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Plant Hormone Transport and Localization: Signaling Molecules on the Move

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Abstract

Plant hormones are a group of small signaling molecules produced by plants at very low concentrations that have the ability to move and function at distal sites. Hormone homeostasis is critical to balance plant growth and development and is regulated at multiple levels, including hormone biosynthesis, catabolism, perception, and transduction. In addition, plants move hormones over short and long distances to regulate various developmental processes and responses to environmental factors. Transporters coordinate these movements, resulting in hormone maxima, gradients, and cellular and subcellular sinks. Here, we summarize the current knowledge of most of the characterized plant hormone transporters with respect to biochemical, physiological, and developmental activities. We further discuss the subcellular localizations of transporters, their substrate specificities, and the need for multiple transporters for the same hormone in the context of plant growth and development.

Contents

INTRODUCTION

The sessile nature of plants limits their ability to escape fluctuations in ever-changing environments, including abiotic stresses such as drought, flood, cold, high temperature, and high salinity

and biotic stresses such as pathogen infection and insect injury. To cope with inconsistent environments, plants have developed efficient mechanisms that allow them to sense and adapt to environmental changes. Plant hormones are the major players in these mechanisms, with essential roles in plant growth, development, and responses to environmental stresses. Several levels of regulation master the overall hormone responses, including hormone biosynthesis, transport, catabolism, perception, and transduction. Notably, the combination of a plant's ability to produce hormones in specific cell types or tissues with transport of the hormones when needed over time and space results in hormone gradients and maxima that are critical for proper responses (79, 111). Hormone movement may involve cell-to-cell, long-distance shoot-to-root or root-to-shoot, or subcellular transport; transport from one tissue to another; or an uptake process that results in sinks. Hormone sinks may be required for induced responses but also may restrict a response in a distal tissue or specific cell types (4). Research in recent years has shed light on where these hormones are produced, where they move, what transporters allow the movement, and where the hormones accumulate and act (4, 79, 111, 122). This review systemically summarizes the characterized transporters for several hormones, including auxin, abscisic acid (ABA), cytokinin (CK), gibberellin (GA), ethylene, and jasmonic acid (JA), with descriptions of subcellular localizations, expression patterns, transport activities, and physiological functions. Finally, we elaborate on hormone transport assays, multisubstrate specificity, and the importance of mapping plant hormones and their metabolites at the subcellular level.

Auxin: the first identified plant hormone that orchestrates many processes, such as cell division; elongation and differentiation; embryonic development; and root growth, development, and tropisms

Abscisic acid (ABA): a long-transported plant hormone that modulates multiple aspects of plant growth, development, and stress responses

Cytokinin (CK): a member of a class of phytohormones that promote cell division, root and shoot development, and responses to biotic and abiotic stresses

Gibberellin (GA): a phytohormone that regulates stem elongation, germination, dormancy, flowering, flower development, suberin formation, and leaf and fruit senescence

Ethylene: a gas plant hormone affecting plant growth, development, fruit ripening, root compactness, and stress responses throughout the plant life cycle

Jasmonic acid (JA): a plant hormone regulating plant responses to abiotic and biotic stresses and plant growth and development

ABSCISIC ACID

Abscisic Acid Background

ABA, a weak acid discovered over six decades ago, regulates many stages of plant growth and development from germination to seed dormancy and modulates plant responses to changing environmental factors (106, 151). ABA was long thought to be transported by the xylem from root to aerial plant tissues to initiate stomatal closure under stress conditions (56, 134, 166, 176). However, grafting assays showed that ABA is synthesized in both the root and shoots (78, 96). Furthermore, aerial organ-derived ABA promotes root growth and regulates plant responses to water deficit (91, 95).

Abscisic Acid Transporters and Distribution

Several ABA transporters have been characterized, shedding light on mechanisms of ABA homeostasis and distribution in vivo (**Figure 1**). The first ABA transporters identified were *Arabidopsis* ATP-binding cassette (ABC) G-family proteins ABCG25 and ABCG40 (64, 77). ABCG25 is a plasma membrane–localized ABA exporter mainly expressed in the vascular veins of leaves. This transporter regulates stomatal closure. ABCG40 is an ABA importer broadly expressed in roots and guard cells of leaves. It is localized on the plasma membrane and regulates stomatal closure (64).

ABA is involved in seed germination and dormancy. Kang et al. (66) showed that ABCG25 and ABCG31 transport ABA out of the endosperm and that ABCG30 and ABCG40 cooperate to transport ABA into the embryo, promoting seed dormancy in *Arabidopsis*. ABA transporters MtABCG20 and LR34res were characterized in *Medicago truncatula* and wheat, respectively. MtABCG20 functions as an ABA exporter and regulates lateral root and nodule development (115). The wheat *LR34res* allele is required for resistance against multiple fungal pathogens (74). The ABA uptake activity of LR34res was confirmed in both a yeast system and *Oryza sativa* seedlings. These reports show that ABCG ABA transporters manipulate ABA homeostasis and distribution in vivo to regulate plant growth, development, and responses to surroundings.

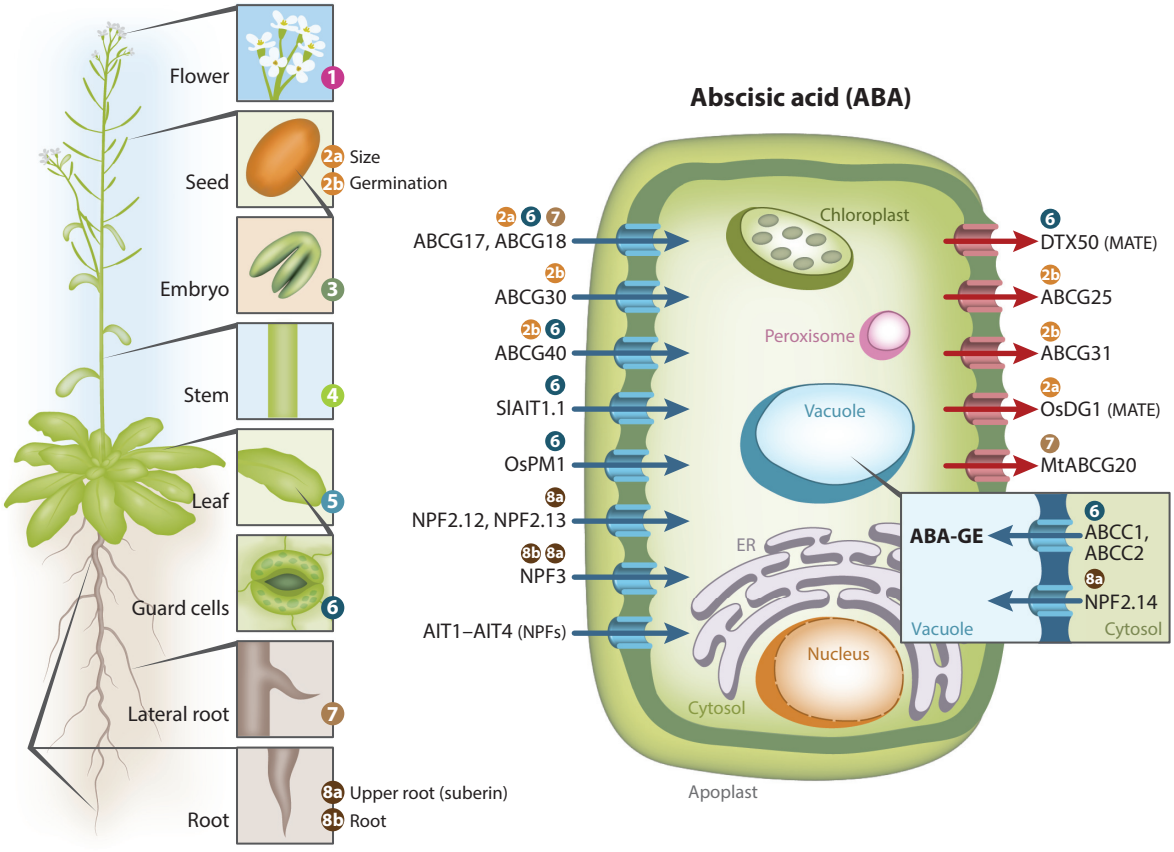

Figure 1

Overview of ABA transporters in plants. (*Left*) Illustration of an *Arabidopsis* plant with magnifications emphasizing different organs. (*Right*) Overview of the characterized ABA transporters illustrated on the schematic of a cell. Blue arrows represent importers; red arrows represent exporters. (*Inset*) Magnification of the indicated organelles. The proteins transport the bioactive ABA unless indicated otherwise. The numbers in circles above transporter names indicate tissues in the illustration on the left (not all tissues express transporters regulating this hormone). All transporters were characterized in *Arabidopsis* unless the transporter name is preceded by a species abbreviation. Abbreviations: ABA, abscisic acid; ABA-GE, abscisic acid glucose ester; ER, endoplasmic reticulum; MATE, multidrug and toxic compound extrusion; Mt, *Medicago truncatula*; NPF, nitrate transporter/peptide transporter; Os, *Oryza sativa*; Sl, *Solanum lycopersicum*.

