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Review

The enemy within: phloem-limited pathogens

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SUMMARY

The growing impact of phloem-limited pathogens on high-value crops has led to a renewed interest in understanding how they cause disease. Although these pathogens cause substantial crop losses, many are poorly characterized. In this review, we present examples of phloem-limited pathogens that include intracellular bacteria with and without cell walls, and viruses. Phloem-limited pathogens have small genomes and lack many genes required for core metabolic processes, which is, in part, an adaptation to the unique phloem environment. For each pathogen class, we present multiple case studies to highlight aspects of disease caused by phloem-limited pathogens. The pathogens presented include *Candidatus* Liberibacter asiaticus (citrus greening), *Arsenophonus* bacteria, *Serratia marcescens* (cucurbit yellow vine disease), *Candidatus* Phytoplasma asteris (Aster Yellows Witches' Broom), *Spiroplasma kunkelii*, *Potato leafroll virus* and *Citrus tristeza virus*. We focus on commonalities in the virulence strategies of these pathogens, and aim to stimulate new discussions in the hope that widely applicable disease management strategies can be found.

Keywords: bacteria, insect vector, pathogen, phloem limited, phytoplasma, spiroplasma, virus.

INTRODUCTION

Phloem-limited agricultural pathogens are spreading at an alarming rate, enhanced by warming climates and increasingly interconnected agricultural systems. Current treatment methods often do not specifically target phloem-limited pathogens, and are frequently preventative rather than curative (Table S2, see Supporting Information). Phloem-limited pathogens include walled intracellular bacteria, intracellular bacteria without cell walls (Mollicutes) and viruses (Bové and Garnier, 2002; Fletcher and Wayadanda, 2002; Hogenhout *et al.*, 2008).

Phloem-limited pathogens represent a significant research challenge because they are difficult to detect within plants, and infected plants exhibit variable symptoms that develop slowly. Moreover, these pathogens have complex infection cycles involving both plant hosts and insect vectors (tritrophic interactions). Most phloem-limited bacteria remain uncultured *in vitro*, meaning that Koch's postulates cannot be fulfilled, and the bacterial species are designated by the preface '*Candidatus*'. Nevertheless, many have been identified as causative disease agents, using either processes developed for viruses or sequence-based identification (Bos, 1981; Fredricks and Relman, 1996).

The plant response to pathogens can be divided into microbe-associated molecular pattern (MAMP)-triggered immunity (MTI) and effector-triggered immunity (ETI). MAMPs are slow-evolving molecules associated with core microbial processes, for example bacterial flagellin (Monaghan and Zipfel, 2012). Damage-associated molecular patterns (DAMPs) are endogenous signals that result from wounding insect damage, and can induce or amplify immune responses (Wu *et al.*, 2014). Both MAMPs and DAMPs are recognized by pattern recognition receptors, which are commonly receptor-like kinases (RLKs). Effectors are fast-evolving molecules associated with infection processes, for example HopZ, and are recognized by nucleotide-binding leucine-rich repeat (NB-LRR) proteins encoded by Resistance (*R*) genes (Dangl *et al.*, 2013; Hogenhout *et al.*, 2009; Schreiber *et al.*, 2016). The hypersensitive response (HR) is linked to ETI, and is often characterized by localized cell death that is thought to limit pathogen spread. MTI and ETI processes are probably interconnected, and basal disease resistance has been described as a combination of MTI and weak ETI minus the susceptibility caused by pathogen effectors (Bellincampi *et al.*, 2014; Jones and Dangl, 2006; Thomma *et al.*, 2011). Disease resistance in plants is typically studied in non-vascular tissues, and it is unclear whether MTI and ETI also occur in the phloem. In addition, plants use endogenous RNA-interference (RNAi) processes to specifically target viral pathogens, and we refer the reader to several excellent reviews on this topic (Duan *et al.*, 2012; Wang *et al.*, 2012).

