REVIEW ARTICLE

The far side of auxin signaling: fundamental cellular activities and their contribution to a defined growth response in plants

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Abstract Recent years have provided us with spectacular insights into the biology of the plant hormone auxin, leaving the impression of a highly versatile molecule involved in virtually every aspect of plant development. A combination of genetics, biochemistry, and cell biology has established auxin signaling pathways, leading to the identification of two distinct modes of auxin perception and downstream regulatory cascades. Major targets of these signaling modules are components of the polar auxin transport machinery, mediating directional distribution of the phytohormone throughout the plant body, and decisively affecting plant development. Alterations in auxin transport, metabolism, or signaling that occur as a result of intrinsic as well as environmental stimuli, control adjustments in morphogenetic programs, giving rise to defined growth responses attributed to the activity of the phytohormone. Some of the results obtained from the analysis of auxin, however, do not fit coherently into a picture of highly specific signaling events, but rather suggest mutual interactions between auxin and fundamental cellular pathways, like the control of intracellular protein sorting or translation. Crosstalk between auxin and these basic determinants of cellular activity and how they might shape auxin effects in the control of morphogenesis are the subject of this review.

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Abbreviations

ABC	Atp-binding cassette
ABCB	ATP-BINDING CASSETTE SUBFAMILY B-TYPE
ABP1	AUXIN BINDING PROTEIN 1
ADA2	TRANSCRIPTIONAL ADAPTOR 2
AFB	AUXIN SIGNALING F-BOX
ARF	ADP-ribosylation factor
ARF	AUXIN RESPONSE FACTOR
ATI	Auxin transport inhibitor
ATP	Adenosine triphosphate
Aux/IAA	AUXIN/INDOLE ACETIC ACID
AUX1	AUXIN 1
BFA	Brefeldin A
CCP	Clathrin-coated pits
CCV	Clathrin-coated vesicles
CHC	Clathrin heavy chain
CHD	Chromodomain helicase DNA
CLASP	CYTOPLASMIC LINKER-ASSOCIATED PROTEIN
CLC	Clathrin light chain
eIF3h	Eukaryotic translation initiation factor 3 subunit H
ER	Endoplasmic reticulum
ETT	ETTIN
GCN5	GENERAL CONTROL NONDEPRESSIBLE 5
GEF	Guanine-nucleotide exchange factor
IAA	Indole-3-acetic acid
ICR1	INTERACTOR OF CONSTITUTIVE ROP 1
LAX	LIKE AUXIN 1
MAP	Microtubule-associated protein
MP	MONOPTEROS
MT	Microtubule

MVB	Multivesicular bodies
ORF	Open reading frame
PARL1	PARALLEL 1
PAT	Polar auxin transport
PILS	PIN-LIKES
PIN	PIN-FORMED
PKL	PICKLE
PP6	PROTEIN PHOSPHATASE 6
PRZ1	PROPORZ 1
PVC	Prevacuolar compartment
RIC	ROP-INTERACTIVE CRIB MOTIF-CONTAINING PROTEIN
ROP	Rho-type
RPL	Ribosomal protein of the large subunit
SCF	SKP, CULLIN, F-BOX
SEC3	SECRETORY 3
SKP2B	S-PHASE KINASE-ASSOCIATED PROTEIN 2B
SLR	SOLITARY-ROOT
SNX1	SORTING NEXIN 1
SPK1	SPIKE 1
STV1	SHORT VALVE 1
TGN/EE	Trans golgi network/early endosomes
TIR1	TRANSPORT INHIBITOR RESPONSE 1
TPL	TOPLESS
TPR	TPL-RELATED
uORF	Upstream ORF

Introduction

Plant growth regulators, also referred to as phytohormones, decisively influence plant development and environmental interactions. Similar to hormones in metazoans, the activity of these compounds is tightly controlled, with sophisticated pathways modulating activity and specificity of phytohormones. Auxin, for example, (indole-3-acetic acid, IAA, representing the predominant compound found in plants), had been implicated in the regulation of plant growth long before its chemical structure was identified (Kögl and Haagen-Smits 1931). Even Charles Darwin speculated about the participation of a mobile signal in the directional growth of plant organs (Darwin and Darwin 1881). Half a century later, Frits Went and Nikolai Cholodny independently demonstrated that auxin functions as a mediator of such tropic growth responses (Went 1926; Cholodny 1927). However, it took another half a century until the first molecular determinants mediating auxin responses were identified.

As with other plant hormones or secondary messengers, the auxin signals first need to be perceived by specific receptor molecules, and the initial signal consequently needs to be transmitted to ultimately promote hormonal responses. This

might be reflected in, for example, adjustments in the transcription of target genes leading to defined cellular responses. Auxin however, is quite unique among phytohormones, as plants have evolved complex machineries mediating intra- as well as intercellular polar auxin transport (PAT). This enables the establishment of hormonal concentration and—hence—activity gradients, thus shaping plant growth and development by active hormone transport mechanisms, which is unparalleled among plant growth regulators (Leyser 2011; Peer et al. 2011; Wabnik et al. 2011; Lau et al. 2012; Barbez and Kleine-Vehn 2013; Ljung 2013; Spalding 2013). In the first sections of this review, we provide an overview, summarizing general aspects of auxin transport and signaling. Further on, we summarize recent work, which has revealed novel insights into auxin-signaling pathways, thereby connecting auxin responses to global cellular activities and thus raising questions about the specificity of auxin-mediated growth control. These novel findings and scenarios, integrating fundamental activities in the regulation of auxin signaling are the main subject of this review.