The nitrate transporter/peptide transporter (NPF) proteins are another family of ABA transporters (21, 67). *Arabidopsis* ABA-IMPORTING TRANSPORTER 1 (AIT1), AIT2, AIT3, and AIT4 (also known as NPF4.6, NPF4.5, NPF4.1, and NPF4.2, respectively) function as ABA transporters in yeast transport assays, with the exception of AIT1, for which an ABA transport function has not yet been confirmed in planta. The tomato NPF SlAIT1.1 imports ABA to regulate stomatal aperture and transpiration (142). Binenbaum and colleagues (11) recently identified a monophyletic clade of NPF transporters required for GA and ABA translocation in *Arabidopsis*. Whereas NPF2.12 and NPF2.13 are plasma membrane–localized ABA importers, NPF2.14 functions as a tonoplast-localized ABA transporter (**Figure 1**). NPF2.12, NPF2.13, and NPF2.14, together with NPF3, regulate GA and ABA movement from the vasculature to the endodermis to induce suberin formation in the root mature zone (11).

The multidrug and toxic compound extrusion (MATE)-type transporter *Arabidopsis* DTX50 has been shown to promote ABA efflux (120, 177). DTX50, which is localized to the plasma membrane, exports ABA in *Escherichia coli*, *Xenopus* oocytes, and *Arabidopsis* protoplast transport assays (178).

AWPM-19-like family member OsPM1 is a rice plasma membrane–localized ABA importer that regulates stomatal closure to respond to drought responses and seed germination (175).

There are various ABA conjugates in plants. The predominant conjugate form, ABA glucose ester (ABA-GE) (13), is detected in the xylem sap of various plants and may be the form of ABA that is transported over long distances (45, 61, 79). Researchers have suggested that ABCC1 and ABCC2, localized on tonoplasts, regulate ABA-GE uptake into the vacuoles for storage in an inactive form (17, 18, 81, 171) (**Figure 1**). However, no significant phenotypes were observed in root or shoot growth of *abcc1* and *abcc2* single or *abcc1 abcc2* double mutants upon drought or osmotic stress treatment. Further research is needed to determine the function of ABA-GE transport.

Several ABA reporters and sensors have been developed in the past few years, including the ABA Förster resonance energy transfer (FRET) biosensors that allow tracking ABA distribution and concentrations in real time (62, 129). More recently, Zhou et al. (185) have modified the FRET-based ABA sensor ABAleon (161) to target the endoplasmic reticulum (ER) membrane through the central ABA sensing module exposed to the cytosol and the ER lumen. The soluble and ER membrane–targeted ABA sensors show an ER-specific increase in the level of ABA under light, cold, and high-sulfate supply conditions compared with cytosolic ABA, suggesting that the ER is of importance in the regulation of subcellular ABA homeostasis during plant growth and stress responses. The use of these and future sensors with higher sensitivity is expected to reveal further details about how ABA moves in the plant and where it accumulates (at whole-plant and subcellular levels) under normal growth and during stress.

Physiological and Developmental Highlights of Abscisic Acid Transport

The discovery that two ABA biosynthetic genes, *ABA2* and *AAO3*, are coexpressed in the phloem companion cells together with *ABCG25* suggests that these cells are the site of ABA synthesis in the vasculature. ABA biosynthesis in the phloem companion cells is sufficient to induce guard cell responses, which suggests that ABA synthesized in these cells is translocated to target cells in a distal tissue to regulate plant responses (100). In addition, two recent studies have shown that leaf-derived ABA controls distal physiological and developmental processes (25). The first study demonstrated that long-distance ABA transport controls seed development in rice in an OsDG1-dependent manner. The *osdg1* mutant has grain-filling defects caused by noticeably reduced starch content in caryopses. Although ABA is synthesized in leaves of both wild-type and *dg1* mutant rice seedlings, only wild-type caryopses accumulate leaf-derived ABA, which activates starch synthesis genes (120). This process is enhanced at above-normal temperatures to impact seed development. Given the observations that ABA biosynthesis occurs mainly in phloem companion cells (78), ABA must first be loaded into the leaf phloem and then unloaded to the caryopses. DG1 expression in the parenchyma cells allows intervascular ABA transfer by loading ABA into the phloem and unloading it into caryopses (120).

In the second study, two ABA importers, ABCG17 and ABCG18, were characterized as regulators of ABA homeostasis in guard cells (181) (**Figure 1**). Interestingly, ABCG17 and ABCG18 are not expressed in the guard cells themselves, suggesting that non-cell-autonomous activity regulates ABA movement. ABCG17 and ABCG18 are localized on the plasma membrane of leaf mesophyll cells, where they promote ABA uptake. Once captured in the mesophyll cells at high levels, much of the free ABA is likely converted to ABA-GE. The strong uptake of ABA into the mesophyll cells by ABCG17 and ABCG18 leads to reduced ABA availability in the guard cells,

tuning stomatal apertures. Importantly, upon abiotic stress, *ABCG17* and *ABCG18* are transcriptionally repressed, resulting in reduced ABA accumulation in the shoot mesophyll cells. Thus, ABA is free in the apoplast to reach the guard cells to control the stomatal aperture. In addition, ABCG17 and ABCG18 mediating ABA accumulation and storage in mesophyll cells affects shoot-to-root ABA translocation to regulate lateral root emergence (181).

OsDG1, ABCG17, and ABCG18 are mediators of two types of ABA transport mechanisms that restrict ABA long-distance translocation and accumulation to regulate distal processes. Importantly, although OsDG1 controls a developmental process (grain filling and lateral root emergence) and ABCG17 and ABCG18 control physiological traits (stomatal aperture), both are gated by the environmental cues of high temperature and water availability (4).

Abscisic Acid: Open Questions

Transporters from different families, including ABCGs, NPFs, and MATEs, have been shown to import or export ABA over short and long distances. However, it remains unclear which cell types produce ABA in normal or stress conditions and whether ABA movement is required to execute specific responses. For example, whether the cortex ABA-dependent root hydropatterning response depends on an external ABA source from the phloem or whether it is produced locally to initiate the response to drought remains unknown (28).

AUXIN

Auxin Background

Auxin, the most well-studied plant hormone, was also the first to be discovered and isolated. Auxin is involved in almost all vegetative and reproductive processes, such as plant architecture, organ patterning, vasculature development, and tropic responses to light and gravity (35). Indole-3-acetic acid (IAA) is the most common bioactive auxin form in plants.

Auxin Transporters and Distribution

Auxin gradients created by the integration of auxin biosynthesis, catabolism, conjugation, and translocation are indispensable for diverse auxin responses. Auxin moves by several mechanisms through nondirectional passive movement, plasmodesmata, vasculature systems, directional cell-to-cell polar auxin transport mediated by transporters, and other nonpolar transport-dependent activity (38). For many years, auxin was thought to be predominantly synthesized in the shoot apical meristem and moved basipetally to the root, but several independent studies have shown that the root meristem maintenance relies on locally produced IAA (15, 20, 93).

