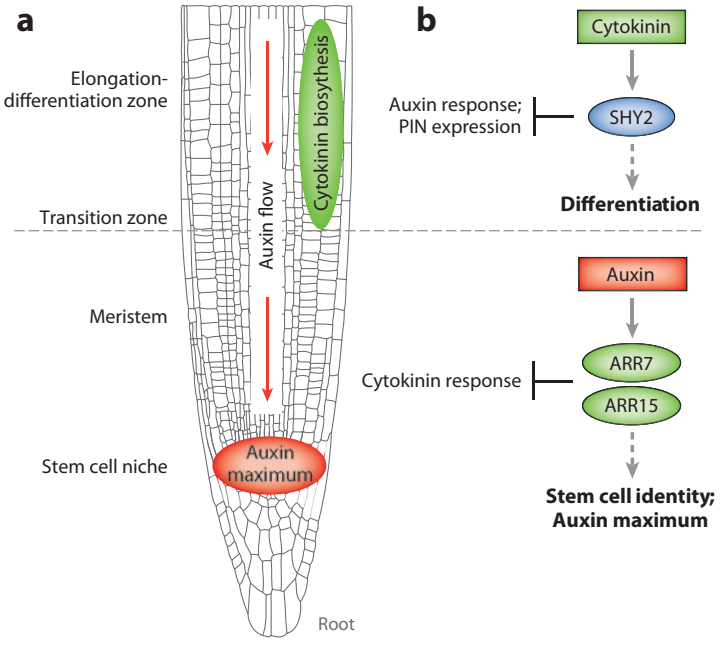

Figure 1

Auxin-cytokinin cross-talk controls root meristem size in *Arabidopsis*. (*a*) In the *Arabidopsis* root, an auxin maximum in the stem cell niche is required for stem cell specification and meristem formation (14). Cytokinin biosynthesis genes are expressed in the elongation-differentiation zone, where meristem cells differentiate and begin to elongate (23). (*b*) In the meristem, cytokinin response is repressed by the auxin-mediated expression of ARR7 and ARR15, repressors of cytokinin signaling. This is required for maintenance of meristem identity (78). In the elongation-differentiation zone, auxin response and redistribution are repressed by the cytokinin-mediated expression of SHY2, a repressor of auxin response and PIN expression (17, 24). Meristem size is controlled through the effects of auxin and cytokinin in the meristematic and differentiation zones of the root and by antagonism between the two hormones.

Auxin-responsive element (*AuxRE*): DNA sequence element found in promoters of auxin-responsive genes

Table 1

Name	Critical residues	Function	References
AuxRE; auxin-response element	5′-TGTCtC-3′	Found in synthetic and endogenous auxin-responsive promoters; core TGTC required for binding of auxin response factors	8, 67, 88, 125, 128
DR5	5′-cctttTGTCTC-3′	Multimers confer auxin responsiveness to heterologous promoters; fusion of multimers to a minimal CaMV 35S promoter generates highly active auxin-responsive promoters	128
PS-IAA4/5 domain A	5′-TGTCCCATtgtt-3′	Confers auxin responsiveness to heterologous promoters; fused to domain B in BA:GUS construct used to generate BA3 transgenic line	88, 128
P3	5′-GAGACAactTGTCTC-3′	P3 contains an inverted repeat of the AuxRE; P3(4X) containing four copies of P3 was used in yeast one-hybrid assays to identify ARF1	125

its distribution is conserved between closely related promoters such as those in related *Aux/IAA* genes in *Arabidopsis* (98). Based on sequence composition, the overall incidence of the *AuxRE* in *Arabidopsis* is predicted to be 2.4 copies per 10,000 base pairs (96). Within individual promoters, the abundance of the *AuxRE* varies (42). This element and its reverse complement, thought to have equivalent function, are found to be overrepresented in sets of genes responsive to both auxin and brassinosteroid (42, 83). However, the motif is not overrepresented in some sets of auxin-responsive genes (83, 134) and is entirely absent from some auxin-responsive promoters (95). It is likely that variants of the canonical TGTCTC are also functional *AuxRE*s. The promoter of *ACS4*, a primary auxin-response gene in *Arabidopsis*, contains only variant *AuxRE* sequences and yet effectively promotes transcription in an auxin-dependent and auxin-specific manner (2). Promoters of *ARR7* and *ARR15*, auxin-responsive cytokinin response factor genes, contain multiple tandem copies of the core TGTC portion of the *AuxRE*. Mutation of these nucleotides significantly diminishes activation of these promoters at auxin maxima in vivo (78). As additional auxin-responsive genes are examined in more detail, it will be interesting to address the specific sequence requirements for auxin-responsiveness in vivo. It is very likely that *AuxRE*s are directly involved in the in vivo recruitment of transcription factors to certain promoters, as discussed below. It is possible, then, that sequence variations in *AuxRE*s act to differentially recruit different transcription factors. It is also likely that the distribution of *AuxRE*s at certain promoters may regulate the amplitude of the auxin response at those loci. Variation in *AuxRE* sequence and abundance may serve as the first level of complexity in the transcriptional regulation of auxin-responsive genes.