Essentials of auxin perception and signaling

The search for proteins that might act as cellular receptors for auxin was already initiated by biochemical approaches in the 1970s. It was straightforward genetics though, that led to identification of *TRANSPORT INHIBITOR RESPONSE 1 (TIR1)*, the so far best-characterized auxin receptor in the model plant *Arabidopsis* (Ruegger et al. 1998; Gray et al. 1999; Dharmasiri et al. 2005a, b; Kepinski and Leyser 2005). TIR1 represents one of numerous F-box proteins that constitute part of a heteromeric F-box E3 ubiquitin ligase complex, which mediates the reversible covalent attachment of the small protein ubiquitin onto target proteins (Jackson and Eldridge 2002; Lechner et al. 2006). In the case of SCF$^{TIR1/AFB}$-type E3 ligases, this reaction depends on auxin binding by TIR1 or by closely related AUXIN SIGNALING F-BOX (AFB) proteins, which in turn enhances an interaction with short-lived AUXIN/INDOLE ACETIC ACID (Aux/IAA) proteins that function as auxin co-receptors (Theologis et al. 1985; Dharmasiri et al. 2003; Tan et al. 2007; Calderon Villalobos et al. 2012) (Fig. 1). Ubiquitylation of Aux/IAA proteins likely occurs as a result of auxin binding, leading to the subsequent degradation of Aux/IAA via the proteasomal pathway (Gray et al. 2001; Yang et al. 2004; Maraschin et al. 2009). Control of Aux/IAA degradation is crucial for plant responses to auxin, as it links hormone perception to the other essential function of Aux/IAA proteins in transcriptional regulation. Aux/IAA forms heterodimers with AUXIN RESPONSE FACTOR (ARF) transcriptional regulators via protein interaction domains located in the C-terminal portion of ARFs and Aux/
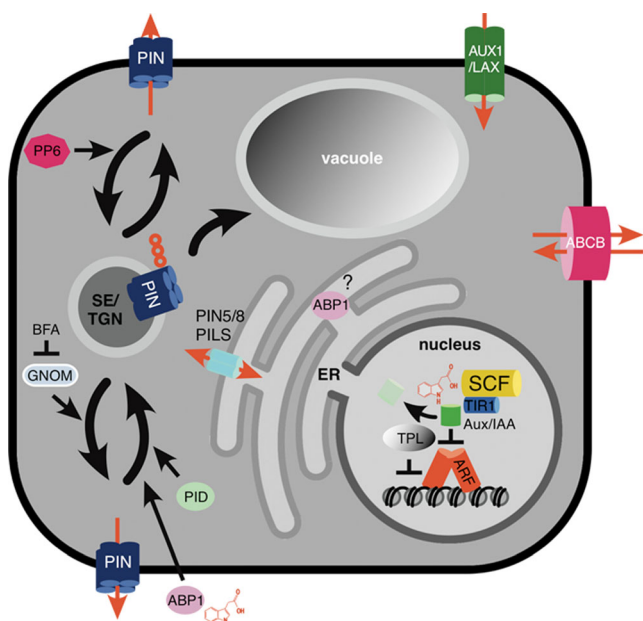
Fig. 1 Essential elements of auxin signaling and transport in plant cells. Auxin perception by nuclear SCF$^{TIR1/AFB}$ (*blue*, *yellow*) triggers ubiquitination and proteasome-mediated degradation of Aux/IAA co-receptors (*green*). As a result transcriptional repression via TPL (*grey*) activity and via Aux/IAA-mediated inhibition of ARF transcriptional regulators (*red*) is relieved. Auxin binding by extracellular ABP1 (*lilac*) impacts on endocytic protein sorting (see also Fig. 2a), whereas the role of ER-resident ABP1 is still not known. Cellular uptake of auxin is mediated by AUX1/LAX-type permeases (*green*) and by selected ABCB-type transporters (*pink*). Cellular auxin efflux requires PIN- (*blue*) and ABCB-type (*pink*) transport proteins. Auxin sequestration between cytoplasm and ER involves activity of PILS and PIN proteins (*turquois*) lacking the central hydrophilic loop that is characteristic for plasma membrane-resident PINs. Auxin transport proteins are subject to intracellular sorting from the plasma membrane to sorting endosomes (*SE*)/trans Golgi network (*TGN*). Recycling from SE/TGN to the plasma membrane involves activity of BFA-sensitive ARF-GEF GNOM, specifically for sorting at the basal cellular domain. PIN sorting and transcytosis is controlled by its phosphorylation status. PID (*light green*) kinase activity promotes sorting of phosphorylated PINs preferentially to the apical plasma membrane domain, a response that is antagonized by PP6 (*purple*) phosphatase activity triggering sorting to the basal domain. Apart from protein recycling and transcytosis between plasma membrane domains, PINs are also subject to endocytic sorting via late endosomes/multivesicular bodies into the lytic vacuole for their irreversible degradation. Sorting via this pathway is controlled by ubiquitination of PINs (*red circles*)

IAAs. Upon auxin-induced degradation of Aux/IAAs, ARF activity is no longer be repressed by heteromerization thus allowing transmission of auxin signals into downstream transcriptional networks (Kim et al. 1997; Ulmasov et al. 1997a, b; Tiwari et al. 2001) (Fig. 1). This, remarkably simple, mechanism of transcriptional de-repression appears to be sufficient for the integration of a highly diverse range of signaling events controlled by auxin. To some extent, this might explain the considerable number of Aux/IAA genes found in the genomes of higher plants (Liscum and Reed 2002), all of which in principle could interact with the

different SCF$^{TIR1/AFB}$ receptors (Calderon Villalobos et al. 2012). Variations in auxin-binding affinities, arising as a result of such variable interactions, might impact on the proteolytic turnover of Aux/IAAs, thereby specifying downstream ARF activities in transcriptional control (Calderon Villalobos et al. 2012; Yu et al. 2013). Moreover, plant genomes are characterized by extensive *ARF* gene families, whose members exhibit highly diverse expression profiles and activities. This allows for efficient fine-tuning and coordination of auxin-controlled transcriptional responses (Okushima et al. 2005; Overvoorde et al. 2005).

Further cellular activities, implicated in shaping auxin effects on transcription, are related to the control of chromatin architecture and histone modifications (Sablowski 2011; Yoshida et al. 2013). Topless (TPL) and TPL-related (TPR) proteins represent transcriptional co-repressors, down-regulating gene expression via interaction with diverse transcriptional regulators (Long et al. 2006; Smith and Long 2010; Wang et al. 2013b). Specifically, TPL/TPR appear to be involved in the recruitment of histone deacetylase activity, thus promoting establishment of a chromatin status, which is less accessible for the transcriptional machinery (Long et al. 2006; Wang et al. 2013b). TPL was demonstrated to physically interact with Aux/IAA proteins, suggesting that apart from sequestering ARFs, Aux/IAA-mediated down-regulation of auxin responses involves TPL-mediated establishment of a repressive chromatin status (Szemenyei et al. 2008) (Fig. 1). Clear-cut genetic evidence linking the regulation of chromatin architecture to established auxin signaling pathways came from screens for suppressors of *slr-1*, a dominant mutation in *SOLITARY-ROOT (SLR)/ IAA14*. *Slr-1* is entirely defective in auxin-regulated lateral root formation, due to a point mutation stabilizing the Aux/IAA protein (Fukaki et al. 2002). Loss of chromatin remodeling activity mediated by *PICKLE (PKL)/GYMNOS*, a CHD subfamily II ATP-dependent chromatin remodeling factor, suppresses *slr-1* lateral root formation defects. Such suppression of *slr-1* phenotypes by *pkl* requires *ARF* transcription factors that act in conjunction with *SLR/IAA14*, a finding that placed *PKL* together with ARFs in transcriptional regulation of lateral root development (Fukaki et al. 2006). Nevertheless, whilst PKL-mediated chromatin remodeling activity was found to determine histone H3 lysine 27 trimethylation levels at repressed loci (Zhang et al. 2012), it is still not resolved, whether auxin itself could influence PKL activities on chromatin. Additional studies support scenarios in which auxin directly impacts on chromatin architecture and histone modifications. Chromatin in the promoter region of *SKP2B*, an *Arabidopsis* F-box protein essential for cell cycle progression during early stages of lateral root formation, undergoes reversible adjustments in the composition of nucleosomes as well as histone acetylation in an auxin-dependent manner (Manzano et al. 2012). This was suggested