To date, four families of auxin transporters have been identified: the auxin efflux transporters PIN-FORMED (PIN) proteins, ATP-binding cassette subfamily B (ABCB) transporters, NPFs, and the auxin influx transporters AUXIN RESISTANT1 (AUX1) and LIKE AUX1 (LAX) (37, 43, 150) (**Figure 2**). There are eight PINs in *Arabidopsis*, including five long PINs (PIN1–PIN4 and PIN7) and three short PINs (PIN5, PIN6, and PIN8) (2, 3, 44, 124). The long PINs are localized to the plasma membrane, whereas two of the short PINs, PIN5 and PIN8, are reported to localize to the ER (29, 105, 160). PIN6 is localized to both the plasma membrane and ER (18, 143) (**Figure 2**). A significant breakthrough in our understanding of PIN activity came from a recent cryo-electron microscopy study that revealed the PIN1 (174), PIN3 (146), and PIN8 (159) structures in an outward-facing state with and without bound IAA as well as in an inward-facing state with bound auxin class hormone *N*-1-naphthylphthalamic acid. The homodimer structure, with each monomer divided into transport and scaffold domains, has a defined auxin-binding site. A proline–proline crossover allows structural changes that are associated with transport. The

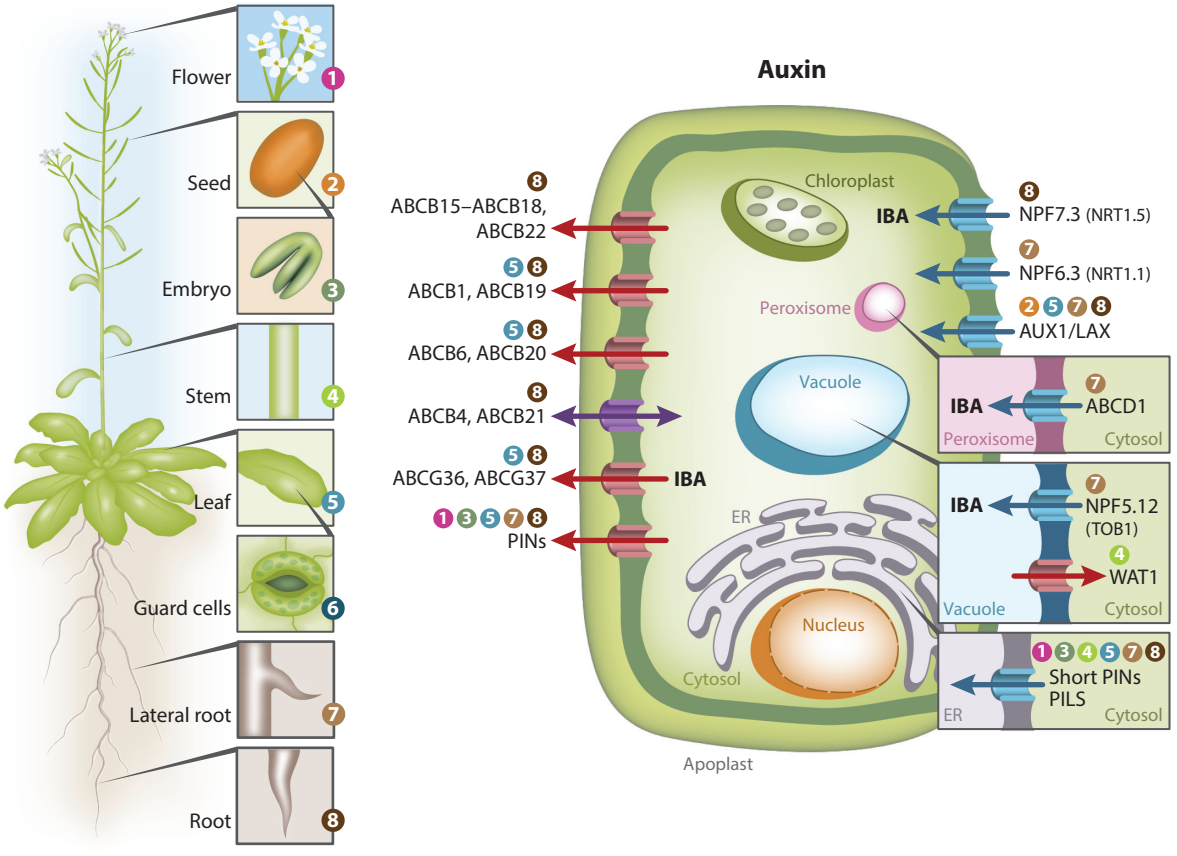

Figure 2

Overview of IAA transporters in plants. (*Left*) Illustration of an *Arabidopsis* plant with magnifications emphasizing different organs. (*Right*) Overview of the characterized auxin transporters. Blue arrows represent importers; red arrows represent exporters. Inset boxes are magnifications of the indicated organelles. The proteins transport bioactive IAA unless otherwise indicated. The numbers in circles above transporter names indicate tissues in the illustration on the left (not all tissues express transporters regulating this hormone). All transporters were characterized in *Arabidopsis*. Abbreviations: AUX, AUXIN RESISTANT; ER, endoplasmic reticulum; IAA, indole-3-acetic acid; IBA, indole-3-butyric acid; LAX, LIKE AUX1; PIN, PIN-FORMED.

transport activity is independent of proton and ion gradients and is likely driven by the negative charge of the auxin (43, 146, 159, 174).

Similar to the short PINs, the transporters of the PILS family localize on the ER (133). PILS6 is a negative regulator of organ growth, and its abundance increases at high temperatures. PILS6 repression by temperature sensitivity regulates the nuclear availability of auxin, contributing to the increase of nuclear auxin signaling and root growth as temperature increases (33). A recent study showed that brassinosteroid signaling transcriptionally and posttranslationally represses the accumulation of PILS proteins at the ER, thereby increasing the nuclear abundance and enhancing signaling mediated by auxin (148).

Several auxin transporters from the ABCB family, such as ABCB1 and ABCB19, are IAA exporters (37, 60, 168). ABCB4 and ABCB21 function as dual IAA exporters and importers to regulate auxin distribution (58). ABCB1, ABCB4, ABCB14, ABCB19, and ABCB21 are reported

to play roles in polar auxin transport to cause an auxin gradient. Recent mathematical modeling suggested that ABCBs enable auxin efflux independently of PINs; however, PIN-mediated auxin efflux takes place predominantly through a codependent efflux of PINs colocalized with ABCBs (98). Another study showed that ABCB6 and ABCB20 are auxin efflux transporters involved in polar auxin transport that modulate shoot and root architecture (59) (**Figure 2**). Loss of function of these two ABCBs causes severely twisted siliques and roots (59, 180). ABCB15–ABCB18 and ABCB22 are implicated in lateral root development (19).

In contrast to the ABCB IAA transporters, members of the ABCG family, ABCG36 and ABCG37, export the auxin precursor indole-3-butyric acid (IBA) (5) (**Figure 2**). A member of the ABCD subfamily, ABCD1 (also known as CTS) functions as an IBA importer into peroxisomes (104). NPFs are also reported to be auxin and auxin precursor transporters: NPF6.3 (also known as NRT1.1) functions as an auxin importer to regulate lateral root development (75). NPF7.3 (also known as NRT1.5) and NPF5.12 (also known as TOB1) are IBA importers localized to the plasma membrane and tonoplast, respectively (101, 165). WAT1 is also localized to the tonoplast but functions as an auxin exporter (121). The AUX1/LAX family includes four auxin influx proteins that regulate the development of various organs (**Figure 2**). The agravitropic *aux1* mutant is insensitive to exogenously applied IAA or 2,4-dichlorophenoxyacetic acid (9). AUX1 mediates high-affinity IAA transport in the physiological range ($K_m \approx 1$ μM) in *Xenopus* oocytes; however, no transport activity has been detected for LAX2 (32). A recent study showed that combining single-cell nucleus morphokinetic tracking with cell type–specific induction of auxin biosynthesis allows the mapping of directional auxin flow in the root and refines the contributions of PIN2 and AUX1 in this process (53).