ARF: auxin response factor

TRANS-ACTING FACTORS REGULATE AUXIN-RESPONSIVE GENES

*AuxRE*s are binding sites for members of the auxin response factor (ARF) family of transcription factors. ARF proteins contain domains associated with DNA binding, transcriptional activation or repression, and protein-protein interactions. ARF activity is regulated in part through interactions with the Aux/IAA repressors. Putative mechanisms for repression of ARFs by transcriptional corepressors are also emerging.

Auxin Response Factors Bind to *AuxRE*-containing Sequence Elements

Footprinting analysis of auxin-responsive soybean promoters revealed binding of nuclear

proteins near *AuxRE*-containing sequence elements (79). Using the *AuxRE* as bait in a yeast one-hybrid screen, Ulmasov and colleagues (125) identified AUXIN RESPONSE FACTOR1 (ARF1), the founding member of the ARF family of auxin response transcription factors. The TGTC bases within the TGTCTC *AuxRE* were shown in electrophoretic mobility shift assays to be critical for binding by ARF1 and several other *Arabidopsis* ARF proteins (125, 127). Mutation of the ultimate C residue to an A significantly diminished in vitro binding by ARF family members ETT/ARF3, ARF4, ARF6, and FWF/ARF8, but to a much lesser extent for ARF1, MP/ARF5, and HSS/ARF2. This suggests some level of DNA sequence binding preference among the ARFs.

ARFs are nuclear proteins with three described protein domains. The amino-terminal DNA-binding domain (DBD) lies within a plant-specific B3-type transcription factor domain, and the middle region is either glutamine rich and associated with transcription activation, or proline rich and associated with repression of auxin-responsive transcription (125, 126, 134). Although the sequence of the DNA-binding domain is highly conserved among ARF proteins, there are some differences among even very closely related members of the family (127). Differences in protein sequence within the DBD may predict different DNA binding preferences. Results of electrophoretic mobility shift assays using full-length and truncated *Arabidopsis* ARF proteins indicate that the DBD is sufficient for binding by ARF1, but that HSS/ARF2, ETT/ARF3, MP/ARF5, ARF6, and FWF/ARF8 require C-terminal amino acids to form stable complexes with DNA in vitro (127). ARF binding to palindromic *AuxRE*s in particular requires C-terminal amino acids. It has been proposed that the C-terminal domain (CTD) enhances DNA binding by enabling ARF dimerization (127). Dimerization may facilitate recognition of tandem or palindromic *AuxRE*s by doubling the number of DNA binding moieties in the protein complex. Dimerization may also enable a low-affinity ARF to be brought into position on the DNA by a higher-affinity ARF.

Truncated versions of activating ARF proteins MP/ARF5, ARF6, NPH4/ARF7, and FWF/ARF8, domains required for DNA binding, remain competent to activate transcription in an auxin-dependent manner in protoplast assays (53, 126). Activation in these experiments is proposed to occur through dimerization with endogenous ARF proteins preassociated with *AuxRE*s (127). If this model is correct, it suggests that at least a portion of the ARF pool is resident on *AuxRE*-containing promoters at low auxin concentrations. It also suggests that ARF dimerization may contribute to transcription activation by enabling an enhanced auxin response from some promoters.

The potential contribution of ARF dimerization to repression of auxin response is less clear. ETT/ARF3, ARF1, HSS/ARF2, and ARF4 are proposed to function as repressors because they repress or do not contribute to the auxin response from synthetic *AuxRE*-reporter constructs in protoplast assays (122, 126). ETT/ARF3 lacks the canonical CTD required for ARF dimerization (125, 127). Similarly, truncated versions of ARF1, HSS/ARF2, or ARF4 lacking canonical CTDs retain repressor function (122). These findings suggest that ARF-mediated repression does not require CTD-mediated dimerization with preassociated ARFs (126). A possible explanation for the observed repression of auxin response mediated by repressive ARFs is that when highly expressed, these proteins displace endogenous ARFs on auxin-responsive promoters but direct a reduced level of promoter activation. Interestingly, a chimeric ARF2-LexA protein represses a *LexA*-containing promoter in yeast assays (134). Given that the ARF2-mediated repression seen in this yeast assay does not involve an auxin-responsive promoter or endogenous ARFs, this result suggests that some repressive ARFs may repress transcription directly. Such a repression mechanism may occur in addition to competition between repressive and activating ARFs for promoter binding.