to modulate *SKB2B* expression in response to the growth regulator, being essential for transmission of hormonal signals on cell proliferation (Manzano et al. 2012). In another report, *PROPORZ1* (*PRZ1*)/*AtADA2b*, an *Arabidopsis* ortholog of ADA2 transcriptional adaptor protein (Sieberer et al. 2003; Vlachonasios et al. 2003), was demonstrated to channel auxin effects on histone acetylation in the promoter region of auxin-controlled loci, which coincided with alterations in auxin-responsive gene expression (Anzola et al. 2010). Similar to ADA2 homologs in other organisms, PRZ1 most likely represents a component of multi-subunit chromatin remodeling complexes that are required for the recruitment of histone acetyl transferase GCN5 to chromatin (Mao et al. 2006). *Prz1* shortcomings in controlling variations in histone acetylation thus could result from very general defects in chromatin remodeling activities (Anzola et al. 2010). Detailed insights into mechanisms of an epigenetic control that could transmit auxin signals via reversible histone modifications have however, not been provided so far.

Identification of another type of auxin receptor was originally based on characterization of auxin-binding activities in cellular fractions (Ray 1977; Cross and Briggs 1978; Jones and Venis 1989). Such experiments resulted in the identification of AUXIN-BINDING PROTEIN 1 (ABP1), which localizes predominantly to the ER (Hertel et al. 1972; Löbler and Klämbt 1985a, b; Shimomura et al. 1986) (Fig. 1). For several decades however, it was not clear, how ABP1 might participate in auxin-controlled processes, and only recently a role for ABP1 in post-transcriptional regulation of hormonal responses has been revealed (Robert et al. 2010; Xu et al. 2010). This work indicates that ABP1 functions as a positive regulator of clathrin-mediated endocytosis from the plasma membrane. ABP1 activity appears to be blocked upon auxin binding, resulting in inhibition of endocytosis (Robert et al. 2010). Furthermore, ABP1 function has been linked to polarity establishment in cells, which involves ABP1-mediated activation of downstream Rho-GTPases (ROP) to affect cytoskeleton organization (Xu et al. 2010). Thus unlike TIR1/AFB pathways, ABP1-mediated transmission of auxin signals primarily affects post-translational responses. To complicate matters further, a recent report has demonstrated additional ABP1 activities in the regulation of Aux/IAA protein via pathways antagonizing SCF$^{TIR1/AFB}$ activities (Tromas et al. 2013). This places ABP1 function in transcriptional regulation of responses to auxin, apart from its role in protein sorting. However, it remains a mystery as to how ABP1 might fulfill these quite different tasks. In particular, we still have no clear clue about mechanisms that would connect a predominantly ER-localized protein to activities at the plasma membrane (Löbler and Klämbt 1985b; Inohara et al. 1989). It appears that at least a minor portion of ABP1 escapes from the ER, and gets released into the extracellular apoplast, where upon auxin binding downstream signaling events might be initiated (Jones and Herman 1993) (Fig. 1). It is still unclear how ABP1 might enter the secretory pathway, as the specific trans-acting determinants involved have not yet been characterized. In addition, signaling from the extracellular apoplast to the cytosolic face of the plasma membrane would require docking to and signal transmission across the plasma membrane (Shi and Yang 2011). Determinants that could be involved in these aspects of ABP1-dependent auxin signaling events are under investigation, but still await functional characterization (Shi and Yang 2011; Sauer et al. 2013).

Key determinants of polar auxin transport

Ever since Darwin's work, an active relocation of endogenous signals has been implicated in the regulation of plant growth responses (Darwin and Darwin 1881; Boysen Jensen 1910). Subsequent experiments repeatedly demonstrated directional, polar transport of auxin along the main plant body axes, and a model has been put forward, integrating early observations and suggesting a remarkably simple mechanism for the transport of the hormone (Went and Thimann 1937; Rubery and Sheldrake 1974; Raven 1975). According to the chemiosmotic model, PAT along transport routes would involve cellular uptake of apoplastic, protonated IAAH either via uptake carriers or via diffusion across the plasma membrane. Once inside the cell, further export of deprotonated cytosolic IAA$^-$ into the apoplast would require activity of specific efflux carriers, and an asymmetric, polar distribution of such carrier proteins could pre-determine the direction of hormone transport within a given cell file (Rubery and Sheldrake 1974; Raven 1975). By making use of the model plant *Arabidopsis*, a number of auxin transport proteins have been identified, which essentially belong to three classes: (1) a family of intrinsic membrane proteins with resemblance to tryptophan permeases implicated in cellular uptake of the growth regulator; (2) a group of ATP-binding cassette membrane proteins involved in cellular efflux and uptake of auxin; and (3) a plant-specific class of membrane proteins involved in auxin cellular efflux as well as in intracellular compartmentalization of the growth regulator. Genetic and cell biological analysis of selected members of these classes of auxin transport proteins has provided substantial insights into the biology of auxin and has essentially confirmed the models for PAT proposed about 40 years ago (Luschnig 2002; Kramer 2004; Paponov et al. 2005; Geisler and Murphy 2006; Bandyopadhyay et al. 2007; Benjamins and Scheres 2008; Zazimalova et al. 2010) (Fig. 1).

AUXIN1 (AUX1) and LIKE AUX1 (LAX1) function in cellular uptake of the hormone, and analysis of mutants deficient in these loci demonstrated their involvement in auxin-regulated processes like organ tropism, control of lateral

root formation as well as phyllotactic patterning of leaves (Bennett et al. 1996; Marchant et al. 1999; Reinhardt et al. 2003; Swarup et al. 2005; Bainbridge et al. 2008). When viewing the localization of AUX1 in root meristems, a polar distribution was revealed in cells along major auxin transport routes. This presumably optimizes cellular uptake of the growth regulator and could be of particular importance for the establishment of transient auxin maxima in the regulation of growth responses (Swarup et al. 2005). Heterologous expression of AUX1 in *Xenopus* oocytes and in *Schizosaccharomyces pombe* indicated auxin uptake activity in a saturable manner at physiological pH, thus providing strong evidence for AUX1 function as an auxin uptake facilitator (Yang et al. 2006; Yang and Murphy 2009).