Pathogens use effector molecules to mould the host environment to suit them; they can (i) block host immune responses, (ii) promote host processes favourable to the pathogen, and/or (iii) reprogram host development in ways that benefit the pathogen. As a result of their intracellular nature, phloem-limited pathogens probably have different effector delivery methods and use effectors for different purposes than the more widely studied extracellular pathogens.

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We first introduce the role of the phloem within the plant, with a particular focus on phloem-localized transport and defence processes. We also briefly review the insect vectors of phloem-limited pathogens before moving on to discuss several well-characterized phloem-limited pathogens from different classes. These bacteria, Mollicutes and viruses were chosen for the extent of their impact on agricultural systems, the breadth of the literature available or to highlight a particular aspect of disease associated with phloem-limited pathogens. Throughout, we emphasize how pathogens interact with their hosts to promote virulence.

THE PHLOEM: TRANSPORTER OF NUTRIENTS AND COORDINATOR OF DEFENCE

The phloem is a microaerophilic environment rich in sugars and nutrients, and an environmental niche for plant pathogens (Fig. 1) (Demmig-Adams *et al.*, 2014; van Dongen *et al.*, 2003; Fatima and Senthil-Kumar, 2015). Transport through the phloem is directional from sugar-producing (photosynthetic) source leaves to growing or storage sink tissues that consume sugars (De Schepper *et al.*, 2013; Knoblauch and Peters, 2013). Long-distance transport through the phloem is thought to be driven by osmotically generated hydrostatic pressure (Schulz *et al.*, 2009; Turgeon, 2010), but the physical aspects of long-distance phloem transport remain poorly characterized (Knoblauch and Peters, 2010).

The phloem transports both signalling and defence molecules long distances, including hormones, RNA and proteins (van Bel *et al.*, 2013; Dinant and Lemoine, 2010). Phloem transport may not be selective, and only a few molecules have been shown to function in sink tissues (Atkins *et al.*, 2011; Haywood *et al.*, 2005; Paultre *et al.*, 2016). Many of the hormones carried by the phloem are involved in systemic defence processes, with jasmonates and salicylic acid being two well-studied examples (Fu and Dong, 2013; Wasternack and Hause, 2013). There are two main systemic defence processes caused by phloem-transported signals: (i) systemic acquired resistance (SAR); and (ii) systemic wound response (SWR) (Gao *et al.*, 2015). Multiple signals have been associated with each of these processes, including hormones, lipid-derived molecules and reactive oxygen species (ROS) (Gaupels and Vlot, 2012). Electrophysiological changes can occur as a result of many triggers, including insect herbivory, and are another form of defence signalling. These signals rapidly propagate throughout the plant via the phloem and are linked to calcium fluxes (van Bel *et al.*, 2014; Hedrich *et al.*, 2016). Calcium is also involved in other defence processes, such as sieve pore occlusion and local defence signalling cascades, which are not well understood at a mechanistic level (van Bel *et al.*, 2014; Furch *et al.*, 2009; Zhang *et al.*, 2014).

Phloem-specific defence responses remain poorly characterized because of the difficulty in studying phloem-specific processes (Fig. 1) (Gaupels and Vlot, 2012; Knoblauch and Peters, 2010). Phloem-localized proteins, such as forisomes and P proteins, are thought to rapidly seal sieve plates after damage (Batailler *et al.*, 2012; Ernst *et al.*, 2012). Forisomes are only found in legumes, expand in size in response to increased Ca^{2+} in injured sieve tubes and are able to partially occlude phloem tubes in a reversible manner (Hafke *et al.*, 2009; Knoblauch *et al.*, 2012; Peters *et al.*, 2010). In-depth studies of SEOR (sieve element occlusion-related) P proteins, however, showed no evidence that sieve tubes were plugged or that phloem translocation was stopped (Knoblauch *et al.*, 2014). The true physiological role of P proteins therefore remains unclear, and further study is needed. Mobile peptide signals in the phloem, such as systemin, act to propagate defence signals and have been implicated in multiple systemic defence processes (Gaupels and Vlot, 2012). Although the function of many of these proteins and peptides remains unclear, their induction or presence is often used in the study of phloem diseases.