ETT: ETTIN

FWF: FRUIT WITHOUT FERTILIZATION

MP: MONOPTEROS

HSS: HOOKLESS SUPPRESSOR

DBD: DNA-binding domain

CTD: carboxy-terminal domain

NPH4: NON-PHOTOTROPHIC HYPOCOTYL4

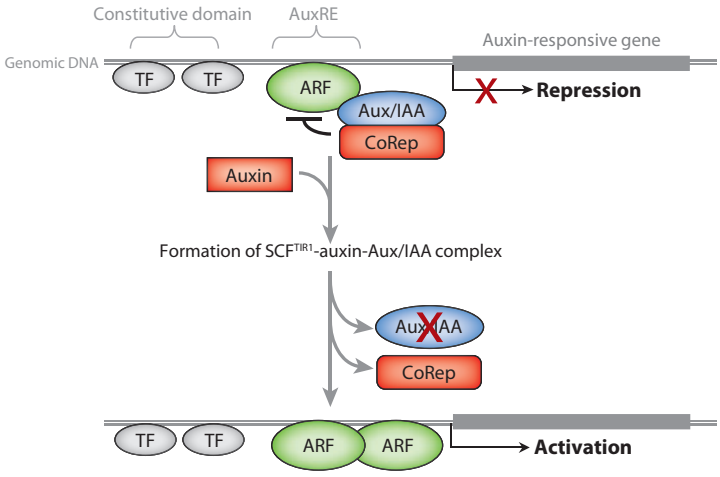

Figure 2

Model for auxin-mediated transcription activation. Activating ARF proteins (ARF) resident at AuxRE-containing promoters of auxin-responsive genes are in a complex with Aux/IAA proteins at low auxin concentrations. Promoter activity is repressed through activities of Aux/IAA proteins and associated transcriptional corepressors (CoRep). Auxin binding by the Aux/IAA-SCF^{TIR1} complex triggers ubiquitylation and degradation of the Aux/IAA proteins. This derepresses ARF activity and enables promoter activation at constitutive elements. Transcription may be supported and further regulated by transcription factors (TF) bound at adjacent elements or interacting with ARF proteins. Double line, genomic DNA; bent arrow, transcription start site and direction of transcription.

ARF CTDs may contribute to ARF specificity by enabling ARF interaction with heterologous protein cofactors. CTDs of ARF1 and NPH4/ARF7 interact with the transcription factor MYB77 (107). MYB77 expression is induced by auxin treatment (64) and enhances the expression of auxin-responsive genes. In *Arabidopsis* roots carrying a *myb77–1* null mutation, expression of several auxin-responsive genes is attenuated, although expression of these genes is still auxin-responsive (107). MYB binding sites are found in promoters of these and other auxin-responsive genes (83). Predicted binding sites for a number of other transcription factors are enriched in large auxin-responsive promoter sets, such as sites for MYC, bZIP, and WRKY transcription factors (83, 95). In the soybean *GH3* promoter, TGA-box elements adjacent to auxin-responsive domains bind a recombinant bZIP protein SBGBF (128). Together with results of ARF binding studies, these findings suggest that multiple *trans*-acting factors interact with auxin-responsive promoters to regulate transcription. This has potential implications for mechanisms of ARF-mediated, auxin-dependent transcription activation (see discussion below, and **Figure 2**).

ARF-mediated Regulation of Gene Expression In Vivo Requires *AuxREs*

Transcript profiles from plants carrying mutations in one or more *ARF* genes have been used to predict genes requiring specific ARFs for expression and auxin responsiveness (80, 85, 87). Although direct in vivo recruitment of ARF proteins to promoters of these genes has not been widely demonstrated, several strong candidates for direct ARF regulation have been reported. Promoters of eight genes differentially expressed across tropic-stimulated tissues in *Brassica oleracea* contain *AuxREs*, and *Arabidopsis* orthologs of these genes are dependent upon *NPH4/ARF7* for auxin response (33). The promoter of the *LAX3* gene contains several copies of the *AuxRE*, and *LAX3* is dependent upon NPH4/ARF7 and ARF19 for auxin induction (114). Similarly, promoters of the *LBD/ASL* genes *LBD16*, *LBD29*, and *CROWN ROOTLESS1*, mentioned above, contain one or more copies of the *AuxRE*, and promoter fragments of each of these genes interact in vitro with recombinant ARF proteins (69, 85). *LBD16* and *LBD29* are dependent upon *NPH4/ARF7* for auxin responsiveness in *Arabidopsis* (85). Finally, expression of the AP2-type transcription factor DORNROESCHEN (DRN) in *Arabidopsis* embryos requires in vivo interactions between MP/ARF5 and canonical *AuxREs* in the *DRN* promoter (18).