Among the plant ABC- or multidrug-resistant-type carrier proteins characterized to date, members of a subclade have been found to be involved in cellular efflux and uptake of auxin (Rea 2007). *ABCB1*, *4*, *19*, and *21* (*ATP-BINDING CASSETTE SUBFAMILY B-TYPE*) function in cellular auxin efflux (Gaedeke et al. 2001; Noh et al. 2001; Geisler et al. 2005; Terasaka et al. 2005; Kamimoto et al. 2012), and additional experimental evidence has demonstrated facultative auxin uptake activities for ABCB4 and ABCB21 which depended on cytosolic auxin concentrations (Terasaka et al. 2005; Kamimoto et al. 2012). Expression and subcellular localization of ABCB proteins, together with phenotypes of *abcb* loss-of-function mutants, and mutant combinations, led to models suggesting rather general functions in long-distance auxin transport and loading into such transport highways (Bandyopadhyay et al. 2007). In addition, ABCB auxin transport protein function has been linked to highly defined growth responses, like root hair formation, adventitious root formation, or phototropism (Cho et al. 2007; Christie et al. 2011; Sukumar et al. 2013). Modulation of some of these growth responses involves interaction between distinct auxin transport activities, specifying auxin distribution via mutual regulation of auxin transport proteins (Bouchard et al. 2006; Blakeslee et al. 2007; Mravec et al. 2008; Titapiwatanakun et al. 2009).

Mutants in some members of the PIN-FORMED (PIN) family, representing a plant-specific family of membrane proteins (Zazimalova et al. 2010), produce phenotypes that are suggestive of severe aberrations in auxin-controlled growth responses. *Pin1* mutant alleles, for example, exhibit broad defects in embryogenesis as well as in development of inflorescences and floral organs, whereas *pin2* alleles have initially been characterized as agravitropic root growth mutants (Bell and Maher 1990; Okada et al. 1991; Chen et al. 1998; Gälweiler et al. 1998; Luschnig et al. 1998; Utsuno et al. 1998). Additional phenotypes affecting diverse aspects of plant development have been identified in mutant combinations deficient in multiple PINs, underlining functional redundancies within this protein family (Blilou

et al. 2005; Vieten et al. 2005). Most importantly however, PIN localization studies revealed asymmetric, polar signals restricted to domains at the plasma membrane, a distribution that conforms to the chemiosmotic model for PAT. PIN1 for example accumulates at the basal end of vascular stele cells where it participates in rootward auxin transport towards the primary root meristem (Gälweiler et al. 1998). Similar results have been obtained for further PIN proteins, which exhibit a polar distribution at the plasma membrane, concurrent with the direction of auxin transport routes in different tissues and cell files (Müller et al. 1998; Friml et al. 2002, 2003; Benkova et al. 2003; Reinhardt et al. 2003; Sorefan et al. 2009). These observations linked PIN function to cellular auxin efflux, and results from auxin transport assays, performed either in plants or heterologous hosts, further supported this notion (Petrasek et al. 2006; Yang and Murphy 2009).

Owing to their central role in plant development, myriads of reports connecting PINs to a large variety of biological processes have been published since their initial discovery about 15 years ago. In that respect it is surprising that we still lack clear mechanistic insights into catalytic activities of PINs, as no transport assay in an entirely defined experimental system has been established. This is also true for PIN topology: no structural model as based on protein crystallization data has so far been provided for the PINs. Thus, for the time being, we need to deal with the fact that we still do not fully understand the function of PINs in auxin efflux in mechanistic terms (Peer et al. 2011). This might explain the rather vague term "auxin transport facilitator" that is frequently used in the literature when referring to PINs.

Apart from conventional PIN proteins characterized by two transmembrane domain regions and separated by a large hydrophilic loop, additional PIN proteins share the transmembrane domains but encode only a small central loop region (Krecek et al. 2009). These proteins appear evolutionary older than conventional PINs and were found to localize to ER membranes, where they have been implicated in the control of intracellular auxin homeostasis (Mravec et al. 2009; Dal Bosco et al. 2012; Ding et al. 2012b; Bender et al. 2013; Cazzonelli et al. 2013; Sawchuk et al. 2013). The purpose of auxin translocation across ER membranes is not fully understood, but it is evident that auxin redistribution between different intracellular compartments could influence a wide range of auxin-controlled signaling events (Barbez and Kleine-Vehn 2013) (Fig. 1). A biological significance of this activity is underlined further by characterization of another class of auxin transport proteins, exhibiting limited similarity to PINs, and therefore termed *PILS* (for *PIN-LIKES*) genes (Barbez et al. 2012). PILS proteins are found throughout the entire plant lineage and, by analogy to ER-resident PINs, appear to modulate intracellular auxin homeostasis (Barbez et al. 2012; Feraru et al. 2012).

While still not fully understood in terms of function, characterization of these different groups of PIN and PILS proteins changed our view on the evolution of auxin transport and signaling (Zazimalova et al. 2010; Feraru et al. 2012). The occurrence of ancestral ER-resident auxin transport proteins suggests that a common ancestor of auxin transport proteins first developed activities, mediating intracellular hormone transport. In the course of acquisition of morphological complexity, plants might have evolved modified PIN proteins that get sorted to the plasma membrane, allowing for directional, intercellular auxin transport. Perhaps, this was one of the prerequisites for orchestrating sophisticated developmental programs upon plants' conquest of land.

Protein sorting and auxin

The key to the establishment of directional intercellular auxin transport is a highly polar distribution of auxin transport proteins at distinct plasma membrane domains. Four major domains, comprising an apical and a basal domain together with proximal (inner) and distal (outer) lateral domains as well as additional sub-domains have so far been described in plant cells (Dettmer and Friml 2011; Yang and Lavagi 2012). Auxin transport proteins have been found at these domains and have been described to undergo dynamic rearrangements in their localization (Friml et al. 2002, 2003, 2004). The functional significance of such a polar distribution, and variations therein, was demonstrated by in planta expression of constitutively mis-localized PIN proteins. This coincided with alterations in auxin distribution and the occurrence of auxin-related growth defects, highlighting additionally a role for dynamic adjustments in PIN localization as a mediator of directional auxin transport (Wisniewska et al. 2006; Dhonukshe et al. 2010; Huang et al. 2010; Zhang et al. 2010).

