Multitude of Long-Distance Signal Molecules Acting Via Phloem

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Abstract As sessile organisms, plants use long-range signalling between organs in order to adapt to their environment. The phloem is an important pathway for such long-distance communication. It transports signals that trigger systemic defence responses to wounding, herbivory and infection by plant pathogens. It also plays a pivotal role for developmental transitions, such as floral induction and tuberization, in response to stimuli perceived by the leaves, and physiological adaptation to nutrient deprivation. The signals involved in these processes include hormones, metabolites, proteins and RNAs, transported by mass flow with the phloem translocation stream. Faster signals, such as electropotential waves, can be propagated by the phloem plasma membrane. Most recent studies showed that these signalling pathways can recruit combinations of signal molecules, and that additional steps, such as molecular 'hopping' and amplification, may occur within the phloem tissue. This provides a basis to explain how plants cope with multiple environmental stimuli to confer long-lasting effects against stresses and maintain plant growth and development.

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G. Witzany and F. Baluška (eds.), *Biocommunication of Plants*,
Signaling and Communication in Plants 14,
DOI 10.1007/978-3-642-23524-5_6,

1 Overview of Phloem Organization and Functions

1.1 The Phloem: A Pathway for Nutrient Allocation and Inter-Organ Communication

Higher plants are organized in specialized organs, which fulfil distinct functions in the uptake of nutrients and energy, storage of metabolites and adaptation to the environment. The exchanges of nutrients and information between organs occur in the vascular tissues, i.e. xylem and phloem, by long-distance transport of water, nutrients, metabolites and signal molecules. The phloem plays a key role in long-distance signalling for many developmental and environmental responses. For example, long-range induction of flowering is a classical case of signalling from the leaves to the shoot apical meristem (Zeevaart 2008). Systemic acquired protection against plant pathogens is another well-known example (Sticher et al. 1997). The propagation of gene silencing has also been shown to follow a similar pathway (Palauqui et al. 1997; Voinnet and Baulcombe 1997). Ultimately, the phloem was identified as a main route for the translocation of such systemic signals. A breakthrough in our comprehension of long-distance communication was the discovery that proteins and RNAs transported in the phloem can act as mobile signals (Lough and Lucas 2006).

Thus, the phloem is essential in a number of adaptation and developmental events that require a coordinated and integrated response of the whole plant. In this chapter, we will successively consider key cases of long-distance signalling *via* the phloem.

1.2 Anatomy and Biochemistry of the Phloem

1.2.1 Phloem Anatomy and Overall Functions

The emergence of the vascular tissue has been an early landmark of the evolution of land plants, with water uptake and transport from the roots carried out by the xylem and allocation of sugars resulting from carbon fixation by aerial organs carried out by the phloem (van Bel 2003a). Thus, the primary phloem function is the partitioning of carbohydrates produced as photosynthates from autotrophic to heterotrophic organs. Both the sieve elements (SEs), i.e. cells conducing phloem sap, and the companion cells (CCs) present a unique cellular organization (Sjölund 1997). The phloem is organized in functional zones specialized in loading, transport and unloading, and named ‘collection phloem’, ‘transport phloem’ and ‘release phloem’ (van Bel 2003a), with the transport phloem making up the major part of the phloem (van Bel 2003b). The driving force for long-distance transport in the sieve tubes makes use of a turgor gradient due to variations in photosynthate accumulation along the pathway that create a hydraulic pressure gradient (Thompson 2006; Knoblauch and Peters 2010). The phloem communications between organs follow an independent succession of vascular connections between source and sink organs, known as orthostichies, which depend on the plant phyllotaxy (Callos and Medford 1994; Orians 2005). This implies that not all sinks are equally supplied by source leaves. A consequence is that systemic signal molecules, such as salicylic acid (SA), move in large part with assimilate movement along an orthostichy and do not trigger a response in all sink leaves (Kiefer and Slusarenko 2003). Another well-established example of this vascular organization is the pattern of systemic colonization during viral infection, which also follows orthostichous phloem connections (Roberts et al. 2007).

1.2.2 Phloem Sap Composition

Phloem sap contains sugars, amino acids, organic acids, secondary metabolites, ions, peptides, hormones as well as a large range of macromolecules, including proteins, small RNAs and mRNAs (Turgeon and Wolf 2009; Dinant et al. 2010). The composition of the phloem sap and the supply in structural components of the SEs are controlled at the interface between the SE-CC complex (Sjölund 1997; Oparka and Turgeon 1999), with an integrated control of loading, lateral exchanges along the transport pathway and unloading (van Bel 2003a). The delivery of molecules from the CCs or adjacent parenchyma cells to the SEs takes place either through the apoplasm, based on a series of carriers and pumps, present on the plasma membrane of SEs and CCs (Lalonde et al. 2003; Dinant and Lemoine 2010), or through fields of specialized plasmodesmata at the CC-SE interface, constituting the plasmodesmata pore units (PPUs) (van Bel 2003a). Most macromolecules present in the SEs are synthesized in the CCs (Turgeon and Wolf 2009). The entry of macromolecules into the SE takes place *via* the plasmodesmata, whereas the loading of metabolites and hormones can follow either symplasmic or apoplasmic steps.

1.2.3 Methods to Analyze Phloem

One major difficulty in studying phloem activity is to sample phloem sap and to sample phloem cells (Sjölund 1997). Several methods are available, such as bleeding, stylectomy or EDTA-facilitated exudation, depending on plant species (Turgeon and Wolf 2009). These methods can be useful for the identification of phloem sap components, although they potentially cause artefacts (Dinant et al. 2010). Carbon isotope labelling has been used to follow the transport in the vasculature of various compounds, such as sugars, SA, methyl jasmonate (MeJA) or other substances (Minchin and Thorpe 1987; Kiefer and Slusarenko 2003; Rocher et al. 2006; Thorpe et al. 2007). Grafting has been widely used as experimental approach to test for the biological activity of a compound translocated in the phloem (Turnbull et al. 2002). Cold-girdling or split-root experiments are also interesting tools to confirm long-distance signalling. Magnetic resonance imaging has been developed for *in vivo* imaging of vascular tissues and can be used to measure phloem sap velocity (Windt et al. 2006; Mullendore et al. 2010). As for the isolation of phloem cells, laser microdissection has been successfully used (Nelson et al. 2006).