Recent studies have demonstrated that diffusion through plasmodesmata is critical for auxin transport, affecting auxin distribution and contributing to plant growth and development (97, 167). Manipulating callose levels influences auxin diffusion through plasmodesmata and regulates auxin distribution, phototropism, lateral root emergence, and leaf hyponasty (97, 113).

Physiological and Developmental Highlights of Auxin Transport

One of the most significant contributions of auxin transport to plant growth and development is its activity in the meristem, which can be visualized as a reverse fountain of auxin flowing rootward through the vascular tissue and redirected shootward through the meristem epidermis (44). The radial inward movement of auxin, released from cells undergoing programmed cell death, was suggested to contribute to periodic peaks that determine lateral root positioning (172). However, the efflux components controlling lateral root formation remained elusive. A recent study identified the missing auxin transporters in the outer tissues of the root. Five closely related ABCBs (ABCB15–ABCB18 and ABCB22) are required for lateral root spacing via modulation of the DR5:LUC oscillation amplitude. Their predominant expression in the lateral root cap and epidermis and the lateral root defects in the knockout lines suggest that they transport auxin in the outer layers of the root meristem to instruct lateral root spacing (19). These five ABCB transporters, which are genetically linked, localize to the plasma membrane, transport auxin out of the cell, and act redundantly to transport IAA shootward through the lateral root cap and epidermis to the maturation zone, allowing lateral root spacing (19).

Auxin: Open Questions

Although auxin transport is well characterized, several questions remain. For example, whether IAA entrance into the nucleus is regulated by active transport is unknown. Such a mechanism would gate IAA binding to its receptor TIR1/AFB proteins (118). The physiological relevance

of this gating, given the recent report that the auxin receptor AFB1 is localized to the cytoplasm (118), adds further complexity to the process. In addition, evidence of direct binding between ABCB4 and PIN2 (27) and evidence from mathematical modeling (98) support dynamic ABCB–PIN interaction (5), adding additional complexity and specificity. Understanding how these groups of IAA exporters work in concert to maintain auxin patterning would be interesting.

CYTOKININS

Cytokinin Background

The first CK to be isolated was Kinetin in 1955, followed by the isolation of *trans*-Zeatin (tZ) from corn endosperm in 1961 (54, 71, 102). tZ and N^6-(Δ^2-isopentenyl) adenine (iP) are the two main active forms of CKs. tZ is produced in the root and then translocated acropetally through the xylem to regulate shoot growth and development, whereas iP is synthesized mainly in the shoot and moves basipetally to the root by phloem to regulate cell division, development, and nutrient processing (52, 76). Grafting experiments indicated that tZ, but not iP, is transported acropetally to shoot and rescues the shoot growth phenotype in the mutant *atipt1 atipt3 atipt5 atipt7* (94). By contrast, iP dominates transport in the basipetal direction and is sufficient for normal root growth (65, 94, 109, 131).

Cytokinin Transporters and Distribution

In 2014, two independent groups showed that in *Arabidopsis* the plasma membrane–localized ABC protein ABCG14 regulates long-distance CK translocation from root to shoot through the vascular system (73, 179) (**Figure 3**). Grafting experiments between wild-type and *abcg14 Arabidopsis* seedlings indicated that root-derived CK is necessary for normal shoot development and that AtABCG14 participates in xylem loading of root-synthesized CKs (73, 179). Further study revealed that AtABCG14-mediated phloem unloading via an apoplastic pathway redistributes CK from root to shoot (182). Five years after AtABCG14 was identified, OsABCG18 was reported to have a similar activity in rice (**Figure 3**). OsABCG18 is a plasma membrane–localized exporter that regulates CK long-distance translocation from root to shoot to promote grain yield in rice (183).

The equilibrative nucleoside transporter (ENT) family members also participate in CK translocation, although these proteins were not shown to directly transport CK in planta (51, 52, 147). In *Arabidopsis*, two azaguanine (AZG) transporter family members, AZG1 and AZG2, transport CKs: AZG1 reportedly acts as a CK importer through an interaction with PIN1 to regulate root development, and AZG2 functions as a CK importer to regulate lateral root development (90, 154, 155). Furthermore, evidence indicates that two ER-localized ABCI subfamily members, ABCI20 and ABCI21, together with their homolog ABCI19, function as CK transporters to fine-tune CK responses (72).

Physiological and Developmental Highlights of Cytokinin Transport

Similar to the long-distance root-to-shoot CK translocation, it is now clear that local CK transport has a huge impact on plant growth and development. The identification of the plasma membrane–localized H^+-coupled high-affinity purine permease PUP14, a CK importer identified in *Arabidopsis*, demonstrated the importance of the biochemical transport process, as without its activity, the plants do not survive the embryonic stage. PUP14 imports CK into cells, thus reducing CK availability in the apoplast, with diluted amounts available for the plasma membrane–localized CK receptors. Therefore, PUP14 is involved in establishing a spatiotemporal CK sink

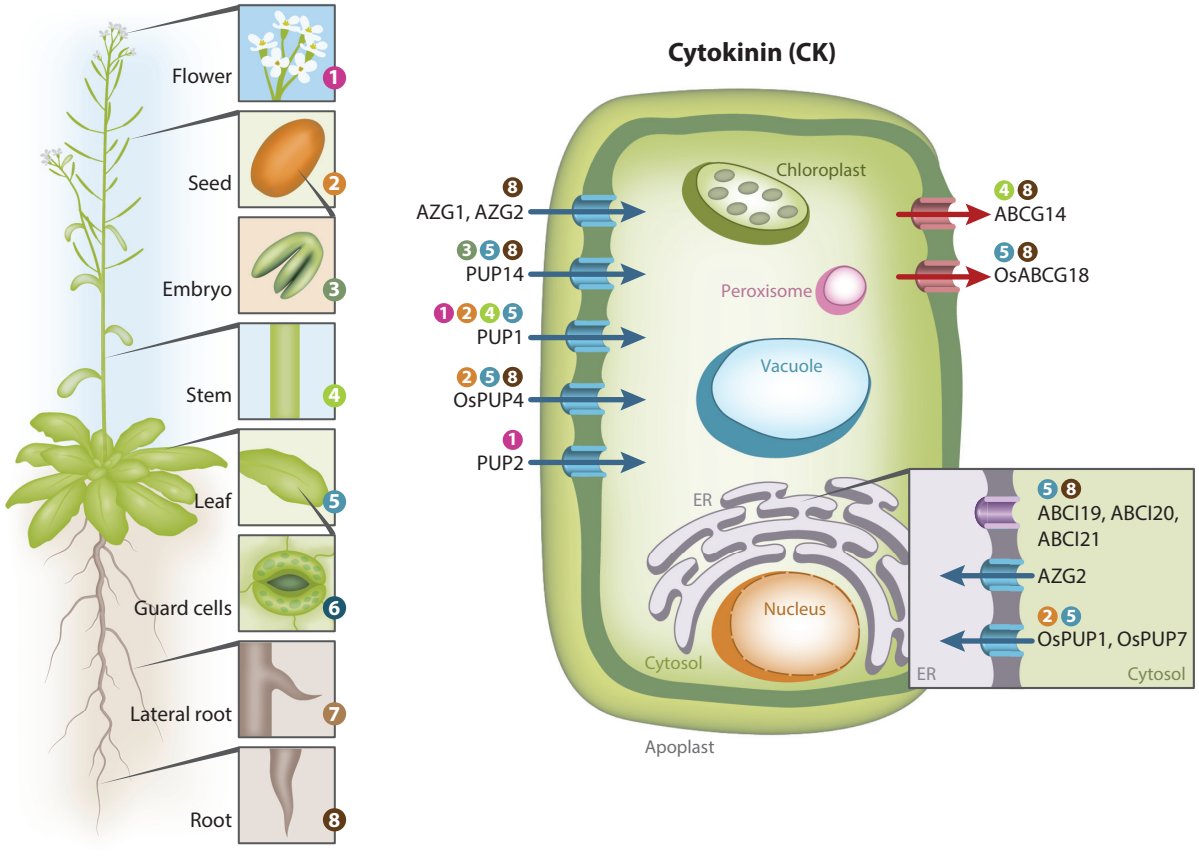

Figure 3

Overview of CK transporters in plants. (*Left*) Illustration of an *Arabidopsis* plant with magnifications emphasizing different organs. (*Right*) Overview of characterized CK transporters. Blue arrows represent importers; red arrows represent exporters. The inset is a magnification of the indicated organelles. The numbers in circles above transporter names indicate locations in the tissues in the illustration on the left (not all tissues express transporters regulating this hormone). The direction of CK transport for the three ER-localized ABCI proteins is currently not entirely clear. All transporters were characterized in *Arabidopsis* unless the transporter name is preceded by a species abbreviation. Abbreviations: CK, cytokinin; ER, endoplasmic reticulum; Os, *Oryza sativa*.