Characterization of the machinery controlling the distribution of auxin transport proteins has revealed pathways that modulate sorting to and from distinct domains at the plasma membrane (Geldner 2009; Titapiwatanakun and Murphy 2009; Grunewald and Friml 2010; Richter et al. 2010; Robinson et al. 2012; Löfke et al. 2013). Plasma membrane proteins are sorted along the secretory pathway and reach their destination at the plasma membrane after passage through Golgi compartments and the *trans* Golgi network/early endosomes (TGN/EE) (Jürgens and Geldner 2007; Marti et al. 2010; Zarsky and Potocky 2010; Cai et al. 2011; Ding et al. 2012a). This is followed by re-internalization via endocytic sorting into TGN/EE, and recycling back to the plasma membrane, a response implicated in modulation of plasma membrane protein function (Geldner et al. 2001) (Fig. 2a). Alternatively, plasma membrane proteins are sorted into multivesicular bodies/prevacuolar compartment for degradation in the lytic vacuole (Richter et al. 2009;

Schellmann and Pimpl 2009; Reyes et al. 2011) (Fig. 2b). Recycling of plasma membrane proteins has been linked to ADP-ribosylation factor (ARF) GTPase activity that is controlled by ARF guanine-nucleotide exchange factors (ARF-GEF). Detailed analysis of PIN1 sorting revealed a Brefeldin A-(BFA)-sensitive ARF-GEF GNOM as an essential regulator for its recycling and transcytosis between distinct plasma membrane domains (Steinmann et al. 1999; Geldner et al. 2003; Kleine-Vehn et al. 2008a, 2010). In addition, protein phosphorylation, mediated by PINOID (PID) and related serine/threonine kinases, was found to affect PIN targeting and plant growth (Friml et al. 2004; Santner and Watson 2006; Michniewicz et al. 2007; Dhonukshe et al. 2010) (Fig. 2a). Specifically, phosphorylation of conserved TPRXS(N/S) motifs and further sites within the PIN central hydrophilic loop domain, appears to promote sorting to apical plasma membrane domains (Dhonukshe et al. 2010; Huang et al. 2010; Zhang et al. 2010), whereas PP6-type heterotrimeric phosphatase antagonizes such activity, favoring PIN sorting to basal cellular domains (Michniewicz et al. 2007; Dai et al. 2012; Ballesteros et al. 2013) (Fig. 2a). Next to intracellular protein cycling, proteolytic degradation via sorting to lytic vacuoles represents another means to adjust auxin transport activities (Abas et al. 2006; Kleine-Vehn et al. 2008b; Laxmi et al. 2008; Marhavy et al. 2011). Plants, by analogy to other eukaryotes, utilize reversible cargo ubiquitination as a recognition signal for protein sorting from the plasma membrane to the vacuole (Reyes et al. 2011; Korbei and Luschnig 2013), which is consistent with observations demonstrating that ubiquitination of *Arabidopsis* PIN2 functions as a vacuolar targeting signal (Leitner et al. 2012) (Fig. 2b).

Recent years have seen a systematic characterization of evolutionary conserved pathways for protein sorting in plants. It turns out that auxin decisively influences these stereotypic sorting processes, which has now established the phytohormone as a plant-specific regulator of universal cellular activities. Paciorek and colleagues were the first to demonstrate that treatment with potent auxin analogs, as well as alterations in intracellular auxin homeostasis, interfere with endocytic sorting of PIN proteins. This is hypothesized to modulate auxin flow as part of a regulatory feedback switch (Paciorek et al. 2005). Auxin effects on plasma membrane protein sorting, however, are quite general and not restricted to PIN proteins, acting via inhibition of clathrin-mediated endocytosis (Paciorek et al. 2005; Robert et al. 2010). In plants, experimental evidence for clathrin sorting has been provided only recently, controlling variations in protein abundance at the plasma membrane via endocyosis, with far-reaching implications for a range of metabolic pathways and signaling cascades (Dhonukshe et al. 2007). Clathrin represents a triskelion-shaped complex, comprising a structural backbone of three clathrin heavy chain (CHC)
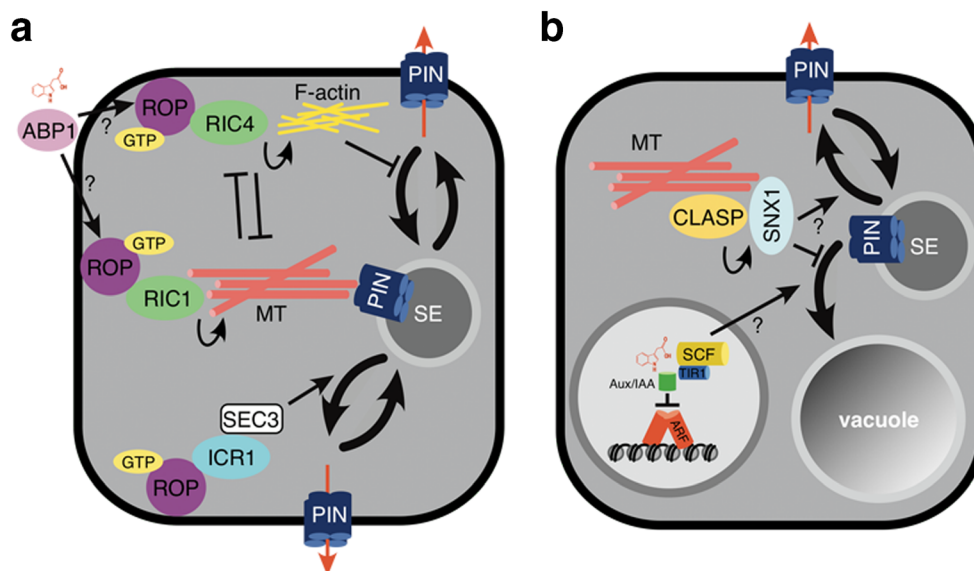
Fig. 2 Auxin and its role in protein sorting. **a** Auxin binding by extracellular ABP1 (*lilac*) causes activation of ROP GTPases (*purple*) and downstream effectors RIC1 and RIC4 (*green*). ROP2-RIC4 stimulates F-actin (*yellow*) accumulation at localized domains, which is suggested to antagonize clathrin-mediated endocytosis of plasma membrane proteins like PINs. This pathway is antagonized by ROP6-RIC1 activity promoting local formation of cortical MT arrays (*pink*), which interferes with activation of ROP2. ROP2 on the other hand sequesters RIC1, thereby blocking formation of ordered MT arrays. ICR1, another ROP-interacting protein (*light blue*) is essential for polarized distribution of PIN proteins at the plasma membrane. This

involves interaction with exocyst vesicle-tethering complex subunit SEC3 (*white*). **b** Decisions about endocytic sorting and further targeting on PIN proteins into the lytic vacuole depend on putative retromer subunit SNX1 (*light blue*), which functions as a gating factor, promoting protein recycling to the plasma membrane and thereby antagonizing vacuolar sorting. CLASP-(*yellow*)-mediated tethering of SNX1 to MTs (*pink*), links PIN sorting to cytoskeleton components and possibly ABP1-mediated signaling. Variations in auxin homeostasis sensed by nuclear SCF$^{TIR1/AFB}$ auxin receptor induce vacuolar sorting of PIN proteins. Mechanisms and pathways involved are still elusive

molecules, and three clathrin light chain (CLC) molecules, which upon interaction form a polyhedral clathrin lattice (Kirchhausen and Harrison 1981; Kirchhausen et al. 1986; Royle 2006). For endocytic cargo sorting, clathrin needs to associate with the plasma membrane, where it interacts with cargo, adaptor protein complex-2 and further accessory proteins, resulting in formation of clathrin-coated pits. In animals, this is followed by maturation into cargo-loaded clathrin-coated vesicles (CCV) upon internalization from the plasma membrane and analogous processes appear to be present in plants (Royle 2006; Kitakura et al. 2011; Ito et al. 2012; Di Rubbo et al. 2013; Fan et al. 2013; Kim et al. 2013; Wang et al. 2013a; Yamaoka et al. 2013).