2 Long-Distance Signalling in Response to Biotic Stress

Given that plants are sessile, they cannot run away from threats or move in search of nutrients or favourable environments. In order to maximize fitness and survival, plants have evolved numerous strategies to perceive environmental signals and adapt their development to different habitats. This encompasses the perception of specific stresses by the different organs and the transmission of the information to the other parts of the plant. Several key cases of long-distance signalling *via* the phloem in response to biotic or abiotic stresses will be described in this section. One classical case is the systemic defence response triggered in the whole plant after an initial injury of the leaves caused by plant pathogens, pests or wounding. The second classical case of phloem long-distance signalling is initiated by nutrient deprivation in the soil. This induces a root-to-shoot signal involving the xylem, then a shoot-to-root phloem signal that allows the plant to maintain the nutrient homeostasis within the whole plant and to adapt rapidly its growth and its development to its environment.

2.1 Long-Distance Signalling to Wounding and Herbivory

2.1.1 Systemin and Jasmonates in Response to Wounding in Tomato

When a leaf is injured, resulting from herbivory or contact with a cutting surface, a systemic signal is transported to non-injured newly forming leaves (Wu and Baldwin 2010). This systemic response is associated with the production of protease inhibitors and the release of volatiles, as a defence mechanism against subsequent insect infestations. The long-distance signalling has been studied in details in tomato. It is initiated by the production of systemin, a small peptide of 18 amino acids, which is produced after cleavage of a propeptide, the prosystemin. Systemin was initially thought to be the systemic signal (Stratmann 2003). However, it is now well established that systemin-induced jasmonic acid (JA), or JA derivative, which moves systemically, represent the major signal molecules in wound response (Lee and Howe 2003; Li et al. 2003; Schilmiller and Howe 2005; Wasternack et al. 2006). This signalling pathway is propagated and amplified within the vascular tissues: the prosystemin is produced in the phloem parenchyma cells (Narváez-Vásquez and Ryan 2004), and the biosynthetic enzymes for the synthesis of jasmonates are present in the CC-SE complexes (Hause et al. 2000, 2003; Stenzel et al. 2003), which further confer to the phloem the ability to amplify the synthesis of jasmonates (van Bel and Gaupels 2004). A systemin-binding SR160/BRI1 receptor at the surface of cells was identified in *Solanum peruvianum* (Montoya et al. 2002; Scheer and Ryan 2002) and proposed to trigger the transduction pathway for the synthesis of jasmonates (Schilmiller and Howe 2005). However, its role has been controversial and recent studies suggested instead that the systemin receptor is a distinct although related BRI-like protein localized in the vascular tissues (Malinowski et al. 2009; Hind et al. 2010), yet to characterize. Hydrogen peroxide has also been proposed to constitute a secondary messenger in sink organs (Orozco-Cardenas et al. 2001).

2.1.2 Jasmonates and the JAZ Proteins

The action of systemin and jasmonates in long-distance signalling is unique to tomato. However, the role of JA and JA derivatives such as the JA-amino-acid conjugate jasmonyl-L-isoleucine (JA-Ile) in response to wounding or to herbivory has been generalized to other species. In *Arabidopsis*, it has been discovered that jasmonates, most likely as JA-Ile, interact with the CORONATIN-INSENSITIVE 1 (COI1) unit of the E3 ubiquitin ligase complex SCF-COI1 (Skip/Cullin/F-box–COI1). A third component of the jasmonate co-receptor complex is inositol pentakisphosphate (Sheard et al. 2010). This complex targets, for subsequent degradation by the 26S proteasome, the JAZ proteins (Thines et al. 2007), which are repressors of the JA-inducible genes (Kazan and Manners 2008; Staswick 2008). Whether this transduction pathway only acts in the leaves or whether it is also in action in the transport phloem to relay and amplify the signal(s) has not been investigated. Other JA derivatives, the JA metabolite *cis*-jasmone (CJ) and MeJA, have been proposed to be active in defence signalling (Birkett et al. 2000; Bruce et al. 2008; Wu et al. 2008), some of them, such as MeJA, being transported *via* the phloem (Thorpe et al. 2007).

2.1.3 Propagation of Electric Potential Waves in the Phloem

Other systemic signals have been proposed to act in wound responses, including oligosaccharides, reactive oxygen species (ROS), hydraulic signals, electrical signals or other plant hormones (Rhodes et al. 1996; Mancuso 1999; Wasternack et al. 2006; Fromm and Lautner 2007; Maffei et al. 2007; Heil and Ton 2008; Shah 2009; Zimmermann et al. 2009). The role of electric potential waves (EPWs) in long-distance signalling in response to wounding was shown in tomato (Rhodes et al. 1996) and further examined in *Vicia faba* and barley (Furch et al. 2007; Zimmermann et al. 2009). EPWs, which are relayed by Ca^{2+} influx, can propagate very rapidly in the phloem, in response to wounding or other stimuli, such as burning or cooling, which in turn triggers various responses in the SE (Furch et al. 2007, 2009, 2010; van Bel et al. 2011a). The propagation rates of EPWs vary from 5 to 200 cm min^{-1}, depending on EPW classes, which is much faster than those driven by components transported by phloem sap (Fromm and Lautner 2007; Zimmermann et al. 2009). The observation that the accumulation of JA-Ile occurs rapidly in distal leaves, as soon as 5 min after wounding (Koo et al. 2009), is consistent with such EPW propagation rates. The preferential transmission of electrical signals in the phloem has been proposed to result from the low electrical conductance of plasmodesmata in lateral direction and on the high degree of electrical coupling *via* the sieve pores in longitudinal direction (Kempers and van Bel 1997; Fromm and Lautner 2007).

2.1.4 The Emerging Action of Reactive Oxygen Species and RbohD

Another main component of rapid propagation of signalling in response to wounding is the accumulation of ROS produced by a *RESPIRATORY BURST OXIDASE HOMOLOG D* (*RBOHD*) gene in *Arabidopsis* (Miller et al. 2009). This pathway is independent of ethylene, JA or SA. It is triggered by wounding, heat, cold, high-intensity light or salinity stresses, at a propagation rate of 8.4 cm min^{-1}. This established that ROS accumulation along a systemic signal front is essential for long-distance signalling in plants (Miller et al. 2009). This signal propagates in the apoplasm of the vascular tissues. The presence of a complete antioxidant system in the phloem sap also suggests a tight control of oxidative stress in this compartment (Walz et al. 2002).