Aux/IAA Proteins and Transcriptional Repressors Repress ARF Activity

In addition to serving as the sites of interaction with other transcription factors, the ARF CTD is required for auxin response and for interactions with Aux/IAA repressors (48, 122, 129, 135). Proteins in the Aux/IAA family contain

four conserved domains (3), with domains III and IV sharing homology with CTD regions of ARF proteins and contributing to Aux/IAA-ARF interactions (63, 75, 89, 125, 126, 129). In yeast- or protoplast-based assays, expression of an Aux/IAA protein blocks ARF-mediated activation of *AuxRE*-containing promoters (63, 122, 126, 136). This mechanism is proposed to involve ARF-Aux/IAA dimerization (126, 127). Similar interactions likely occur in planta, as plants expressing stabilized Aux/IAA proteins fail to regulate auxin-responsive genes (66, 114, 140). Expression of a chimeric IAA17-based transcriptional activator results in ectopic expression of auxin-responsive genes in the absence of exogenous auxin treatment (66). This suggests that IAA17 associates with chromatin at auxin-responsive genes in the absence of auxin. Direct DNA binding by Aux/IAAs has not been demonstrated, so Aux/IAA recruitment to chromatin may occur through interaction with ARF proteins.

Although the mechanisms of ARF- and Aux/IAA-mediated repression are not fully understood, a few proteins involved in auxin response are now known to act in transcriptional corepression and chromatin remodeling. Constitutive repression of auxin response by the mutant *slr-1/iaa14* protein requires *PICKLE* (*PKL*) (38). PKL is a homolog of the animal chromatin-remodeling factor CHD3/Mi-2, which represses transcription in concert with histone deacetylases (84). The *TOPLESS* (*TPL*) family of transcriptional corepressors is required for the embryo polarity defects observed in *bdl/iaa12* mutant plants (115). TPL interacts with BDL/IAA12 through an ERF-associated amphiphilic repression (EAR) motif found in domain I of Aux/IAA proteins (123). This motif is found in a number of transcription factors and is required for efficient transcriptional repression (56). In yeast two-hybrid assays, TPL also interacts with many other Aux/IAA proteins, although interactions have not yet been demonstrated between TPL and AXR2/IAA7 or MSG2/IAA19 (115). It is possible that other members of the *TPL* gene family interact with these and other Aux/IAA proteins. In addition to regulating auxin response through the Aux/IAA proteins, transcriptional coregulators may also interact directly with the ARF proteins. ETT/ARF3 interacts with SEUSS, a protein associated with transcription repression through *LEUNIG* (93, 109). *LEUNIG* is predicted to lack DNA-binding activity but act as a transcriptional corepressor (110). This reiterates that an important function of ARF proteins may be to recruit and tether other *trans*-acting factors to specific loci. Combinatorial interactions among ARF proteins, Aux/IAA proteins, transcriptional regulators and other *trans*-acting factors likely contribute a second level of complexity to the transcriptional regulation of auxin-responsive genes.

SLR-1: SOLITARY ROOT1

BDL: BODENLOS

MSG2: MASSUGU2

AUXIN PERCEPTION AND SIGNAL TRANSDUCTION EFFECT AUXIN RESPONSE

Activity of ARF transcription factors is enabled through the auxin-dependent degradation of the Aux/IAA repressors; Aux/IAA degradation is the critical event in auxin signaling. F-box protein auxin receptors interact with Aux/IAA repressors in an auxin-dependent manner, initiating their degradation by the 26S proteasome. Aux/IAA degradation likely dissociates transcriptional corepressors from ARF proteins residing on promoters of auxin-responsive genes, effecting auxin response. Several components of SCF E3 ubiquitin ligase complexes are required for auxin responses.

Aux/IAA Repressors Are Substrates for Degradation by the 26S Proteasome

Short-lived Aux/IAA proteins are stabilized in plants mutant for the F-box protein *TRANSPORT INHIBITOR RESPONSE1* (*TIR1*) (47). *TIR1* is required for auxin response in *Arabidopsis* (55, 102) and is a member of a six-gene clade of F-box proteins that also includes *AUXIN SIGNALING F-BOX PROTEIN1* (*AFB1*) and *AFB2*, *AFB3*, *AFB4*, and *AFB5* (25, 27, 74). TIR1 purified from cell extracts or translated in vitro interacts directly with Aux/IAA proteins,

SCF^{TIR1}: SKP1-CULLIN-F-BOX PROTEIN complex containing TRANSPORT INHIBITOR RESPONSE1 protein

and these interactions are stabilized in a dose-dependent manner by the addition of auxin (25, 47, 61, 62). Auxin interacts directly with TIR1-IAA7 complexes purified from plants, and structural analysis of *Arabidopsis* TIR1 in a complex with a peptide from IAA7 demonstrates that the interaction of TIR1 with Aux/IAA proteins forms a pocket in which auxins such as IAA, NAA, and 2,4-D bind (117). Thus, *TIR1* and the *AFB* proteins function as auxin receptors (25, 62). The pocket occupied by auxins is internal within the structure of TIR1-IAA7 and is formed by faces of both proteins. Thus, both the F-box protein and the Aux/IAA protein contribute to auxin binding and may be considered to function as coreceptors. As these proteins are each encoded by multi-gene families, this raises the possibility that numerous combinatorial interactions may occur between F-box protein and Aux/IAA auxin coreceptors.