to regulate morphogenesis (187). Two other PUP family members, PUP1 and PUP2, promote CK import to regulate *Arabidopsis* growth and development (16, 39). There are 12 PUP family members in rice. OsPUP7 is localized to the ER and transports the CK derivative caffeine, affecting plant growth, developmental processes, and stress responses. OsPUP4 might function in CK loading into vascular bundles to regulate long-distance CK transport (119, 170). OsPUP1 also localizes to the ER and is predominantly expressed in the root vascular cells; its expression is induced by CK treatment. It was hypothesized that OsPUP1 is a long-distance CK transporter involved in unloading shoot-derived or phloem-transported CKs out of the vasculature by cell-to-cell transport. OsPUP4, a homolog of OsPUP7, is localized to the plasma membrane, directs CK cell-to-cell transport, and influences CK homeostasis by regulating CK long-distance transport and local allocation (170). Thus, the PUP CK transporter family members are major regulators of plant growth and development.

Cytokinin: Open Questions

The role of the vacuole as a storage organelle to maintain CK homeostasis has been proposed but not confirmed yet. Such vacuolar CK import activity would have a profound effect on the ER–CK receptor–mediated response.

GIBBERELLINS

Gibberellin Background

GAs were chemically characterized in the late 1950s. During the Green Revolution in the 1960s, alterations in GA biosynthesis and responses were employed to dramatically enhance crop yields. GAs regulate many aspects of plant growth and development, such as germination, stem elongation, flower development, dormancy, leaf senescence, and fruit ripening (12, 48, 70, 116).

Gibberellin Transporters and Distribution

GA homeostasis is regulated at multiple levels, including biosynthesis, catabolism, signal perception and transduction, and transport (46–48, 108, 136, 173). GA movement plays a pivotal role in the GA distribution that is necessary to regulate plant growth (10). A GA receptor was first identified in rice in 2007 (158), and about a decade later in 2016, the first GA transporter, NPF3, was identified (26, 152) (**Figure 4**). NPF3 localizes to the plasma membrane and imports GAs in a pH-dependent manner. The glucosinolate transporter NPF2.10 (also known as GTR1) serves as a multifunctional transporter for the structurally distinct compounds glucosinolates, JA-Ile (the conjugated form of JA), and GA to positively modulate *Arabidopsis* stamen development (21, 130). Using a yeast-modified two-hybrid system to detect GA transport activity, researchers showed that NPF2.3, NPF2.4, NPF2.5, NPF2.7, AIT1, and AIT3 are GA transporters (21). The transport activities of these proteins were confirmed in *Xenopus* oocytes with six different GAs (82); however, the physiological importance of these biochemical activities in plants remains uncharacterized.

In *Arabidopsis*, SWEET13 and SWEET14, members of the Sugars Will Eventually Be Exported Transporters (SWEET) family, were also confirmed to be GA transporters (68, 103). SWEET13 and SWEET14 import GAs as shown in yeast and oocyte transport assays (68). SWEET13 and SWEET14 redundantly function to regulate anther development, and exogenous application of GAs to the double mutant *sweet13 sweet14* rescues anther dehiscence defect (68). In rice, OsSWEET3a functions as both a sugar transporter and a GA transporter to regulate seed germination and early shoot development (103) (**Figure 4**).

Rizza et al. (127) engineered a GA perception biosensor to report on GAs at the cellular level, demonstrating that GA concentration is highest in the elongation zone. The transporters that are responsible for GA distribution in the root have not yet been identified, but data obtained with this sensor indicate that GAs are mobile (125–127). A ratiometric GA signaling biosensor based on the DELLA protein RGA also revealed GA transport in planta, while also reporting on changes of GA contents at a cellular level in the shoot apical meristem (139). Barker et al. (8) characterized GA biosynthesis sites in *Arabidopsis*, and rescue experiments indicated GA_4 movement as well as evidence for GA_{12} long-distance movement but no evidence of shoot-to-root transport of GA_9. Exogenous application of fluorescently labeled GA_3 led to exclusive accumulation in mesophyll cells, and this process is controlled by two transcription factors, TEM1 and TEM2, which were shown to negatively control NPF-specific (GTR1, NPF3, and NPF2.3) GA transporter expression, leading to variable GA accumulation and distribution in mesophyll cells to regulate trichome initiation in the epidermis, supporting the hypothesis that GA moves from one tissue to another in plants (92).

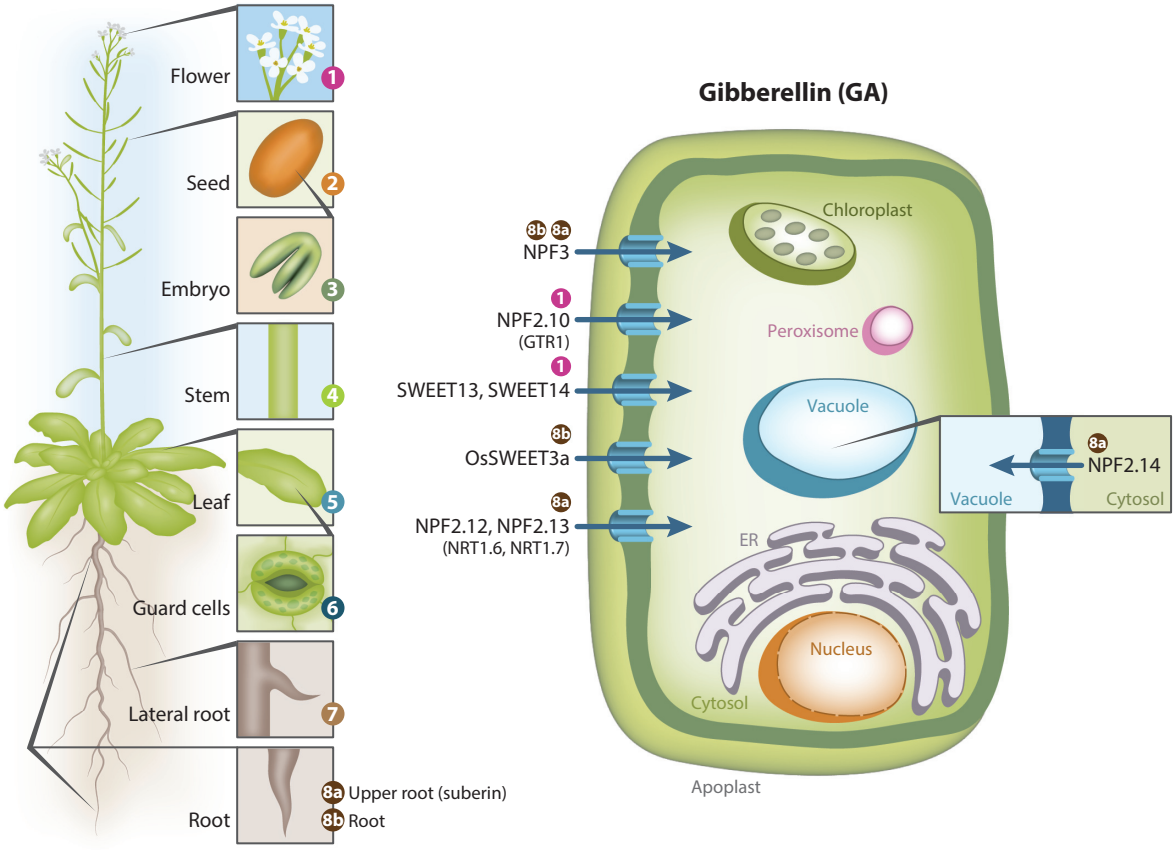

Figure 4

Overview of GA transporters in plants. (*Left*) Illustration of an *Arabidopsis* plant with magnification emphasizing different organs. (*Right*) Overview of characterized GA transporters. Blue arrows represent importers; red arrows represent exporters. The inset is a magnification of the indicated organelles. The numbers in circles above the transporter names indicate localization in the tissues in the illustration on the left (not all tissues express transporters regulating this hormone). All transporters were characterized in *Arabidopsis* unless the transporter name is preceded by a species abbreviation. Abbreviations: ER, endoplasmic reticulum; GA, gibberellin; NPF, nitrate transporter/peptide transporter; Os, *Oryza sativa*; SWEET, Sugars Will Eventually Be Exported Transporter.