Airborne signals also participate in long-distance signalling to wounding or herbivory (Heil and Silva Bueno 2007), overcoming the restrictions resulting from the plant's orthostichy (Frost et al. 2007; Heil and Ton 2008). Altogether, these observations support the idea that multiple long-distance signalling systems operate, JA-acting either in a cell-autonomous or in a cell-non-autonomous signalling pathway (Heil and Ton 2008; Koo and Howe 2009).

2.2 Systemic Response of Plants to Pathogen Attack

2.2.1 SA, MeSA and SABP: An Integrated Pathway in Tobacco

The role of the phloem in the mounting of systemic defences in plant immune responses has been also investigated in details (Durrant and Dong 2004; Grant and Lamb 2006). During interactions with an avirulent plant pathogen, the recognition of pathogen-associated molecular patterns (PAMPs) by host cells first triggers a local response, known as hypersensitive response (HR) (Jones and Dangl 2006), then a general immune response, resulting from the generation by infected leaves of a long-distance signal transported *via* the phloem (Durrant and Dong 2004). This long-lasting response known as the systemic acquired resistance (SAR) is characterized by an enhanced resistance to plant pathogens in newly formed organs associated with the production of pathogenesis-related (PR) proteins and an oxidative burst (Sticher et al. 1997; Durrant and Dong 2004; Grant and Lamb 2006; Zhang and Zhou 2010). The triggering of this signalling pathway is associated with the production of SA. In tobacco, it has been demonstrated that the activity of a SAMT (SA methyl transferase 1) in inoculated leaves enables the production of MeSA from SA (Park et al. 2007). MeSA is then transported systemically and constitutes a critical signal for the establishment of the systemic response (Seskar et al. 1998). In the systemic tissues, MeSA is hydrolyzed into SA by the MeSA esterase activity of SA-binding protein 2 (SABP2) and this newly generated SA triggers SAR (Forouhar et al. 2005). This mechanism is also active in *Arabidopsis* and potato (Kumar and Klessig 2003; Park et al. 2007; Vlot et al. 2008b; Manosalva et al. 2010).

2.2.2 Lipid-Derived Molecules: Modulators or Relays?

The identity of the systemic mobile signal(s) for SAR is so far still unclear, and other signals have been identified (Vlot et al. 2008a). Plant pathogen interactions trigger locally the synthesis of a lipid transfer protein (LTP) DIR1 (Maldonado et al. 2002) and a plastid glycerolipid factor, dependent from the biosynthetic genes *FAD7*, *SFD1* and *SFD2* (Kachroo et al. 2001; 2004; Chaturvedi et al. 2008), which probably form a complex. Both MeSA and this DIR1-lipid complex, acting as mobile signals, are required for the systemic activation of SAR (Liu et al. 2011a). *DIR1* transcripts were found in the phloem companion cells (Ivashikina et al. 2003), providing support in favour of a role as a phloem-specific carrier of signal (van Bel and Gaupels 2004). Other compounds, such as terpenoids or peptides, which are released by the action of extracellular proteases, have also been implicated in systemic signalling (Durner and Klessig 1999; Suzuki et al. 2004; Xia et al. 2004; Rustérucci et al. 2007; Shah 2009). A recent study also showed the role of azelaic acid, a nine-carbon dicarboxylic acid, in priming systemic defences in *Arabidopsis* (Jung et al. 2009). Azelaic acid induces the expression of *AZI1*, a gene encoding a predicted secreted protease inhibitor/LTP, which modulates production and/or translocation of the mobile signal during SAR. These signal molecules would act together with MeSA. Alternatively, they may act as relays for the amplification of the initial signal(s).

2.2.3 Hormone Crosstalks and the Multifactorial Plant Immune System

Jasmonates have also been described as signals essential for establishing systemic immunity in response to *Pseudomonas syringae* (Truman et al. 2007). However, this model is still quite controversial (Shah 2009), since conflicting evidences indicated that neither MeSA nor jasmonate were essential as systemic signals for

SAR (Cui et al. 2005; Mishina and Zeier 2007; Attaran et al. 2009). There is also a large body of evidence of antagonist interplays with other hormones such as auxin or abscisic acid (Chen et al. 2007; Wang et al. 2007; Ding et al. 2008; De Torres Zabala et al. 2009; Fan et al. 2009a; Truman et al. 2010). It has been proposed that depending on the combination of pathogen attackers, complex hormone crosstalks are activated to fine-tune induced defences (Leon-Reyes et al. 2009, 2010; Makandar et al. 2010). Interestingly, most hormones have been identified in the phloem sap (Hoad 1995), including auxin, cytokinins, gibberellins, abscisic acid, 1-aminocyclopropane-1-carboxylic acid (the precursor of ethylene), MeJA and SA, with the exception of brassinosteroids and strigolactones. Overall, the idea is emerging that multiscale and multifactorial defence systems can operate proper temporal and spatial integration to confer lasting disease resistance and prevent unfavourable signal interactions to concomitantly defend against multiple pathogens (Bruce and Pickett 2007; Spoel et al. 2007; Parker 2009; Shah 2009).

2.2.4 Nitric Oxide and the Concept of Molecular ‘Hopping’

Nitric oxide (NO) is also involved in signalling (Crawford and Guo 2005; Durner and Klessig 1999; Leitner et al. 2009). NO and S-nitrosothiols (SNO) are produced in the phloem CCs, in response to biotic and abiotic stresses, and have been proposed to be important signals, acting in the phloem cells downstream of SA (Rustérucci et al. 2007; Gaupels et al. 2008). One mode of NO action in the phloem would be through binding to some enzymes, thereby modifying their activity, which in turn would induce signal synthesis or activation (Gaupels et al. 2008). This led to the interesting model, proposed by van Bel and Gaupels (2004), that the role of the phloem, including production, release and distribution of signal molecules, may also encompass modulation and amplification of signals along the pathway, as observed in tomato for wound response (Wasternack et al. 2006). This concept, recently termed molecular ‘hopping’ by van Bel and co-workers (van Bel et al. 2011b), is based on long-standing observations that release/retrieval processes occur along the transport phloem pathway (Minchin and Thorpe 1987; Ayre et al. 2003; Hafke et al. 2005). It assumes a key role played by the CCs and phloem parenchyma cells, which are connected to the SEs by the PPUs, in relaying and/or amplifying signal(s).