Callose deposition at sieve plates and companion cell plasmodesmata (PD) is an important phloem-localized response to wounding and pathogens (Hao *et al.*, 2008; Millet *et al.*, 2010; Zavaliev *et al.*, 2011). Although the reported timing of callose deposition varies, it is considered to be a slower process than P protein accumulation at sieve plates (Knoblauch and Peters, 2010; Voigt, 2014). Callose deposits are thought to limit pathogen dispersal, and are considered to be part of MTI (Hao *et al.*, 2008; Luna *et al.*, 2011). Deposits do not completely seal openings, and are important components of plant viral defence (Brunkard *et al.*, 2013; Zavaliev *et al.*, 2011). At present, it remains unclear whether callose deposition in the phloem is a component of MTI. Many studies of phloem-localized pathogens, however, use callose deposition as a diagnostic indication of disease (Koh *et al.*, 2012).

Secondary plant metabolites, including glucosinolates and pyrrolizidine alkaloids, act to protect plants from herbivores and pests (De Schepper *et al.*, 2013; Savage *et al.*, 2016). Many of these metabolites are inducibly synthesized in response to wounding, and glucosinolates are a particularly well-studied example of this (Bekaert *et al.*, 2012; Textor and Gershenzon, 2009). Some phloem-localized pathogens target synthesis or accumulation of secondary metabolites, because their insect vectors are susceptible to them.

Global alterations in resource distribution can be triggered by altered source–sink relationships caused by herbivory and infection (Gómez *et al.*, 2010; Savage *et al.*, 2016). These alterations also lead to the accumulation of signalling molecules and defence compounds in phloem sinks (Arnold *et al.*, 2004; Savage *et al.*, 2016). One example of redistribution is the growth response, in which infected plants increase photosynthesis in healthy leaves and activate dormant meristems (Järemo and Palmqvist, 2001; Lebon *et al.*, 2014). Redistribution can also be used to compartmentalize portions of the plant