Auxin's effect on endocytic sorting has been linked to the control of clathrin recruitment at the plasma membrane. In fact, synthetic auxin analogs and IAA were found to interfere with recruitment of *Arabidopsis* CLC and CHC isoforms to the plasma membrane, thereby interfering with CCV assembly and endocytic sorting (Robert et al. 2010; Wang et al. 2013a). Inhibitory effects of auxin on CLC recruitment to the plasma membrane appear to be mediated by auxin-binding by ABP1, whereas SCF$^{TIR1/AFB}$-controlled auxin perception seems dispensable thus supporting models in which ABP1 acts as positive regulator of clathrin-dependent endocytosis (Kitakura et al. 2011; Wang et al. 2013a). Downstream components

linking ABP1 signaling to endocytic sorting comprise ROP-type small GTPases, which were demonstrated to be activated by auxin in an ABP1-dependent manner (Xu et al. 2010) (Fig. 2a). ROPs represent the only small GTPase family found in plants, with several of its members implicated in intracellular cargo sorting via regulating actin and microtubule components of the cytoskeleton (Molendijk et al. 2001; Gu et al. 2003; Vernoud et al. 2003; Fu et al. 2009; Craddock et al. 2012) and a number of elegant studies have now established their role in auxin responses via organization of the cytoskeleton. *Arabidopsis ROP2* was shown to affect PIN1 endocytosis in emerging lobe regions of interdigitated leaf pavement cells (Nagawa et al. 2012). This involves the activity of the *ROP2* effector *RIC4* (ROP-INTERACTIVE CRIB MOTIF-CONTAINING PROTEIN), which stimulates localized accumulation of F-actin and is suggested to antagonize clathrin-dependent endocytosis of PIN1 (Nagawa et al. 2012) (Fig. 2a). A related pathway has been proposed for PIN2 sorting in root meristem cells, with the SPK1-(for SPIKE1, an activator of ROP6)-ROP6-RIC1 regulatory module promoting actin filament stabilization and supposedly interfering with clathrin-dependent PIN2 endocytosis (Chen et al. 2012; Lin et al. 2012). PIN retention at the plasma membrane might cause elevated auxin flow into the apoplast, which in turn could induce auxin signaling via apoplastic

ABP1, altogether constituting a robust feed-forward loop essential for auxin-driven growth responses (Yang and Lavagi 2012).

Auxin-controlled ROP activity has been connected to microtubules (MT) as well, seemingly antagonizing auxin effects mediated via control of the actin cytoskeleton. ROP6 was found to bind and activate RIC1 a MT-associated protein (MAP) in an ABP1-dependent manner (Fu et al. 2005, 2009; Xu et al. 2010). This in turn would promote localized accumulation of cortical MT arrays that are aligned perpendicular to the axis of cell expansion and are implicated in guidance of cellulose synthase activity (Crowell et al. 2009; Bringmann et al. 2012) (Fig. 2a). Variations in ROP6 activity could thus modulate cell expansion via differential cellulose deposition at the cell wall. Activated ROP2, on the other hand, locally sequesters RIC1 to interfere with ordered MT alignment, whereas RIC1-mediated MT array organization suppresses activation of ROP2 (Xu et al. 2010). Thus ROP2 and ROP6 pathways mutually inhibit each other in the organization of the cytoskeleton, which presumably feeds back on the sorting of PINs and corresponding auxin transport activities in the control of morphogenesis (Yang and Lavagi 2012) (Fig. 2a). Another link between ROP activity and PIN sorting was established by Hazak and colleagues, who demonstrated an involvement of the ROP effector ICR1 (INTERACTOR OF CONSTITUTIVE ACTIVE ROP1) in the control of polar PIN distribution at the plasma membrane (Hazak et al. 2010). Notably, an earlier report demonstrated interaction between ICR1 and SEC3, the latter representing a subunit of an *Arabidopsis* vesicle-tethering exocyst protein complex (Lavy et al. 2007; Zarsky et al. 2009; Zhang et al. 2013) (Fig. 2a). Such interaction would suggest a role for ROP-ICR1 in secretory protein sorting, potentially modulating exocyst activity and its effects on PIN distribution at the plasma membrane (Drdova et al. 2013).

While it seems evident that the organization of the cytoskeleton feeds back on auxin distribution via sorting of auxin transport proteins, mechanisms linking, e.g., PIN sorting to the cytoskeleton remain to be resolved (Geldner 2009; Heisler et al. 2010; Brandizzi and Wasteneys 2013). A recent report has come up with an intriguing model, linking MTs, the predicted *Arabidopsis* retromer component SNX1 (SORTING NEXIN 1) and PIN sorting (Ambrose et al. 2013). The authors demonstrated that a MAP termed CLASP (CYTOPLASMIC LINKER-ASSOCIATED PROTEIN) interacts with SNX1 to tether retromer-associated endosomes to MTs (Fig. 2b). SNX1 has been implicated in PIN2 sorting, presumably acting as a gating factor that promotes recycling of endocytosed PINs back to the plasma membrane (Jaillais et al. 2006, 2008; Kleine-Vehn et al. 2008b). In the absence of either SNX1 or CLASP, PIN2 no longer efficiently recycles to the plasma membrane but relocates to the vacuole for its degradation, underlining a role for both proteins as positive effectors of PIN recycling

(Kleine-Vehn et al. 2008b; Ambrose et al. 2013). While conflicting evidence for CLASP function in PIN sorting has been published elsewhere (Kakar et al. 2013), data presented by Ambrose and colleagues strongly support a function for MTs in PIN recycling, presumably controlled by SNX1/CLASP-mediated tethering of sorting endosomes to MTs (Ambrose et al. 2013). Perhaps, ROP effects on microtubule organization modulate such interaction, indirectly affecting sorting and recycling of PIN proteins.