2.2.5 Alternative Long-Distance Signalling Pathways

Several observations provide support in favour of additional long-distance pathways. First, the pattern of signalling does not always strictly follow phloem orthostichies (discussed in van Bel and Gaupels 2004). Root-to-shoot signalling has been shown to trigger systemic defences, such as induced systemic resistance (ISR) (van Loon et al. 1998). This is also supported by the observation that the pattern of sucrose distribution over the leaves, revealing phloem mass flow, overlapped only partially that of the SAR induction (Kiefer and Slusarenko 2003). One main additional pathway is phloem-to-xylem transfer of signals, since it was shown that SA transported *via* the phloem is redistributed upward in small amounts *via* the xylem (Rocher et al. 2006), and MeJA moves both in the phloem and in the xylem (Thorpe et al. 2007). Xylem can also transport from root-to-shoot a large range of nutrients, metabolites and hormones acting potentially as signals. In addition, airborne signals, including MeSA, MeJA and green leaf volatiles, directly contribute to these defence mechanisms (Farmer 2001; Frost et al. 2007; Shah 2009).

2.3 Phloem Conductivity in Response to Injury and Aphid Feeding

2.3.1 Sieve Element Occlusion in Response to Injury

Strikingly, the properties of transport in the phloem can be altered in response to biotic or abiotic stresses. A key case of such changes is the dispersion of protein bodies, named forisomes, observed in the SEs of *Vicia faba* in response to wounding or heating, which was associated with a transitory arrest of mass flow in sieve tubes (Furch et al. 2007; Thorpe et al. 2010). A similar process has been observed in *Cucurbita maxima* after burning of the leaf tip and was proposed to result from the aggregation of proteins in the vicinity of sieve plates (Furch et al. 2010). These rapid, reversible processes depend on the generation of an EPW and on Ca^{2+} influx (van Bel et al. 2011a). Their downstream effects on defence signalling are not known.

2.3.2 Manipulation of Phloem by Aphid Feeding

Aphid infestation induces defence mechanisms whose effects are defeated by aphids. Indeed phloem-feeding insects express ‘decoy’ defences and suppress the JA-regulated defences that affect insect performance (Thompson and Goggin 2006; Walling 2008; Giordanengo et al. 2010). During feeding, aphids inject in sieve tubes a saliva that contains compounds preventing occlusion of sieve elements (Will and van Bel 2006; Will et al. 2007, 2009). Aphid feeding can also induce in the phloem a systemic response potentially modifying transport properties. In response to aphid infestation of celery by *Myzus persicae*, it was shown that the transport phloem responded by a systemic transcriptional reprogramming, leading to multiple adjustments, potentially impacting metabolic pathways as well as phloem transport (Divol et al. 2005). The expression of several genes acting on cell wall modifications and water uptake was affected, which could modify the conductivity of the phloem tissue. These changes were specifically regulated by aphid infestation, since viral or bacterial infections led to a different response (Divol et al. 2005).

3 Long-Distance Signalling in Response to Nutrient Deficiency

In response to fluctuations in nutrient concentration, plants generate local and systemic signals in order to communicate the nutrient status to the whole plant and trigger adaptive responses (Forde 2002a; Schachtman and Shin 2007; Giehl et al. 2009; Chiou and Lin 2011). Recent advances in phosphate and nitrate homeostasis are illustrative examples of signalling in response to nutrient availability.

3.1 Response to Phosphate Starvation

3.1.1 Coordinated Root-to-Shoot and Shoot-to-Root Signalling

Plant cells maintain inorganic phosphate (Pi) concentrations, despite large variations of Pi availability in the soil. The complex regulation of Pi homeostasis involves local signalling, long-distance transport through the xylem and phloem, transcriptional and post-transcriptional gene control and several types of non-coding regulatory RNAs (Chiou and Lin 2011). Pi is acquired in roots through phosphate transporters encoded by PHT1 genes (Forde 2002a; Mudge et al. 2002; Misson et al. 2004; Shin et al. 2004). Once Pi status is sensed, local and systemic signals are triggered. It has been proposed that systemic signals are transported in the xylem from roots to shoots, which in turn generate secondary long-range signals that move to roots *via* the phloem (Chiou and Lin 2011). Under Pi deprivation, primary root growth is arrested and the number and length of lateral roots increase, a response that depends on local signalling (Linkohr et al. 2002; Svistoonoff et al. 2007). In addition, Pi starvation induces changes in gene expression to facilitate Pi uptake, remobilization and recycling (Chiou and Lin 2011). Pi uptake is noticeably regulated by long-distance signals (Liu et al. 1998; Burleigh and Harrison 1999; Thibaud et al. 2010).

3.1.2 The Role of Hormones and Sucrose

Several plant hormones are involved in Pi starvation responses, but they seem to affect mainly local responses, rather than systemic signalling (Chiou and Lin 2011). However, the recently identified hormones strigolactones might play a role in long-distance communication. Up-regulation of strigolactones by Pi deficiency contributes to changes in shoot architecture (Yoneyama et al. 2007; López-Ráez et al. 2008; Umehara et al. 2010; Kohlen et al. 2011). Moreover, strigolactones have been detected in *Arabidopsis* xylem sap, suggesting that these hormones act as root-to-shoot signals involved in Pi starvation responses (Kohlen et al. 2011). Split-root experiments have indicated the existence of systemic suppressors of phosphate starvation-induced genes when Pi is available to one portion of the roots (Liu et al. 1998; Burleigh and Harrison 1999; Franco-Zorrilla et al. 2005). Pi itself has been proposed to act as such mobile signal. However, down-regulation of one of these genes occurs before internal Pi levels increase, and, in addition, a reduction in Pi flow does not affect this down-regulation, suggesting that the systemic signal is not Pi (Burleigh and Harrison 1999; Thibaud et al. 2010). Another putative long-distance signal is sucrose, as Pi starvation leads to increased levels of sugars in leaves, and these sugars are transported in the phloem to roots (Chiou and Lin 2011). Conclusive evidence on the role of sucrose as a systemic signal has been hindered, however, by the difficulty in separating its signalling from its metabolic role.