Results of genetic and biochemical experiments indicate that degradation of Aux/IAA proteins requires activity of the 26S proteasome (47). Proteins are tagged for proteasome-mediated degradation through ubiquitylation, which is done by ubiquitin protein ligases. TIR1 and related proteins serve as the specificity determinant for the SCF class of E3 ubiquitin ligases, which target substrate proteins for polyubiquitylation and subsequent degradation (74). The SCF complex is named for its components: a Skp1-related protein, a Cullin, and an F-box protein. TIR1 interacts in *Arabidopsis* with ASK1 (ARABIDOPSIS SKP1 HOMOLOG1) or ASK2, CUL1, and RBX1 to form SCF^{TIR1}. This complex is required for degradation of Aux/IAA proteins and auxin response (45–47, 61). Recent studies involving protoplast-based assays confirmed that SCF^{TIR1} mediates ubiquitylation and degradation of the Aux/IAA proteins SHY2/IAA3 and BDL/IAA12 (30). In addition to TIR1, several other components of the SCF^{TIR1} complex are implicated in auxin response in vivo. Plants mutant for *ASK1* are defective in auxin response and lateral root formation (45). AXR1 and AXR1-LIKE function in post-translational modification of CUL1 and are required for auxin responses and development (26). The *CUL1* mutants *cul1–6* and *cul1–7* have abnormal morphology and *cul1–7* mutants fail to degrade an Aux/IAA-reporter fusion protein (40).

Degradation of Aux/IAA Proteins Is Critical for Auxin Responses

Despite the importance of Aux/IAA domains I and III/IV in auxin responses (in corepressor interaction and ARF interaction, respectively) the majority of *aux/iaa* mutants with severe defects in development and auxin response carry mutations in domain II (37, 50, 81, 100, 101, 118, 120, 138). These are gain-of-function mutations that stabilize the protein and include *Arabidopsis* mutants *axr3/iaa17*, *msg2/iaa19*, *shy2/iaa3*, *axr2/iaa7*, *slr/iaa14*, *bdl/iaa12*, and others. Plants carrying these mutations have various auxin-related defects in embryo development, root development, hypocotyl elongation, tropisms, and other processes (37, 50, 81, 100, 101, 118, 120, 138).

Domains I and II of Aux/IAA proteins are associated with Aux/IAA instability, and fusion of these domains to heterologous proteins confers instability to those proteins as well (47). This instability is dependent upon *TIR1/AFB* auxin receptors (27, 47). Domain II contains a GWPPV amino acid motif that is highly conserved among Aux/IAA proteins and is required for Aux/IAA degradation (97, 118). The domain encompassing this motif is frequently referred to as the degron, due to its importance in Aux/IAA degradation. Analysis of the crystal structure of the TIR1-IAA7 complex revealed that the amino acids in the degron contribute to the auxin-binding pocket. Thus, mutations in the degron enhance the stability of Aux/IAA proteins because they prevent formation of the TIR1-auxin-Aux/IAA coreceptor complex (117).

Model for the Mechanism of Auxin Action in Gene Regulation

Based on these results, a model for auxin-regulated gene expression has been proposed

that places the SCF^{TIR1}-auxin-Aux/IAA complex at its center (**Figure 2**). In this model, auxin triggers Aux/IAA degradation and derepression of ARF activity, enabling promoter activation. This mechanism has been proposed and reviewed previously (9, 25, 62, 74, 119, 122, 127) and predicts that in the absence of auxin, Aux/IAA proteins and corepressors are present at sufficient concentrations to repress activating ARFs. Further exploration of ARF-promoter and ARF-repressor interactions in vivo will be essential for testing this model.

It is important to note that the model does not address all of the cellular effects of auxin. Some cellular responses occur too rapidly to depend directly on de novo gene regulation, such as changes in pH and membrane physiology (16). Also, other auxin-binding proteins such as ABP1 are involved in certain auxin responses and may function as auxin receptors (11, 15, 58, 121). These aspects of auxin response are beyond the scope of this review, and we refer the reader to the cited literature for discussion of these topics.