Experiments and results, linking auxin-binding by ABP1 to cytoskeleton organization and PIN endocytic sorting, suggest that variations in PIN retention time at the plasma membrane modulate auxin efflux rates that are further translated into developmental cues. Notably, another link between actin and auxin transport has been established, highlighting effects of auxin transport inhibitors (ATI) on the dynamic distribution of the auxin transport machinery. Specifically, 2,3,5-triiodobenzoic acid and 2-(1-pyrenoyl) benzoic acid, which both efficiently block cellular auxin efflux, were found to interfere with organization of the actin cytoskeleton with drastic consequences for protein endocytosis and vesicle motility, including the sorting of PINs (Geldner et al. 2001; Dhonukshe et al. 2008). Whether or not treatment with ATIs affects pathways overlapping with those controlled by ABP1 is currently not known. Nevertheless, ATI effects on the actin cytoskeleton underline the significant role for intracellular vesicle dynamics in the regulation of PAT.

Crosstalk between ABP1 and clathrin has established a plausible function for this auxin receptor. However, auxin signaling via SCF$^{TIR1/AFB}$-controlled pathways contributes to the regulation of endocytic sorting as well. Apart from auxin-induced inhibition of PIN endocytosis, the opposite effect, namely enhanced degradation of PINs, has been observed upon alterations in auxin homeostasis (Sieberer et al. 2000; Vieten et al. 2005; Abas et al. 2006; Baster et al. 2013). PIN2 in particular, undergoes vacuolar sorting in response to altered auxin levels, presumably mediated by increased protein ubiquitination, which signals enhanced turnover of the auxin carrier protein (Leitner et al. 2012). It seems possible that down-regulation of PINs in response to auxin antagonizes inhibitory auxin effects on plasma membrane protein endocytosis, resetting cellular PIN protein levels back to default. This could be of particular importance for the control of differential growth responses that involve transient establishment of auxin maxima (Band et al. 2012). When trying to elucidate pathways involved, it turned out that SCF$^{TIR1/AFB}$-controlled auxin signaling is essential for PIN vacuolar sorting, while ABP1 is not, demonstrating that both major auxin-signaling pathways are involved in overlapping but distinct aspects of intracellular sorting of PIN proteins (Sieberer et al. 2000; Baster et al. 2013) (Fig. 2a,b).

Insights into pathways transmitting effects of auxin perception by ABP1 or SCF$^{TIR1/AFB}$ to the sorting of

membrane proteins in general, or PIN proteins in particular, are still rudimentary. However, given the prominent phenotypes that can be observed, when disturbing such signaling, it seems clear that auxin-mediated regulation of protein sorting is one of the key regulators of plant morphogenesis. Consistently, genetic or pharmacological interference with cytoskeleton organization and/or clathrin-mediated sorting processes results in phenotypic alterations, characteristic for auxin signaling and/or transport mutants (Dhonukshe et al. 2008; Kitakura et al. 2011; Wang et al. 2013a). While this underlines essential roles for auxin in a multitude of developmental processes, it seems quite unlikely that all the classical "auxin-related" phenotypes that can be observed upon affecting, e.g., endocytic sorting processes, arise as an exclusive consequence of altered auxin transport or signaling. Rather it appears that phenotypes observed in auxin signaling and transport mutants reflect widespread, combinatorial consequences of altered protein sorting, not necessarily directly related to a disturbance of PAT. Perhaps, it will be necessary to reevaluate causes and consequences of the broad phenotypic responses that arise as result of highly pleiotropic activities of this universal plant growth regulator.

Auxin and translational control

Auxin-clathrin crosstalk underlines the hormone's role in an evolutionary conserved pathway, whereas analysis of mutants defective in ribosomal function have linked auxin signaling to translational regulation, another fundamental feature of gene expression control. Mutants affected in ribosomal protein functionality exhibit growth defects reminiscent of phenotypes observed upon disturbing auxin transport or signaling (Van Lijsebettens et al. 1994; Ito et al. 2000; Weijers et al. 2001; Degenhardt and Bonham-Smith 2008; Szakonyi and Byrne 2011). Similar auxin-related defects are caused by a mutation in the nucleolin PARL1 (PARALLEL1) likely required for ribosomal maturation (Petricka and Nelson 2007). It remains unclear though, as to how defects in such general determinants of cellular metabolism could result in rather specific auxin-related phenotypes. A mechanistic link between auxin, translational control, and protein sorting was established when screening mutagenized Arabidopsis seedlings for defects in vacuolar cargo sorting (Rosado et al. 2010). In this report the authors identified mutations in the ribosomal proteins RPL4A and RPL4D, and found that both loci are required for efficient vacuolar sorting of synthetic reporter proteins (Miao et al. 2008; Rosado et al. 2010). In addition, rpl4a turned out to be deficient in vacuolar targeting of PIN2, and mutant vacuolar sorting defects could be phenocopied by application of high concentrations of auxin, causing secretion of reporter proteins, instead of sorting to the vacuole (Rosado et al. 2010). Intriguingly, the authors observed that expression of RPL4A

is responsive to auxin and to inhibition of auxin transport, which led them to suggest that auxin could modulate ribosomal biogenesis, linking ribosome function to auxin signaling and protein sorting (Rosado et al. 2010).

Similar to characterized ribosomal protein or ribosome biogenesis mutants, rpl4 alleles exhibit developmental aberrations that appear related to altered auxin responses, and models have been put forward in an attempt to explain these rather specific growth defects. Formation of heterogeneous populations of ribosomes characterized by incorporation of different ribosomal protein isoforms has been proposed to cause variations in the ribosomes' specificity for different transcripts or transcript groups. As an alternative, a role for ribosomal gene dosage, rather than variations in ribosome composition has been suggested to modulate efficiency of protein translation, which might affect cellular processes primarily related to auxin signaling (Giavalisco et al. 2005; Komili et al. 2007; Carroll et al. 2008; Rosado et al. 2010). However, all these models fall short when trying to explain the specific defects of ribosomal protein mutants, without further knowledge about downstream targets modulated by such translational control.