3.1.3 A New Actor in the Landscape: miR399, a Major Signal in Pi Homeostasis

Recent studies on the role of a microRNA (miRNA), miR399, in phosphate homeostasis have shed light on the identity of the phloem-transmissible signal(s). MiR399, which is induced by Pi deficiency, down-regulates the levels of its target transcript *PHO2*, encoding a ubiquitin-conjugating E2 enzyme required to prevent over-accumulation of Pi in shoots (Delhaize and Randall 1995; Fujii et al. 2005; Aung et al. 2006; Bari et al. 2006; Chiou et al. 2006). *PHO2* and miR399 are expressed in the vasculature and play a role in the systemic regulation of Pi uptake and translocation (Aung et al. 2006; Bari et al. 2006; Chiou et al. 2006). In addition, this miRNA has been detected in the phloem sap of two plant species (Pant et al. 2008). All this suggested that miR399 might act as a systemic Pi homeostasis signal. Indeed, shoot-to-root movement of mature miR399 has been demonstrated independently by two research groups, using grafting experiments in *Arabidopsis* and tobacco (Lin et al. 2008; Pant et al. 2008). MiR399-overexpressing (miR399-OX) scions caused a down-regulation of *PHO2* in rootstocks, and both miR399-OX/wild-type- and wild-type/miR399-OX-grafted plants showed increased Pi levels in scions, indicating biological activity of transported miR399 molecules (Lin et al. 2008; Pant et al. 2008). Although these results have been obtained using miR399-OX plants and, therefore, confirmation that the same mechanism operates in wild-type plants is still needed, they strongly argue for a role of miR399 as a phloem-mobile signal in Pi homeostasis. The existence of additional, miR399-independent systemic signals triggered by vacuolar Ca^{2+}/H^{+} transporters has been recently pointed out (Liu et al. 2011b). Identification of these long-distance molecules awaits further research.

3.2 Nitrate Homeostasis

3.2.1 Nitrate Uptake and Root Architecture and the N Status of the Plant

In addition to being a nutrient source, nitrate also functions as a signal molecule, regulating gene expression (Stitt 1999; Liu et al. 2009; Castaings et al. 2011; Krouk et al. 2010a). NO_3^- homeostasis at the plant level is controlled by sensing of exogenous NO_3-, but also by systemic N signalling. One example is the N regulation of root architecture. This response involves (1) a local response, implicating the nitrate transceptor NRT1.1 (Remans et al. 2006) and the transporter NRT2.1 (Filleur et al. 2001), both acting on NO_3^- uptake and signalling (Little et al. 2005; Remans et al. 2006); (2) a root-to-shoot signalling event, involving cytokinins (Takei et al. 2001, 2002; Rahayu et al. 2005); and (3) a shoot-to-root signalling of the N status regulating nitrate uptake and root branching. Experiments with split-root systems have clearly demonstrated the existence of systemic controls on the specific repression of root NO_3- uptake systems and root branching by high N status of the plant and provided strong evidence that the regulatory signals arise in the shoot (Forde 2002a).

3.2.2 NO_3- and Amino Acids as Signals

Many investigations attempted to identify the nature of the systemic shoot-to root signal molecule. NO_3^- per se might be a signal since it is transported long-distance through the phloem by the nitrate transporters NRT1.7 and NRT1.9 (Fan et al. 2009b; Wang and Tsay 2011), although there is little evidence of a long-range role as signal molecule rather than metabolite. Because nitrate is assimilated into amino acids, it was proposed that the increase in the pools of amino acids, such as Gln, Glu and Asn, may provide a systemic signal of the N status of the plant to regulate root response and repression of NO_3- uptake (Cooper and Clarkson 1989; Forde 2002b; Miller et al. 2008; Forde and Walch-Liu 2009). However, conflicting data have been reported and did not always support this hypothesis. In the *hni* mutants, a class of mutants affected in systemic shoot-to-root response, there was an inverse correlation between amino acids levels and repression of the nitrate transporter *NRT2.1*, suggesting that amino acids are not involved as systemic signals (Girin et al. 2010). Because amino acids are also an N source and can be metabolized, it is unclear whether their effect on NO_3- uptake results from a role as signalling molecules or from a role in overall N supply. Uptake of N is also tightly coordinated with C assimilation in shoots, supported by the observation that NRT2.1 and NRT1.1, as well as other inorganic nutrient transporters, are regulated by sugars (Lejay et al. 1999, 2003; Liu et al. 2009). In addition, an uncharacterized oxidative pentose phosphate pathway–dependent sugar-signalling pathway has been recently identified (Lejay et al. 2008). Hormone control was also proposed to participate in the shoot-to-root long-range signalling; auxin acts directly on root architecture, in coordination with nitrate signalling, and the recent demonstration that NRT1.1 transports not only nitrate but also auxin establishes a connection between nutrient and hormone signalling (Guo et al. 2002; Krouk et al. 2010b). However, the nature of the signal(s) acting in shoot-to-root signalling of N status is still unknown.

3.2.3 Transduction of N Signal and Roles for miR167, miR169 and miR393

Several signalling components triggered by N status have been identified, and include sensors, such as the transceptor NRT1.1, kinases (CIPK8), ubiquitin ligases (NLA) and transcriptional factors or regulators, such as NLP7, LBD37/38/39 and the master clock control gene CCA1, acting on the control of nitrogen assimilation genes (Peng et al. 2007; Gutiérrez et al. 2008; Castaings et al. 2009; Hu et al. 2009; Rubin et al. 2009). Furthermore, in roots, this transduction pathway interplays with auxin signalling that also affects nitrate nutrition (Krouk et al. 2011). Several miRNAs have been identified in this feedback control, including miR393, miR167 or miR169 (Gifford et al. 2008; Vidal et al. 2010; Zhao et al. 2011). Interestingly, two of these miRNAs, miR167 and miR169, were detected in the phloem sap of pumpkin or rapeseed, suggesting a role in phloem long-distance signalling (Yoo et al. 2004; Buhtz et al. 2008, 2010). These findings and the recent demonstration of the systemic role of miR399 in phosphate starvation (Pant et al. 2008; Lin et al. 2008) may indicate a general role of miRNAs in long-range signalling in response to nutrient starvation (Yoo et al. 2004; Kehr 2009).

4 Long-Distance Signalling in Developmental Programs

Plant tissues and organs develop from meristems, which are usually sheltered to prevent their damage. This protection entails a trade-off: Meristems cannot directly detect many environmental signals. However, external cues are perceived by different parts of the plant body, like leaves or roots. Therefore, communication among different tissues and organs is essential to achieve coordinated development. Examples of cell-to-cell communication, long-distance signalling through the phloem and xylem and secretion of regulatory molecules to modulate development have been described (Giakountis and Coupland 2008; Lehesranta et al. 2010; Sieburth and Lee 2010; Urbanus et al. 2010; Domagalska and Leyser 2011; Proust et al. 2011; Van Norman et al. 2011). This section focuses on developmental processes regulated by long-range signals *via* the phloem and the mobile molecules that have been identified so far, as well as others that might be involved.