The discovery that SCF^{TIR1} interacts directly with Aux/IAA proteins led to the conclusion that this interaction is the critical feature of the auxin signal transduction pathway (48, 60, 117). A surprising implication of this conclusion is that the auxin signaling pathway is quite short. In contrast, the brassinosteroid and cytokinin signaling pathways involve many steps ultimately leading to activation and repression of hormone-responsive genes (77, 133). This might suggest that the auxin signaling pathway offers fewer points for modulation and regulation of the response compared with more complex pathways. However, despite the relative simplicity of the pathway, there are many opportunities for further regulation. Different Aux/IAA-ARF-promoter complexes probably vary in auxin sensitivity, given that Aux/IAA proteins differ in stability (31). Similarly, different auxin concentrations may regulate expression of different gene sets (90). Also, F-box protein auxin receptors may vary in abundance and auxin binding affinities. RUB/Nedd8 activity and other aspects of SCF and proteasome assembly may modulate the stability of Aux/IAA proteins (28). Thus, interactions between auxins, F-box protein auxin receptors, Aux/IAA proteins, and other components of SCF E3 ubiquitin ligases may all contribute an additional level of complexity to the regulation of auxin-responsive genes.

ELABORATION AND SPECIALIZATION OF AUXIN-SIGNALING PATHWAYS

Auxin has been associated with core growth processes such as tropic growth and apical dominance in many plants. Accordingly, proteins involved in regulating auxin distribution, perception, and signaling were probably present in the last common ancestor of land plants. Recent studies indicate that auxin-signaling components proliferated extensively throughout evolution. In angiosperms such as *Arabidopsis*, specialized functions are attributed to some members of the *ARF* and *Aux/IAA* gene families. Distinct and overlapping expression patterns among the components of the auxin-signaling module also create combinatorial regulatory potential.

Auxin Distribution Is Regulated Throughout Land Plants

Several studies indicate that the components required to regulate auxin distribution appeared early in the evolution of land plants. In the alga *Chara*, IAA is transported through apical and basal tissues, although polar auxin flow has not been clearly demonstrated (29). In low-light conditions, the moss *Funaria* displays auxin influx and efflux in protonemata (39). The genome of the moss *Physcomitrella patens* encodes auxin influx and efflux carriers as well as auxin-conjugating enzymes, suggesting that auxin distribution and homeostasis are regulated in this organism (72, 99). In *P. patens*, the highest auxin levels are found in young tissues and dividing cells based on expression of auxin reporter genes (12), although the contribution of auxin maxima to growth regulation

in this organism is unclear (36). Asymmetric auxin distribution results in differential gene expression and ultimately in differential growth responses in several plant species, including *Selaginella* and *Arabidopsis* (13, 32, 33). Auxin distribution is also associated with apical dominance in flowering plants (116). Although roles for auxin in growth are not understood in many early diverged plants, regulating auxin distribution appears to be important for many plant lineages (21).

Auxin Signaling Components Have Proliferated Throughout Land Plant Evolution

Genome sequences indicate that the components of auxin signal transduction have proliferated significantly throughout land plant evolution. The last common ancestor of land plants is predicted to have possessed one TIR1/AFB auxin receptor, three auxin response factors, and one Aux/IAA repressor, whereas the genome of the moss *P. patens* encodes four F-box protein receptors, 14 ARFs, and two repressors (99). These gene families have further expanded in *Arabidopsis*, poplar, and rice (*Oryza sativa*). Overall, the proportion of the plant genome that is given to known regulators of auxin homeostasis, transport, and signaling has increased from 0.14% in *P. patens* to 0.65% in *Arabidopsis thaliana* (99). The increased contribution of auxin-related genes to genomes of more complex plants suggests a parallel increase in the contribution of auxin pathways to developmental complexity (20). If this idea is correct, specific auxin pathways might be involved in distinct aspects of development of complex plants. Specialization of auxin pathways can indeed be seen in *Arabidopsis*, where the contribution of specific ARFs and Aux/IAAs to development and auxin response is well studied.

Specialization of ARF-Aux/IAA Pathways Contributes to Regulatory Potential

More than 20 *ARF* genes have been identified in the *Arabidopsis* genome. These genes fall into four groups based on sequence (49, 87). One group forms a gene cluster on chromosome I and contains genes expressed during embryogenesis (87). These genes are unusual among the ARFs in that they encode proteins with a repression domain found in several other B3-type transcription factors (56). Among the remaining ARFs, unique defects are associated with loss of function of *HSS/ARF2*, *ETT/ARF3*, *MP/ARF5*, *NPH4/ARF7*, or *FWF/ARF8* and with double mutants, including *ett/arf3 arf4*, *arf6 fwf/arf8*, and *nph4/arf7 arf19*.