A study by Nishimura and colleagues provided some insights into mechanisms that could link translational control to the regulation of auxin responses (Nishimura et al. 2005). The authors identified a mutant they termed short valve 1 (stv1), exhibiting apical-basal patterning defects in the gynoceum that are reminiscent of mutants defective in the ARF transcriptional regulators ETTIN (ETT/ARF3) and MONOPTEROS (MP/ARF5) (Sessions et al. 1997; Hardtke and Berleth 1998). Cloning of STV1 revealed that it encodes RPL24B, a ribosomal protein found in archaebacterial and eukaryotic genomes and implicated in enhancing translational efficiency (Dresios et al. 2000). On top of that, Arabidopsis RPL24 was found to interact with a viral transactivator protein, and to stimulate translational efficiency via translation reinitiation of polycistronic viral RNA (Park et al. 2001). In eukaryotes, translation reinitiation has been shown to modulate translation of ORFs that are flanked by an upstream, translatable ORF located in the 5′-leader region of the mature mRNA (Kozak 1999; Roy and von Arnim 2013). Upon initiation of translation, such uORFs are recognized by the scanning translation initiation complex that moves along the mRNA, prompting translation of these—often times very small—ORFs (Rajkowitsch et al. 2004). Subsequent translation of the "main" ORF, located downstream of the uORF requires efficient translation reinitiation, ensuring that the ribsome resumes scanning to recognize downstream Start AUGs (Park et al. 2001; Zhou et al. 2010). Transcripts of both, ETT and MP encode uORFs, which might suggest that stv1 patterning defects could reflect deficiencies in the translational control of these ARF genes. Indeed, when expressing an engineered ETT transcript lacking its 5′ uORF, stv1 patterning defects were partially suppressed, supporting scenarios, in

which *RPL24B* modulates auxin responsive organ development via controlling translational reinitiation of *ARF* genes (Nishimura et al. 2005). Related observations have been made with *rpl4d* and *rpl5a* ribosomal protein mutants and with a mutant in translational initiation factor eIF3h, seemingly affected in translation of *ARF* loci that all are characterized by uORFs in their 5′-regions (Zhou et al. 2010; Rosado et al. 2012) (Fig. 3).

Control of ARF expression via reinitiation of translation might represent an integral part of auxin signaling cascades, controlling intracellular protein sorting via adjustments in transcriptional control of auxin responses (Rosado et al. 2010, 2012). However, about one third of *Arabidopsis* mRNAs appears to contain uORFs (Kim et al. 2007), all potentially subject to expression control via translation reinitiation. Assuming that *RPL24B* and additional determinants of translational control are involved in expression control of all these loci, it appears questionable that auxin-related growth defects arise as an exclusive consequence of diminished expression of such a huge proportion of the *Arabidopsis* proteome. Analogous to the situation described for crosstalk between auxin and components of the cytoskeleton, phenotypes of ribosomal mutants clearly reflect the outstanding importance of auxin signaling and transport. However, a closer look on phenotypes and the proteome of these mutants is definitely required to characterize the role of translational control in higher plants.

Another even more puzzling link between translational control and auxin signaling was established when characterizing a dominant, auxin-resistant *Arabidopsis* mutant derived from a screen performed in the presence of sirtinol (Perry et al. 2005). Apart from being less responsive to externally applied auxin, mutant plants exhibited defects in apical hook formation upon germination in the dark and developed less lateral roots, both representing hallmark features of auxin-response mutants. The mutation responsible for these phenotypes was found in the anticodon loop of a tRNA^{Ala}, changing its anticodon from 5′-CGC-3′ to 5′-CAC-3′, which no longer recognizes alanine but valine codons, instead (Perry et al. 2005). Given that further tRNA identity determinants are not affected by this mutation, it seems likely that, although charged with alanine, the mutant tRNA will correctly associate with ribosomes and valine triplett codons, resulting in translation of mutant proteins. The *Arabidopsis* genome is predicted to contain 630 tRNA loci, amongst which 33 will recognize a codon for alanine, whereas 30 will bind to valine codons. When not considering wobbling, seven tRNA^{Ala} will recognize 5′-GCG-3′ codons, whereas 8 tRNA^{Val} will interact with 5′-GUG-3′ codons, suggestive of a substantial degree of functional redundancy within these tRNA families ((Lowe and Eddy 1997); http://gtrnadb.ucsc.edu/Athal/). In that respect it is quite surprising that a mutation in a single tRNA locus is sufficient to cause such dramatic effects on plant development. Perhaps even more surprising is the observation that defects in auxin-controlled growth responses appear to represent the major consequence of this mutation. Unfortunately, we still lack detailed information on tRNA expression control in plants (Lin et al. 1992; Stange et al. 1992; Carneiro et al. 1994; Ulmasov and Folk 1995). So, it remains a mystery as to how a single tRNA anticodon mutation could produce highly defined growth defects, as those observed by Perry and colleagues (Perry et al. 2005).

Outlook

In recent years, the plant community experienced an almost inflationary increase of data, linking auxin to essentially every
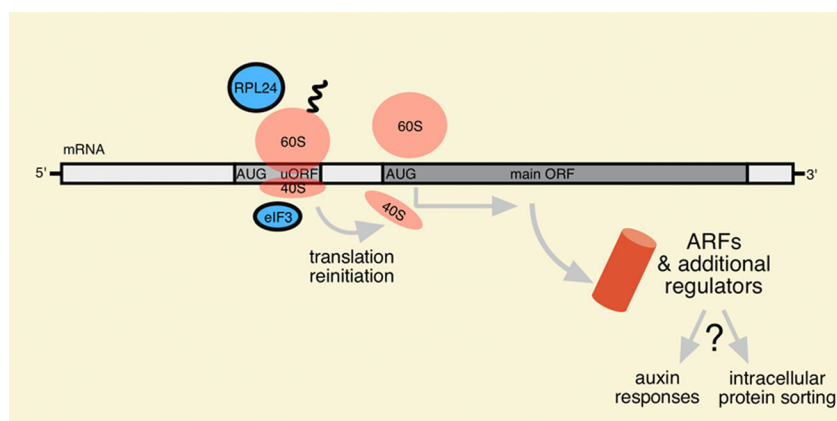

Fig. 3 Translational control as a mediator of auxin signaling. Translation of mRNAs comprising uORFs commences with initiation of translation at the AUG of the uORF (ribosomal subunits in *pink*). Further translation of the main ORF positioned downstream of the uORF, depends on efficient translation reinitiation, which is stimulated by ribosomal proteins like RPL24 or translation initiation complex subunit eIF3 (*blue*). Several mRNAs encoding ARF transcription factors were found to contain uORFs. Variations in availability and/or functionality of rate-limiting determinants of translation reinitiation like *RPL24* could define amounts of ARF protein and additional regulatory proteins to control auxin responses and intracellular protein sorting

aspect of plant growth and development. By pursuing a range of experimental approaches, substantial progress has been made in the molecular characterization of auxin signaling cascades, metabolism as well as transport processes. However, in-depth analysis and integration of all these findings into coherent networks lags behind. This is particularly true for some key components of the auxin network like the PIN proteins and ABP1, as their actual function is still not entirely resolved. Also, new approaches are needed to elucidate crosstalk between auxin signals and general cellular activities like cytoskeleton organization or translational control. In the light of these far-reaching auxin effects, a systematic characterization of the underlying mechanisms and targets involved should be given highest priority. This will greatly improve our understanding of plant growth in general, and will also provide a solid foundation for further studies aiming at an integration of auxin responses into a multidimensional network of cellular activities.

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