4.1 *Plant Reproduction: The Identification of a Florigen Component*

4.1.1 The Mysterious Florigen

The existence of long-distance signals regulating flowering was demonstrated in the 1930s, on the basis of grafting experiments between plants induced and non-induced to flower. These findings led to the concept of floral stimulus or 'florigen', a transmissible substance that induces flowering in all higher plants (reviewed by Lang 1952). Experimental evidence suggested that leaf-generated inhibitors of flowering also exist, and later on it was proposed that the floral stimulus must have a complex composition, including several different molecules (Bernier 1988). The mobile signal, simple or complex, is produced in leaves and is transported in the phloem to the shoot apical meristem, where flowers develop (Bernier 1988). Many different molecules have been postulated as components of the florigen, including sucrose, gibberellins (GAs), cytokinins, other plant hormones, certain amino acids, proteins, mRNAs, small RNAs and SA (Bernier 1988; Corbesier and Coupland 2005; Suárez-López 2005). Diverse biochemical and physiological approaches, however, failed to demonstrate, during decades, that these molecules are systemic flowering signals, except perhaps for GAs in a grass species (Bernier 1988; King and Evans 2003; Corbesier and Coupland 2005; Suárez-López 2005).

4.1.2 Evidence on the Major Role of FLOWERING LOCUS T

Molecular genetics experiments, however, pinpointed a possible florigen component. The description of the expression pattern of several flowering-time genes, the use of tissue-specific promoters to express these genes in the phloem or in the shoot apical meristem and the exploitation of classical grafting techniques have been crucial for this advance. Two major players in the photoperiodic regulation of flowering, the transcriptional regulator CONSTANS (CO) and the small globular protein FLOWERING LOCUS T (FT), were shown to be expressed in leaf vascular tissues of *Arabidopsis* plants, suggesting their possible involvement in long-distance signalling (Takada and Goto 2003; An et al. 2004). In addition, expression of *CO* specifically in phloem companion cells or in the minor veins of mature leaves, but not in the shoot apical meristem, was sufficient to complement the late-flowering phenotype of *co* mutants and to induce *FT* expression in the phloem (An et al. 2004; Ayre and Turgeon 2004). In wild-type *Arabidopsis*, *FT* mRNA is expressed mainly in the leaves and absent, or present at extremely low levels, in the shoot apex (Kobayashi et al. 1999; Takada and Goto 2003; Abe et al. 2005; Wigge et al. 2005; Corbesier et al. 2007). However, FT acts in the shoot apex through its interaction with the bZIP transcription factor FD, which is preferentially expressed in the shoot apex of *Arabidopsis* and maize (Abe et al. 2005; Wigge et al. 2005; Muszynski et al. 2006). Furthermore, two FT-like proteins, one of them highly homologous to FT, were detected in the phloem sap of *Brassica napus* (Giavalisco et al. 2006). All these results pointed to FT as a good candidate for a florigen component. The fact that FT is a small protein also fitted with the hypothesis of FT being mobile.

Finally, 70 years after Chailakhyan coined the term 'florigen' (Chailakhyan 1936), evidence that a molecule acts as a long-distance flowering signal has been obtained. Monocot and dicot plant species, as well as long-day, short-day and day-neutral plants, have been shown to use FT as a florigenic molecule (Corbesier et al. 2007; Jaeger and Wigge 2007; Lin et al. 2007; Mathieu et al. 2007; Tamaki et al. 2007). The first indication that a product of the *FT* gene might be part of the floral stimulus was obtained in tomato by showing that plants overexpressing *SINGLE FLOWER TRUSS* (*SFT*, the tomato *FT* orthologue) grafted onto *sft* mutant stocks rescue the late-flowering phenotype of these mutants (Lifschitz et al. 2006). Movement of the *SFT* mRNA could not be detected, indicating that either the SFT protein or a downstream target moves to the shoot apical meristem to induce flowering. In addition, the results of Lifschitz et al. (2006) suggested that *SFT*-stimulated signals are conserved in different plants.

Then, several landmark papers, using diverse approaches including comparison of the localization of endogenous *FT* mRNA and engineered FT proteins fused either to reporter proteins or to small tags, tissue-specific expression and tissue-specific silencing of FT, expression of non-mobile versions of this protein and grafting experiments to test the transmission of the effects of FT on flowering time provided strong evidence that *Arabidopsis* FT and rice Hd3a—an orthologue of FT—proteins move in the phloem to the shoot apical meristem (Corbesier et al. 2007; Jaeger and Wigge 2007; Mathieu et al. 2007; Tamaki et al. 2007). Experimental support for translocation of FT in the phloem and transmission of its effect was also obtained in cucurbits using heterografts between two cucurbit species (Lin et al. 2007). In this work, two FT-like proteins were detected in the phloem sap of *Cucurbita maxima* (Lin et al. 2007). Although movement of endogenous FT proteins from the leaves to the shoot apex has not been demonstrated yet, all these findings strongly support that FT is a component of florigen.

4.1.3 A Model for the Mode of Action of FT in *Arabidopsis*

Based on the results described above, a model for the regulation of *Arabidopsis* flowering by long-distance signals has been proposed. Inductive photoperiodic conditions perceived in the leaf lead to stabilization of CO, which induces *FT* transcription in the leaf phloem (An et al. 2004; Valverde et al. 2004). Once translated in the phloem CCs, the FT protein enters the phloem stream and moves to the shoot apical meristem, where it interacts with FD to activate the expression of at least one floral meristem identity gene, *APETALA1* (*AP1*) (Abe et al. 2005; Wigge et al. 2005; Corbesier et al. 2007; Jaeger and Wigge 2007; Lin et al. 2007; Mathieu et al. 2007; Tamaki et al. 2007). In the shoot apical meristem, FT also up-regulates the expression of *SOC1*, which is another gene involved in flowering-time control (Turck et al. 2008).