HSS/ARF2 is involved in apical hook formation in seedlings, and *hss/arf2* mutants also have abnormal leaf size, flower morphology, and flowering time (86, 87). Phenotypes of *arf2* mutants are enhanced in *arf1 arf2* double mutants (87). Mutations in *ETT/ARF3* cause defects in floral organ number and gynoecium patterning (106). In *ett/arf3 arf4* double mutants, defects are also observed in leaf development. Although both ARFs repressed auxin response from a synthetic reporter in protoplast assays (122), *ett-1* mutants can be restored by ectopic expression of ETT/ARF3 or ARF4 fused to a VP16 activation domain, but not a repressor domain (91). Plants expressing reduced amounts of *MP/ARF5* have embryonic patterning defects and abnormal leaf venation patterns (52, 53). *nph4/arf7* mutants enhance the phenotypes of plants with reduced *MP/ARF5* expression, and hypocotyls of *nph4/arf7* mutant seedlings are nonphototropic (53, 54, 113) (**Figure 3**). Seedlings of double mutants *nph4/arf7 arf19* have reduced gravitropism and phototropism and delayed formation of lateral roots (87). In the mutant *fruit without fertilization* (*fwf/arf8*), fruit development is uncoupled from pollination and parthenocarpic fruit are produced (43). Double mutants *arf6 fwf/arf8* have decreased jasmonic acid concentrations and fail to complete flower development (80). These genetic analyses indicate partially redundant functions for related ARFs in some tissues but suggest that, overall, members of the ARF family are functionally specialized.

ARF specialization may be conferred through differential expression profiles,

interactions with distinct target genes, interaction with specific Aux/IAA proteins, or other mechanisms. Results of microarray-based transcript profiling and RNA gel blot hybridization experiments indicate that *ARF* genes are broadly expressed in seedlings and in root and aerial tissues of mature plants (59, 87, 119, 127). Finer resolution analyses using promoter-reporter fusion constructs and in situ hybridization have been done for a few ARFs and indicate largely overlapping expression profiles. For example, in *Arabidopsis* seedlings, the *NPH4/ARF7* promoter drives expression of a reporter gene in aerial tissues and vascular tissue in primary roots. The *ARF19* promoter is active in roots and vascular tissue in aerial portions of seedlings (87). The expression profile of *NPH4/ARF7* also overlaps with that of *MP/ARF5* in embryos (53) (**Figure 3**). Thus, expression patterns alone are insufficient to explain the unique phenotypes associated with *arf* loss-of-function mutants. It is likely that target gene specificity contributes to specialization of ARF function.

A significant number of auxin-responsive genes are dependent upon *NPH4/ARF7* or *ARF19* for the hormone response in seedlings (54, 87). In contrast, *arf2* mutant seedlings are not significantly compromised in auxin-responsive gene expression, although *HSS/ARF2* is involved in seedling growth (86). In developing flowers, auxin-mediated regulation of some genes requires *ARF6* and *FWF/ARF8* (80). These findings suggest some level of specificity for target genes among the ARFs. It is an intriguing possibility that different ARF proteins interact with different subsets of auxin-responsive genes. Clearly much work remains to be done to define the contribution of each ARF to auxin-responsive transcription and to developmentally regulated gene expression.

In addition to target specificity, the bases for ARF specialization likely include specific or preferred interactions with Aux/IAA proteins. Genomes of rice, poplar, and *Arabidopsis* each encode more than 20 Aux/IAA proteins, some of which show specific expression patterns (59, 108). Many gain-of-function *aux/iaa* mutations are associated with reduced response to exogenous auxin, but developmental defects among these mutants are frequently more specific and suggest that specific ARF-Aux/IAA pairs function in certain developmental contexts in vivo. Embryo patterning defects in *bdl/iaa12* mutants or plants expressing a stabilized IAA13 protein resemble those of the *ARF5* mutant *mp* (50). These defects are not effectively triggered by the *shy2–2* mutation in *IAA3* or by loss of ARF16 function (51, 136). However, *shy2–2/iaa3* but not *bdl/iaa12* inhibits *NPH4/ARF7* and *ARF19* activities in roots (136). These