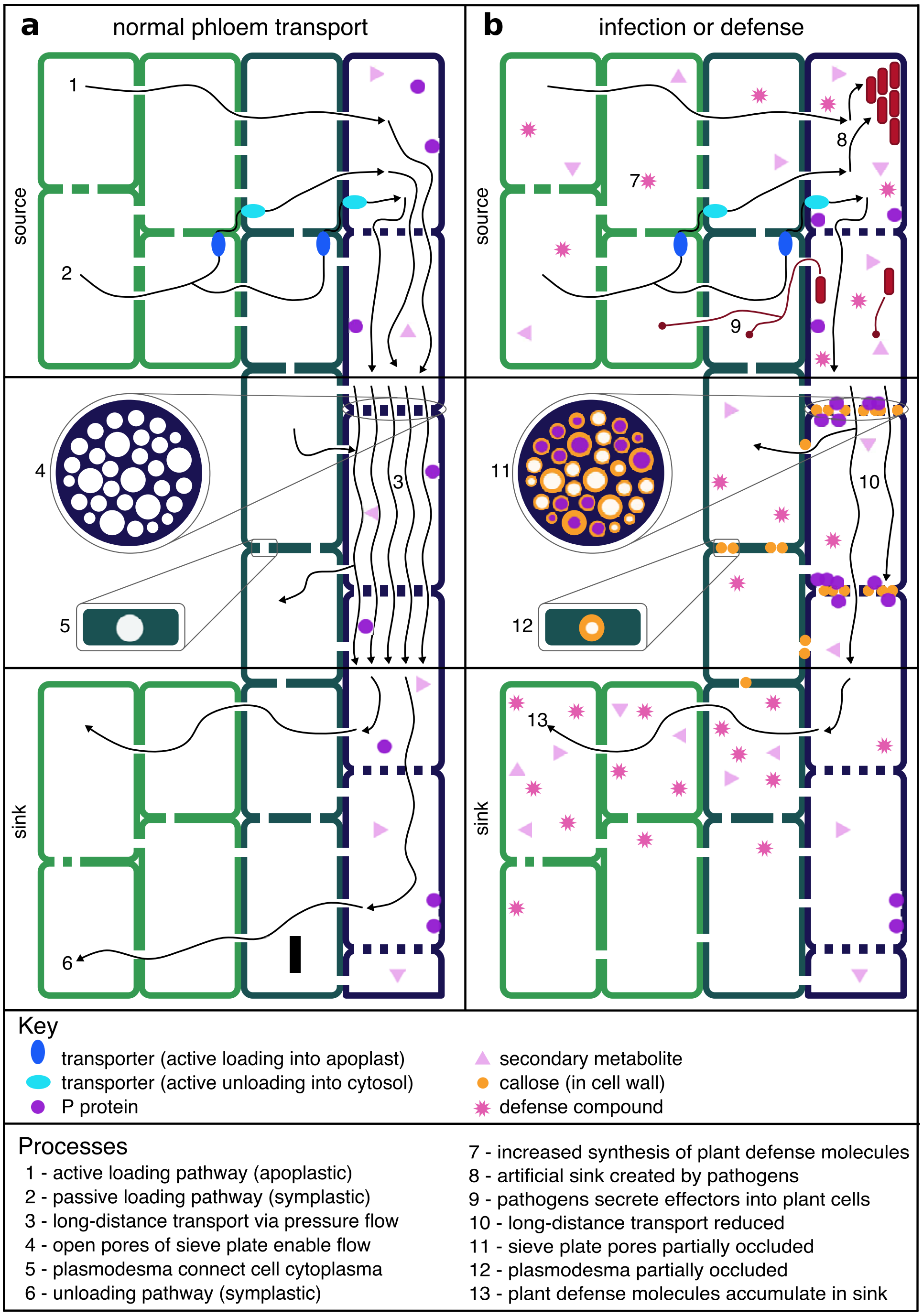

Fig. 1 Normal phloem transport (a) and disruption of transport during infection or defence (b). Green cells are mesophyll, teal cells are companion cells, purple cells are phloem cells and all gaps between cells are plasmodesmata, except for sieve plate pores between phloem cells. Numbered generalized processes are shown in the figure and described in the processes section for representative pathogens. The temporal order of infection and defence processes in the phloem remain unclear (see text for details).

or withdraw resources from affected aerial tissues (sequestering) (Appel *et al.*, 2012; Frost and Hunter, 2008; Gómez *et al.*, 2010). These strategies make resources unavailable to herbivores, and can allow later regrowth. There is some debate as to whether large-scale resource reallocations represent energetically efficient defence strategies, but it is clear that pathogens can have a significant effect on plant source–sink allocations (Demmig-Adams *et al.*, 2014; Huot *et al.*, 2014).