4.1.4 Role of FT Homologues in Other Species

At least part of this mechanism of regulation is conserved, with some variations, in rice, tomato and cucurbits (Yano et al. 2000; Izawa et al. 2002; Lifschitz et al. 2006; Lin et al. 2007; Tamaki et al. 2007). In several other species, CO and/or FT homologues are also involved in the regulation of flowering time, and the interaction between FT and FD has also been shown or suggested (Pnueli et al. 2001; Li and Dubcovsky 2008; Turck et al. 2008). However, in rice, an FD homologue has not been identified yet (Tsuji et al. 2011). Interestingly, recent results suggest that rice has at least two florigen components: Hd3a, which promotes flowering under short days, and RFT1—another FT-like protein highly similar to Hd3a—that promotes flowering, much later, under long days (Tamaki et al. 2007; Komiya et al. 2009). Three members of the FT protein family, but, intriguingly, not Hd3a and RFT1, have been detected in the phloem sap of rice, suggesting that other proteins of this family might also be mobile (Aki et al. 2008). In pea, evidence suggesting that two FT genes are also involved in long-distance promotion of flowering has recently been obtained (Hecht et al. 2011).

4.2 Other Components Acting on Flower and Tuber Induction

4.2.1 Other Transcription Factors Involved in Flowering

In addition to FT, several *Arabidopsis* FT homologues are also involved in flowering. TWIN SISTER OF FT (TSF) affects flowering partially redundantly with FT, might also act as a long-distance signal and, as mentioned above, is present in the phloem of *B. napus* (Michaels et al. 2005; Yamaguchi et al. 2005; Giavalisco et al. 2006; Mathieu et al. 2007). TERMINAL FLOWER 1 (TFL1) and BROTHER OF FT AND TFL1 (BFT) repress flowering and play redundant roles in inflorescence meristem development (Shannon and Meeks-Wagner 1991; Yoo et al. 2010). The presence of the TFL1 protein in places of the shoot apical meristem where its mRNA is not present suggests that TFL1 moves cell-to-cell (Conti and Bradley 2007). These results emphasize the ability of the small FT-like proteins to move.

Some plants require exposure to low temperatures to flower (vernalization). The MADS-box transcription factor FLC plays an important role in the response to vernalization (Amasino 2010). FLC levels are high in late-flowering *Arabidopsis* plants that respond to vernalization (Michaels and Amasino 1999; Sheldon et al. 1999). FLC represses the production of systemic signals (FT) in the leaves and prevents the shoot apical meristem from being competent to respond to these signals, by repressing FD and SOC1 expression, until plants are vernalized (Searle et al. 2006). When plants are vernalized, *FLC* mRNA and protein levels are reduced and flowering can occur (Michaels and Amasino 1999; Sheldon et al. 1999, 2000; Searle et al. 2006).

4.2.2 Role of Hormones in Systemic Induction of Flowering?

Several plant hormones affect the induction of flowering. Among them, GAs seem the most likely to act as mobile flowering signals. They affect flowering in many plants and can be transported in the phloem and xylem sap (Bernier 1988; Davis 2009; Mutasa-Göttgens and Hedden 2009). In the grass *Lolium temulentum*, when flowering is induced, the bioactive GAs, GA_5 and GA_6 increase at the shoot apex shortly after an increase of their GA_{20} precursor in leaves. Moreover, when labelled GA_5 is exogenously applied, it is transported to the shoot apex (King et al. 2001; King and Evans 2003). This suggests that GA_5, and perhaps GA_6, might act as florigenic molecules. It has been proposed that selective degradation of certain GAs just below the shoot apex restricts their access to the shoot apical meristem, but GA_5 is protected from this degradation, allowing this GA to reach the shoot apex and induce flowering (King et al. 2008). In *Arabidopsis*, levels of GA_4 and sucrose increase in the shoot apex before floral initiation under short days. These increases probably result from transport of GA_4 and sucrose produced outside the shoot apex (Eriksson et al. 2006). These results suggest that the florigenic GAs might be different in different species.

Cytokinins are also considered putative florigen components, and the results supporting this view have recently been reviewed (Bernier 2011). However, a recent report shows that cytokinins promote flowering and induce transcription of TSF in *Arabidopsis* leaves, suggesting that cytokinins might act upstream of long-distance signals (D'Aloia et al. 2011). Nevertheless, previous results indicated a direct effect of cytokinins at the shoot apical meristem, and therefore further research is required to show whether cytokinins act as mobile signals or not.

4.2.3 A Role for Sucrose

In addition to increasing at the shoot apex just before floral initiation, sucrose also increases rapidly in leaf phloem exudates (Corbesier and Coupland 2005; Eriksson et al. 2006). Mutants affected in starch synthesis or mobilization exhibit altered flowering times (Corbesier and Coupland 2005). Under certain conditions, sucrose can complement the late-flowering phenotypes of several mutants, including *co*, but not that of *ft* (Roldán et al. 1999; Ohto et al. 2001). Altogether, these observations suggest a long-range signalling role for sucrose, which would act downstream of *CO* and upstream or in parallel with *FT*. In addition, complex interactions between sucrose, cytokinin and GA signalling have been proposed (Périlleux and Bernier 2002; Suárez-López 2005). Given that GAs, sucrose and cytokinins affect many aspects of plant growth and development, it is difficult to demonstrate whether their effects on the systemic regulation of flowering are direct or indirect.

4.2.4 The Roles of miR172 and BEL5 in Tuber Formation

Tuber formation is a mode of vegetative reproduction regulated, like flowering, by long-distance signals generated in the leaves (Abelenda et al. 2011). The photoreceptor phytochrome B (PHYB) represses tuberization in potato, whereas the homeobox transcription factor StBEL5 and the microRNA 172 (miR172) promote tuber formation (Jackson et al. 1996; Chen et al. 2003; Banerjee et al. 2006; Martin et al. 2009). Movement of *StBEL5* mRNA through grafts correlates with tuber induction (Banerjee et al. 2006). Plants with reduced levels of PHYB tuberize earlier than wild-type plants and show reduced abundance of *StBEL5* transcript in leaves and increased abundance in stolons at early stages of tuber development, suggesting that PHYB might regulate *StBEL5* mRNA movement (Jackson et al. 1996; Martin et al. 2009).

Interestingly, PHYB affects miR172 levels in a similar way as it affects *StBEL5* mRNA. This, together with the presence of miR172 in vascular bundles and the transmission of its effect on tuberization through grafts, has led to the hypothesis that miR172 might be a long-distance signalling molecule or might regulate mobile signals (Martin et al. 2009). The role of miR172 in flowering-time control in several species and its detection in the phloem sap of *Brassica napus* are consistent with this hypothesis (Buhtz et al. 2008; Zhu and Helliwell 2011). Alternatively, it has been speculated that miR172 might function as a cell-to-cell signal mediating the effect of PHYB from the mesophyll on the expression of FT in the phloem in *Arabidopsis* (Abelenda et al. 2011).