Physiological and Developmental Highlights of Gibberellin Transport

A recent study revealed the importance of GA transport in a specific developmental context: suberin formation in the root. Two new GA and ABA importers, NPF2.12 and NPF2.13, and one tonoplast importer, NPF2.14, coordinately regulate suberin formation (11) (**Figure 4**). NPF2.12 and NPF2.13 are membrane-localized proteins, expressed in leaf phloem companion cells, that promote GA_{12} transport from the shoot to the root (11). These results provide the missing mechanism behind GA_{12} long-distance transport. Once GA_{12} docks in the root, it is converted to GA_4 by the GA20ox and GA3ox enzymes. GA_4 and ABA are imported into the pericycle by NPF2.12. In the pericycle, the hormones are transported into the vacuole by the pericycle-specific NPF2.14 tonoplast-localized transporter. Vacuolar accumulation of GA and ABA initiates in the phloem unloading zone, around the root elongation zone, where the two hormones are kept in vacuolar storage as the root matures and differentiates. Only later in development are the hormones

taken into the endodermis by NPF3 to promote suberization. These findings suggest that GA and ABA work nonantagonistically to regulate plant development (11). In addition, the novel mechanism explains for the first time the developmental importance of long-distance GA_{12} shoot-to-root movement and the biological importance of bioactive GA_4 and ABA accumulation in the endodermis to regulate endodermal suberization.

Gibberellin: Open Questions

Whether there are GA exporters capable of transporting GA from inside the cytosol to the apoplast is unknown. No such proteins have been identified so far, yet proteins with this function must exist in order to overcome the GA ion-trapping mechanism.

JASMONIC ACID

Jasmonic Acid Background

JAs are formed by the oxygenation of fatty acids and were first isolated in 1957 as *cis*-jasmone, a fragrant constituent of the essential oil of *Jasminum grandiflorum*. JA biosynthesis happens in chloroplasts, peroxisomes, and cytosol, and the major bioactive form is JA-Ile (164). JAs are involved in vegetative and reproductive processes such as root elongation and fertility and are best known for their importance in plant adaptation to environmental stimuli, including abiotic and biotic stresses (40, 162).

Jasmonic Acid Transporters and Distribution

JA biosynthesis is rapidly induced upon wounding and stresses. Several studies support transport-mediated JA translocation in plants upon biotic stresses: JA and JA precursors are transported from wounded shoots to unwounded roots in a LOX2-dependent manner (36, 137). Grafting experiments between wild-type *Arabidopsis* seedlings and JA-deficient mutants confirmed the transport of oxylipin from shoot to root (36). Using deuterium-labeled analogs of JA and JA-Ile, Sato et al. (132) demonstrated that JA and JA-Ile transport occurs following leaf wounding in both tobacco and tomato, with JA-Ile showing higher mobility than JA. In addition, following shoot wound, endogenous JA precursor 12-oxo-phytodienoic acid (OPDA) and its derivatives were transported long distances to coordinate shoot-to-root responses during plant stress acclimation (135).

JA biosynthesis initiates in chloroplasts, where OPDA is synthesized; OPDA then moves to the peroxisomes. Two transporters, JASSY and OPDAT1, export OPDA out of chloroplasts and plastids in *Arabidopsis* and poplar, respectively (42, 184) (**Figure 5**). JASSY is localized to the outer chloroplast envelope, and plants mutated in *JASSY* show increased sensitivity to abiotic stresses as well as biotic stresses due to reduced JA accumulation and response (42). OPDAT1 is localized to the plastid inner envelope (184). Mutants of *opdat1* have reduced JA levels and increased susceptibility to spider mite infestation (184). In *Arabidopsis*, ABCD1, a peroxisomal membrane–localized protein, imports OPDA into peroxisomes, where the final step of JA synthesis occurs (156).

Several NPF members function as weak JA transporters for in vitro transport assays (69). For example, AIT1 and AIT3 import not only ABA and GA but also JA-Ile in yeast transport assays (21). Similarly, NPF2.10 functions as a JA-Ile importer in the *Xenopus* oocyte transport system (130). The physiological roles of NPF protein transport activity are not entirely clear (69).

Physiological and Developmental Highlights of Jasmonic Acid Transport

Although grafting experiments and analyses of exogenous radiolabeled JA and JA-Ile showed that JAs can act as the transmissible wound signal from a site of local damage to systemic leaves,