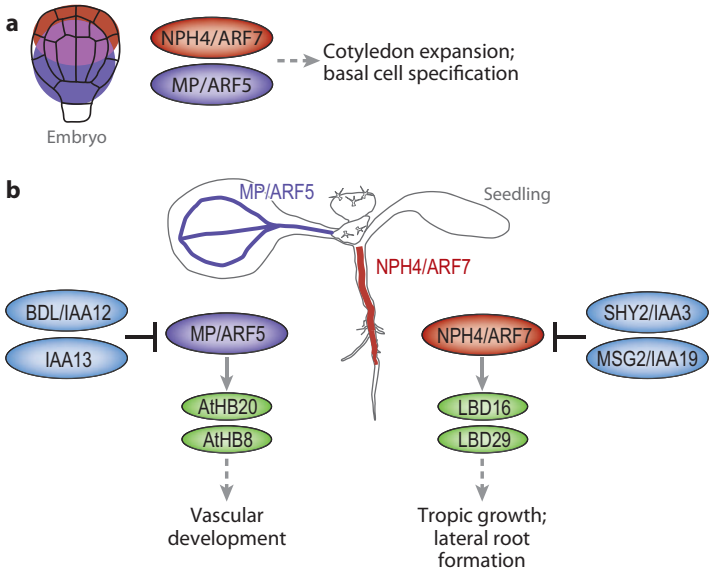

Figure 3

Functional specialization of NPH4/ARF7 and MP/ARF5 during early growth of *Arabidopsis*. (*a*) In the early *Arabidopsis* embryo, NPH4/ARF7 and MP/ARF5 are expressed in overlapping domains. NPH4/ARF7 is more abundant in developing cotyledons than in basal cells of the embryo and is not required for, but contributes to, basal cell fate specification (53). MP/ARF5 is required for specification of basal cell fate (52, 94). (*b*) In *Arabidopsis* seedlings, MP/ARF5 is expressed in developing vasculature and is a limiting factor in expression of *AtHB8* and *AtHB20*, leucine zipper transcription factors associated with procambial development (52, 53, 73). NPH4/ARF7 is expressed in hypocotyl tissue and is required for hypocotyl phototropism (54, 68, 87, 113). NPH4/ARF7 is also expressed in root tissues and is required for auxin-induced expression of *LBD16* and *LBD29*, LOB-domain transcription factors involved in lateral root formation (85, 87). Regions of ARF expression associated with the indicated developmental processes are indicated with colored lines in the seedling diagram. MP/ARF5 activity is regulated by BDL/IAA12 and IAA13, whereas NPH4/ARF7 is regulated by SHY2/IAA3 and MSG2/IAA19 (50, 118, 136).

results suggest that MP/ARF5 and BDL/IAA12 or IAA13 preferentially interact, whereas NPH4/ARF7, ARF19, and SHY2/IAA3 work together in roots (**Figure 3**). *NPH4/ARF7* also functions in hypocotyl phototropism, and defects in *arf7* mutants are also seen in *msg2/iaa19* (68, 103, 118). Together, this implies that NPH4/ARF7 is regulated by SHY2/IAA3 in roots and MSG2/IAA19 in hypocotyls. Therefore, ARF activities may be regulated by multiple Aux/IAA proteins in a tissue-specific manner. Together, ARF-Aux/IAA expression patterns, target genes, and the relative abundance, stability, and auxin sensitivity of each complex compose a suite of specialized complexes with the ability to regulate gene expression in diverse ways.

CONCLUDING REMARKS

The distribution and abundance of auxin response elements, the expression patterns of ARF proteins, and the differing stabilities of the Aux/IAA proteins (the auxin code) (119), coupled with the possibility for combinatorial interactions among ARFs, Aux/IAAs, transcriptional coregulators, and TIR1/AFB–Aux/IAA protein auxin coreceptors, have extraordinary regulatory potential. Although each component of auxin signaling is a member of a multiprotein family, there is currently little reason to believe that diverse family members act by mechanisms different from the one outlined here. Therefore, it is tempting to imagine numerous pathways, each mediating specific transcriptional outputs in different tissues and in response to different auxin concentrations or other stimuli. Considering also the intersections among different hormone signaling pathways, the roles of hormone signaling in regulating expression of the genome seem very complex indeed. It will be exciting to continue to unravel the networks effecting hormone action in plants.

SUMMARY POINTS

1. Auxin is perceived through direct interaction between Aux/IAA proteins and the TIR1/AFB family of F-box proteins. TIR1/AFB proteins assemble into SCF-type E3 ubiquitin ligase complexes that bind Aux/IAA proteins in an auxin-dependent manner and initiate their proteasome-mediated degradation.
2. The abundance of Aux/IAA proteins interprets auxin status to regulate activity of ARF transcription factors resident at *AuxRE*-containing promoters dispersed throughout the genome. *Aux/IAA* and *ARF* are each represented by multi-gene families encoding proteins that homo- and heterodimerize through interactions at conserved domains. Opportunities exist for combinatorial interactions among the Aux/IAA and ARF proteins, providing the potential for many layers of regulatory control.
3. Many genes are regulated by auxin through the auxin response factors (ARFs). ARFs are conserved throughout plant evolution and many have specialized functions in plant development.

FUTURE ISSUES

1. Although the *AuxRE* appears to be important for expression of some auxin-responsive genes, the function of the *AuxRE* in ARF-promoter interactions remains unclear. Analyses of ARF-promoter interactions in vivo, as well as analyses of ARF interactions with other transcription factors, are needed to characterize the mechanisms of ARF-promoter interaction.

2. Relatively little is known about the roles of auxin-responsive transcription factors in development and auxin response. Recent studies have elucidated the functions of some of these factors in specific developmental pathways, and additional studies of this type are needed to understand the contribution of auxin-responsive genes to plant growth and development.

DISCLOSURE STATEMENT

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Errata

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