A sucrose transporter, StSUT4, affects tuber induction, suggesting that sucrose plays a role in the systemic regulation of this process (Chincinska et al. 2008), but since sucrose is required to form starch, a major component of tubers, it is difficult to distinguish a metabolic from a signalling role of sucrose. Recently, it has been proposed that a potato FT homologue might be a mobile signal for tuberization, although results supporting this hypothesis have not been reported yet (Abelenda et al. 2011).

4.2.5 Still Unanswered Questions

Despite the impressive knowledge recently acquired on the systemic regulation of flowering, many questions are still unanswered. FT does not seem to be ‘the’ florigen, but a major florigen component, as other FT-like proteins also act as mobile flowering signals. It remains to be shown whether other types of molecules might play a similar role together with, or alternatively to, FT and its homologues. For example, GAs seem to play a systemic role in *L. temulentum*, but recent evidence suggests that FT might also affect flowering in this plant (King et al. 2006; Skøt et al. 2011).

In beet, two FT homologues play opposite roles in floral induction, but no evidence that any of the two is mobile has been reported so far (Pin et al. 2010). The CO/FT module also regulates seasonal growth cessation in trees (Böhlenius et al. 2006), but whether transport of FT is required for this process has not been tested yet. In order to understand fully the long-distance signalling process, it will be necessary to understand how FT is loaded into the phloem, transported and unloaded in target tissues, as well as the mechanisms that control the response of these tissues to the mobile signal. Part of this response is mediated by FD in the shoot apex, but FT promotes flowering both through FD-dependent and independent pathways, suggesting that additional genes are involved (Wigge et al. 2005).

4.3 Vegetative Development and Morphogenesis

4.3.1 Role of Long-Distance Transport of RNAs in Morphogenesis

Although flowering is a paradigm of systemic signalling in the field of plant development, other developmental events also involve long-distance signals. Leaf development was shown to be affected by a graft-transmissible RNA in tomato (Kim et al. 2001). mRNAs encoding other developmental regulators, as well as small RNAs that down-regulate the expression of developmental genes, have been detected in phloem sap, and some of them are transmissible through graft junctions, suggesting that RNAs can also act as long-distance signals for the control of plant development (reviewed in Lough and Lucas 2006). However, further demonstrations that RNAs act as mobile signals for developmental regulation have to be obtained (Kehr 2009; Turgeon and Wolf 2009).

4.3.2 Role of FT as a General Regulator of Plant Development

In addition to their role in flowering, FT proteins are involved in other developmental events. In tomato, SFT affects leaf development and maturation, stem growth and the formation of abscission zones through long-distance signalling (Shalit et al. 2009). Ectopic expression of rice *Hd3a* in vascular tissues, as well as overexpression of *Arabidopsis FT* or *FD*, affects vegetative traits, such as internode elongation or leaf development (Teper-Bamnolker and Samach 2005; Wigge et al. 2005; Tamaki et al. 2007). Taken together, these observations indicate roles of FT proteins beyond flowering and further point out FT as a general systemic regulator of plant development.

4.3.3 Role of PHYB and SPA1 in Response to Light Perception

At least two genes involved in light perception and signalling, *PHYB* and *SUPPRESSOR OF PHYA-105* (*SPA1*), regulate the production of FT through their effect on the stability of the CO protein (Valverde et al. 2004; Laubinger et al. 2006). PHYB influences other developmental events involving intercellular and inter-organ communication, as well as long-distance signalling for other processes, including tuberization and plant disease resistance (Jackson et al. 1998; Bou-Torrent et al. 2008; Griebel and Zeier 2008). SPA1 is required in the phloem to control not only flowering time but also seedling photomorphogenesis and leaf expansion, but SPA1 itself is not mobile, indicating that SPA1 affects non-cell-autonomous regulators of these processes (Ranjan et al. 2011). Identification of the mobile molecules acting downstream of PHYB and SPA1 to control vegetative development awaits further investigations.

4.3.4 Other Potential Long-Distance Signal Molecules Acting on Development

Long-range signalling is also involved in vascular development. In *Arabidopsis*, xylem expansion associated with hypocotyl and root secondary growth is promoted after floral induction and requires graft-transmissible signals (Sibout et al. 2008). Interestingly, low levels of FLC, a flowering-time regulator, correlate with xylem expansion (Sibout et al. 2008). Recent results suggest that GAs might be the mobile signal (Ragni et al. 2011), but the identity of this signal has not been proven yet. Given that FLC represses FT, it would be interesting to test whether FT plays a role in this process. Other hormones are also candidates for mobile signals regulating vegetative development. Auxin is known to affect many developmental events, and although there is evidence of transport of auxin in the phloem, the best-studied mechanisms of auxin transport do not involve this vascular conduit (Lehesranta et al. 2010; Peer et al. 2011).

5 Concluding Remarks

Long-distance signalling *via* the phloem has been shown during the past decade to recruit a variety of signal molecules, including hormones, peptides, macromolecules, nutrients and metabolites. These signals are involved in many developmental and adaptive processes. At least some phloem-mobile signals may be common to several processes, as is the case for FT. However, in most cases, the nature of these signals is still elusive, and the conclusive demonstration of a signalling role for candidate signal(s) is often controversial. In contrast, it is now well established that chemical signals act together with electrical signals acting faster in a long-distance range. Further, the concept of molecular ‘hopping’ for relay and amplification of signal molecules in the transport phloem opens up new avenues to address the mechanism of long-distance signalling in higher plants and needs to be further tested in the future.

A main issue in a near future will be to determine the molecular mechanisms coordinating the action of multiple signalling pathways acting in the phloem tissue. Are they based on crosstalks during signal transduction or are they regulated at a gene-network level, as proposed recently in the context of integration of hormone signalling (Jaillais and Chory 2011)? This points out that we need to improve our knowledge on gene expression networks acting in the phloem, which are still poorly characterized (Vilaine et al. 2003; Le Hir et al. 2008), and on the subsets of macromolecules, proteins, mRNAs and miRNAs, loaded into the sieve elements, translocated long-distance and acting non-cell autonomously. Another major exciting issue is the identification of the factors required for transport of macromolecules in the translocation stream. The recent discovery of the formation of large ribonucleoprotein complexes in the phloem sap suggests indeed that this process is highly regulated and might be involved in the specific transport of selected molecules (Ham et al. 2009; Ma et al. 2010; Li et al. 2011). Understanding how the mobile signals leave the phloem to reach their target tissues also requires further research.

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