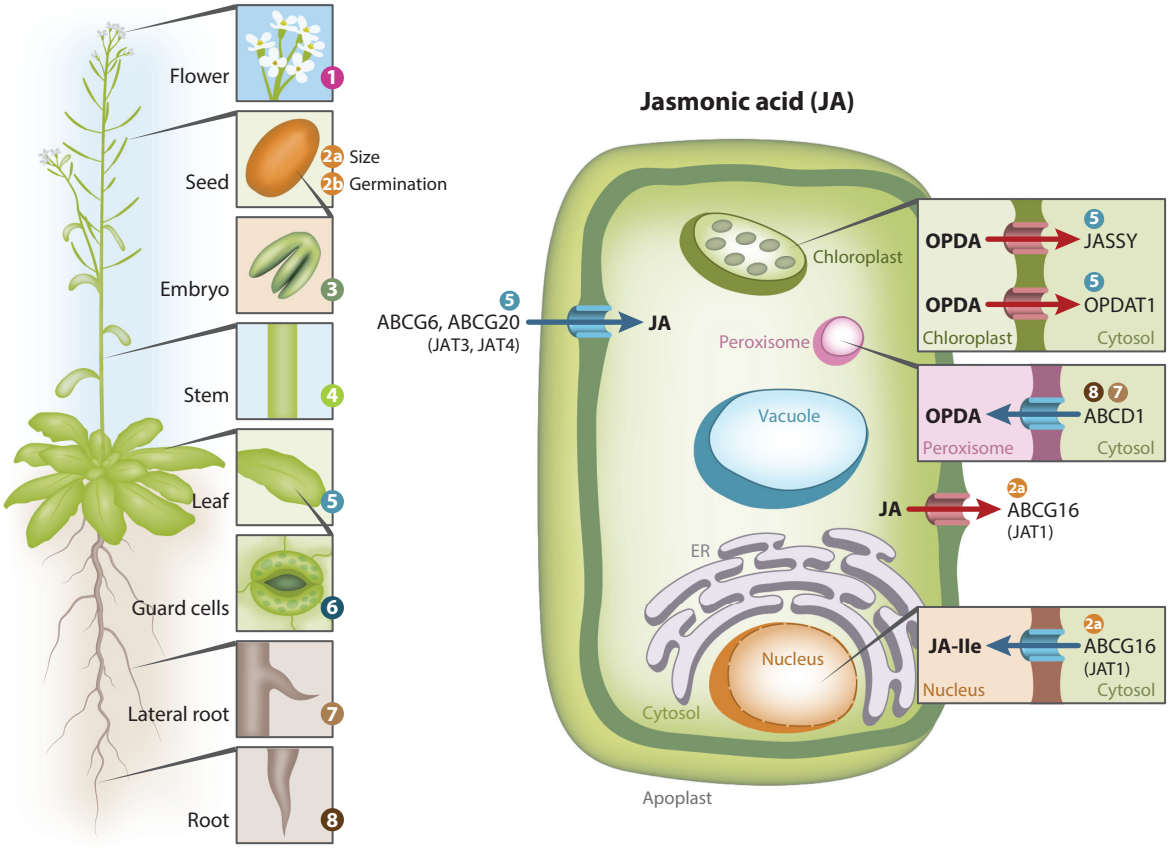

Figure 5

Overview of JA transporters in plants. (*Left*) Illustration of an *Arabidopsis* plant with magnifications emphasizing different organs. (*Right*) Overview of characterized JA transporters. Blue arrows represent importers; red arrows represent exporters. The insets are magnifications of the indicated organelles. The proteins transport the indicated bioactive hormone. The numbers in circles over transporter names indicate localization to the tissues in the illustration on the left (not all tissues express transporters regulating this hormone). All transporters were characterized in *Arabidopsis*. Abbreviations: ER, endoplasmic reticulum; JA, jasmonic acid; OPDA, 12-oxo-phytodienoic acid.

the specific molecular form that is translocated remains to be determined. By setting up rosette-petiole grafting experiments in *Arabidopsis*, Li et al. (85) showed that JA could relocate from a site of local damage to systemic leaves. Direct evidence showing that JA is the mobile form of JA-dependent wound signals came from tracing leaf-to-leaf translocation of d5-JA (84). In addition, members of the ABCG family, ABCG16, ABCG6, and ABCG20 (also known as JAT1, JAT3, and JAT4, respectively), function as jasmonate transporters in JA leaf-to-leaf translocation in *Arabidopsis* (**Figure 5**). ABCG16 is localized to both the plasma membrane and nuclear envelope, and it facilitates JA export out of the cell and JA-Ile import into the nucleus (86, 157). ABCG6 and ABCG20 localize to the plasma membrane and are expressed in the phloem, regulating JA translocation from the site of synthesis to distal leaves (84). Knockout mutants *acbg6* and *abcg20* result in a 70% decrease in translocated JA, leading to significant compromise or abolished

wound-induced systemic response/immunity, as determined by the expression of JA-responsive marker genes and resistance to the necrotrophic fungal pathogen, *Botrytis cinerea* (85).

Jasmonic Acid: Open Questions

Though several JA or JA-Ile transporters have been identified, most transport assays have been carried out using in vitro systems, so direct transport activities in planta must be confirmed. The transporters that are involved in JA long-distance transport remain mysterious, and more screens should be carried out to identify additional transporters of JA and its derivatives.

ETHYLENE

Ethylene Background

Ethylene is associated with many different physiological processes such as seedling growth, organ development, senescence, fruit ripening and abscission, and immune pathogen responses (99). In some of these processes, ethylene has synergetic or antagonistic interactions with other plant hormones such as auxin and JA (117). Ethylene is found in plants as a gas and has high rates of diffusion within cells as well as through lipid membranes.

Distribution and Transporters of the Ethylene Precursor

There are no direct transporters for ethylene; however, transport of the ethylene precursor 1-aminocyclopropane-1-carboxylic acid (ACC) is regulated (114, 141). ACC is not found as a gas and therefore does not diffuse. The *Arabidopsis ACC-resistant2* (*are2*) mutant shows a dose-dependent resistance to exogenously applied ACC but has a normal response to ethylene (22). *ARE2* encodes the amino acid transporter LHT1. Recently, a second ACC transporter, AtLHT2, was identified by complementing AtLHT1 ACC insensitivity (22). LHTs were previously identified as positively charged histidine, lysine, and arginine amino acid transporters (50). Presently, the physiological relevance of a dual ACC and amino acid transport activity is not understood. Although the mechanism is still unclear, LHTs appear to be the main means of transport in the ethylene pathway. ACC has been found in the xylem, suggesting that it participates in long-distance signaling and a systemic ethylene response.

Physiological and Developmental Highlights of Ethylene Transport

Although ethylene diffusion is not regulated by active transporters, conditions that alter the ease with which ethylene diffuses from the site of production to its target sites may have a profound effect on the ethylene response. For example, it was recently shown that compact soils allow significantly less gas diffusion, owing to a reduction in air-filled pores relative to loose soils, thereby causing ethylene to accumulate in root tissues and trigger hormone responses that restrict the growth of *Arabidopsis* (57, 110). Thus, the volatile ethylene hormone acts as an early warning signal for roots to avoid compacted soils. Recent work in rice has shown that the mechanism is conserved in monocots and that the ethylene response in compact soils requires ABA and auxin biosynthesis as well as AUX1-mediated auxin transport (110).

Ethylene: Open Questions

The recent discovery that compacted soils lead to significantly lower levels of ethylene diffusion (63) is intriguing and raises the possibility that similar mechanisms take place over time and space in other physiological processes in plants.

ADVANTAGES AND LIMITATIONS OF DIFFERENT HORMONE TRANSPORT ASSAYS

There are several ways to test the potential capacity of transporters in hormone movement. For example, methods such as combining mutants with hormone measurements in specific tissues (144) or utilizing a hormone-specific reporter to test for shifts in hormone response (6, 126, 181) have been employed. However, transport assays must be carried out to validate the biochemical activity of transporter proteins directly. Transport assays may be carried out in planta using protoplasts (38, 180, 181, 187) or in heterologous systems such as yeast or oocytes (24, 63, 80, 181). Each method has its disadvantages and advantages.

Plant protoplast-based transport assays can provide useful information even when an unknown factor is required for the activity. This type of assay was used to demonstrate the requirement for D6PK protein kinases to regulate the transport activity of PINs (7, 30). D6PK and PINOID kinases activate PIN-mediated auxin efflux and are essential for PIN-mediated auxin export in oocytes (186). Another example where the protoplast assay was crucial was in the analysis of the half-size ABCG proteins that form homo- and heterodimers to allow transport activity (31, 41). A half-size ABCG that forms a heterodimer cannot function in a heterologous system such as the oocyte (30).

Nonplant heterologous yeast or oocyte systems are often used to confirm the activity of a specific transporter. *Xenopus* oocytes are large cells (>1 mm in diameter) with low endogenous transport activity. Therefore, oocytes are highly suitable for electrophysiological measurements, which is an accurate method for characterization of the kinetic properties of transporter proteins (80). The disadvantages of the yeast and oocyte heterologous systems are the advantages of the plant protoplast assays: The nonplant systems are not informative if additional genetic or chemical factors are needed.

Whether the transport assays rely on *Xenopus* oocytes, yeast, or protoplasts, one needs a way to detect the hormones (14, 68, 144). Possible methods for hormone detection include direct measurement using gas chromatography tandem mass spectrometry (GC-MS/MS), radioactive isotope-labeled (180, 181, 187) or fluorescently labeled hormones, and fluorescently tagged genetic hormone sensors (6, 55, 62).

WHY SO MANY TRANSPORTERS FOR ONE HORMONE?

Most plant hormones, including auxin, ABA, CKs, GAs, and JA (4), have multiple transporters. Several factors, explained below, have likely led to this phenomenon.

Specificity

All hormones come in a plethora of forms, including precursors, active forms, and catabolites. In the case of GA, these sum to over 130 different GA metabolites (89). Since structure, polarity, and size differences vary among metabolites, a specificity in transport level is required. Gene duplication and specificity acquired over the course of evolution resulted in multiple transporters from the same family. These might possess similar biochemical activities, leading to genetic redundancy, or may vary in substrate recognition. For example, ABCG17 and ABCG18 have redundant activities transporting ABA (181), whereas ABCG14 functions as a single copy factor to transport CKs from root to shoot (73, 179).

Subcellular Localization

Plant cells have multiple membranes, including the plasma membrane and internal organelle membranes. These membranes are composed of different mixtures of fatty acid–based lipids and

proteins and are surrounded by diverse pH environments that drive proton-mediated transport, adenosine triphosphate (ATP) availability, and more. Thus, cells require specific transporters that function efficiently in each setting (e.g., the plasma membrane, ER, chloroplast, and tonoplast) (4). The most studied example of such diversity is the PIN protein family: The short PINs localize to the ER, and the long PINs localize to the plasma membrane (4). More examples are provided by NPF2.12 and NPF2.13, which are localized to the plasma membrane, and their neighbor on the phylogenetic clade, NPF2.14, which is localized to the tonoplast (11).

Expression Pattern and Transcriptional Response to the Environment

Multiple copies of the PIN transporters, each with unique cell type–specific expression and subcellular localization, drive auxin flow. The root reverse fountain auxin flux and shoot phyllotaxis are both examples of how PIN expression patterns influence environmental responses (2). The NPF2.12–NPF2.14 and NPF3 GA and ABA transporters are another example of how a group of transporters expressed in proximity cell types allows hormone movement and accumulation. In this case, NPFs have the ability to facilitate shoot-to-root hormone translocation and also root pericycle-specific accumulation (11). Thus, heterogeneous transporter expression patterns permit versatile hormone gradients that influence plant growth and development. Furthermore, to respond to the changing environmental conditions, plants use hormone gradients to balance endogenous signals, which highly depend on transport levels and demand multifarious transporters. With the recent rapid development of genetic and biochemical approaches, new families of transporters will likely be discovered, shedding additional light on how translocation and redistribution of hormones control hormone homeostasis and govern plant growth and development.

Hormone homeostasis: a state of equilibrium in plant hormones regulated at many levels, including hormone biosynthesis, catabolism, and transport

Phytohormones: chemicals produced by plants (i.e., plant hormones) to regulate their growth, development, reproductive processes, longevity, and response to the environment

MULTISUBSTRATE ACTIVITY FOR A SINGLE TRANSPORTER

Plant transport systems and mechanisms appear to be vast and diverse, but this variety alone cannot account for the specificity and selectiveness of the transporters when dealing with the even more divergent nature of metabolites. Across the plant kingdom, there are hundreds of thousands of metabolites, and the metabolomes of most species consist of thousands of metabolites, including many signaling molecules (34, 163).

A number of transporter families are relatively conserved throughout the plant kingdom, such as the ABC, MATE, and NPF transporter families. Although conserved, these families vary in the number of members as well as substrate specificity between species (83). Despite the high amino acid similarities between members, it seems that families are not constricted to a specific metabolite or even transport mechanism (uptake versus efflux). One of the most robust transporter families in the plant kingdom is the NPF family, which includes 52, 70, and 79 members in *Arabidopsis*, rice, and tomato, respectively (88). Originally characterized as nitrate transporters, it is now clear that transporters of this family are involved in the transport of a much wider range of substrates, including phytohormones such as GA, ABA, IAA, IBA, and JA-Ile (24, 140, 165, 169). The NPF member NPF2.10 (GTR1) transports more than one substrate: GA, ABA, glucosinolates, and JA-Ile (21, 130). Systematic studies of *Xenopus* oocytes and the yeast *Saccharomyces cerevisiae* showed that multiple family members possess multisubstrate activity (21, 107, 130, 152). It is currently unclear what mechanism regulates this phenomenon.

The two systems most often used to characterize NPF members are *Xenopus* oocytes and the yeast *Saccharomyces cerevisiae*. Each system has the advantage of allowing the identification of substrates with micromolar affinities (21, 152); however, the fact that these methods are heterologous transport systems that may not accurately recreate a complicated biological organism must be taken into account. Competition between substrates, effects of other metabolites, pH levels, codon

optimization, and changes in membrane deposition are just a few of the variables that are hard to predict and replicate in vitro that could potentially have a determining effect on actual transport in living systems. Further research and new in vivo methods are needed to study transporter substrate coupling.

One way to verify the importance of transport activity is to test the mutant phenotypes in plants. If a phenotype is driven by lack of hormone accumulation/gradient at the right time and place due to loss of transporter activity, one would expect it to be rescued by treatment with the hormone. Indeed, a recent study used this approach to test the in planta activity of two new GA and ABA importers, NPF2.12 and NPF2.13, and a tonoplast importer, NPF2.14 (11). Combinations of the *npf2.12*, *npf2.13*, and *npf2.14* mutants showed reduced endodermal suberization. Importantly, this phenotype was rescued by either ABA or GA (11), indicating that these genes encode transporters of these hormones. Transport assays in plant protoplasts (128), fluorescently labeled hormones tested in planta (181), and hormone quantifications in different plant tissues in the mutant background (181) are additional approaches that should be used to validate the multisubstrate hormone data found in heterologous transport systems.

As to why the phenomenon of multisubstrate transport activity exists, one explanation may be that many of these transporter families are conserved throughout evolution (e.g., NPF and ABC transporters appear in eukaryotes and prokaryotes) (111, 112, 123) and the lack of selectivity has not proven to be costly and therefore prevailed. Another possibility is that multisubstrate transporters offer an evolutionary solution to how outnumbered transporters are in relation to the number of different metabolites and provide efficient transport mechanisms. We imagine a scenario where two substrates generally acting antagonistically are imported and exported by the same transporter or, similarly, a number of substrates are needed for a common function and are transported by the same transporter.

PLANT HORMONE DISTRIBUTION AT THE SUBCELLULAR LEVEL

Most hormone transporters identified so far are localized on the plasma membrane (1, 4). Although these transporters explain hormone transport from cell to cell, loading and unloading to the phloem or xylem for long-distance hormone translocation, and the creation of local hormone sinks, they do not explain the observed subcellular localization of hormones and their precursors (4). In many cases, plant hormones must be transported within the cell to initiate signal transduction. The receptors of most hormones, including IAA, JA, GA, SA, and ABA, are in the nucleus, but the majority of these hormones are biosynthesized in the plastids, ER, and cytoplasm (49). Only one nucleus-localized transporter, ABCG16, which is a JA-Ile importer into the nucleus, has been identified (157). How precursors exit from the plastids is also not clear. Therefore, subcellular hormone precursor transporters are predicted to be required for proper hormone homeostasis and response (23).

Another crucial layer of regulation of hormone distribution at the subcellular level is the storage and degradation that take place in the vacuoles. Vacuoles are the storage space for not only sugars, minerals, and special chemicals but also hormones and their conjugates (153, 177). However, only a few transporters have been identified that are localized to the tonoplast to promote the storage of hormones. We speculate that additional tonoplast transporters will be identified in the near future, which will further our understanding of the role of the vacuole in hormone responses.

A major challenge in the field is the quantification of hormones in their different forms at the subcellular level (145). Methodologies that will allow the mapping of bioactive hormones, their precursors, and conjugated forms at the organelle level will be a milestone in the field.

FUTURE PERSPECTIVES

Over the past years, the plant hormone research community has gained significant knowledge of the mechanisms that result in hormone movement and homeostasis in plants. This review summarized most of the characterized transporters responsible for short-distance, long-distance, and organelle-based transport of plant hormones. Small signaling molecules produced in the plant that function as cascade amplification signals at a distal location likely meet the functional definition of a hormone. In addition to mobile classic and small peptide hormones, should mobile proteins that move to allow responses be considered hormones? The florigen FLOWERING LOCUS T (FT) protein is an excellent example of a protein that executes a critical function after long-distance translocation: regulating flowering time after translocation from leaves to the shoot apical meristem (138). The recent identification of MCTP-SNARE complex–mediated endosomal trafficking (87) and temperature-sensitive membrane phospholipid binding mechanisms (149) that control the movement of FT further demonstrates the complex regulation behind the transport of signaling molecules. We expect that the research community will continue to identify new hormones and novel transport mechanisms using advanced genetic, biochemical, and metabolomics tools in the coming years.

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67. Identifies *AIT1/NRT1.2* as an ABA importer regulating stomatal aperture in inflorescence stems.

68. Shows that AtSWEET13 and AtSWEET14 regulate GA transport and plant growth.

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