INSECT VECTORS: GATEWAY INTO THE PHLOEM AND ALTERNATIVE HOSTS

The insect vectors of phloem-limited pathogens feed on phloem sap by inserting their stylets into sieve elements. This allows pathogens to directly enter the phloem, bypassing numerous barriers and defence mechanisms within the plant. Key aspects of pathogen transmission are linked to uptake and retention by the insect. The terms used to describe the characteristics of uptake and retention were developed when studying viral pathogens and are used inconsistently in the literature when discussing non-viral, insect-transmitted pathogens. For the purposes of this review, we define the three main terms applied to insect-transmitted pathogens as follows: (i) circulative: pathogens can cross insect cell membranes and be carried internally; (ii) persistent: long feeding times are required for pathogen uptake and pathogens are maintained internally throughout the lifespan of the insect; and (iii) propagative: pathogens replicate in the insect. Phloem-limited pathogens, with the exception of some viruses, are often circulative. All phloem-limited pathogens require long feeding times for uptake by the insect, and are internally maintained by the insect for at least a few days (semi-persistent) or until the end of its life (persistent). Some phloem-limited pathogens replicate in the insect vector (propagative), whereas others are protected from degradation in insects, but only replicate in plants (non-propagative) (Gray *et al*., 2014; Ng and Zhou, 2015; Perilla-Henao and Casteel, 2016; Rosen *et al*., 2015). As a result of the difficulties in studying tritrophic interactions, transmission characteristics remain unclear for many phloem-limited pathogens.

Plant defence responses to phloem-feeding insects include local wound responses that block the flow of phloem sap (Will *et al*., 2009, 2013). Aphids are used as model phloem-feeding insects, and their saliva has been shown to contain effectors that act to repress plant defence responses (Bos *et al*., 2010; Hogenhout and Bos, 2011; Pitino and Hogenhout, 2013). In resistant plants, aphid effectors are recognized and induce local and systemic defence responses consisting of a combination of MTI, ETI and SWR. At present, it is unclear which mechanisms are more important or how they function together in field conditions (Giordanengo *et al*., 2010; Will and van Bel, 2008; Züst *et al*., 2016). By locally removing sugars from the phloem, phloem-feeding insects create artificial sinks where they are feeding, which disrupts carbohydrate partitioning in the plant. The presence and strength of other sinks, either formed by the plant or created by pathogens, can affect how much of the host's resources can be obtained by the phloem-feeding insect (Heard and Buchanan, 1998; Inbar *et al*., 1995; Larson and Whitham, 1997; Savage *et al*., 2016). Disruption of normal sink–source relationships by insect vectors can contribute to symptom development.

Insects are especially important vectors for plant viruses, and multiple viruses are often transmitted by the same insect species (Gray *et al*., 2014; Gray and Banerjee, 1999). For phloem-limited bacteria, the insect–vector relationship and pathogen niche is a polyphyletic trait, indicating that it has evolved independently multiple times (Orlovskis *et al*., 2015; Perilla-Henao and Casteel, 2016). Many insect vectors also carry endosymbionts (Akman Gunduz and Douglas, 2009; Łukasik *et al*., 2013), which provide them with nutrients and protection, and, in some cases, are closely related to phloem-limited pathogens. Once within the plant, many phloem-limited bacteria are able to alter the infected plant, such that the insect vector is attracted to it, and will move the bacteria to a new host (Mann *et al*., 2012; Mas *et al*., 2014).

WALLED PHLOEM-LIMITED BACTERIA

Walled phloem-limited bacterial pathogens are gammaproteobacteria from several different taxa. The insect vector host range appears to be the limiting factor determining which plant species can be infected. These pathogens are primarily found in phloem sieve tubes, but, in some species, they are also present in parenchyma. Phloem-limited bacterial pathogens have reduced genomes, and have often have lost core metabolic pathways in favour of importers to obtain products made by the plant. Interestingly, these pathogenic bacteria are often closely related to endosymbionts. Much of the experimental work has been carried out in non-host systems, such as *Nicotiana* spp. and periwinkle, which have been found to be more tractable than the host plants of phloem-limited bacteria (Bové and Garnier, 2002). We discuss three examples of these pathogens that illustrate infection mechanics, as well as different evolutionary paths leading to pathogenesis by phloem-limited microbes.

Liberibacter bacteria: turning the citrus immune system against itself

Citrus greening or Huanglongbing (HLB) is a disease that affects all economically important citrus species, and some close citrus relatives (Tables 1, S1, see Supporting Information). *Candidatus* Liberibacter asiaticus (*C*Las) is the primary causative agent of HLB, but *Candidatus* Liberibacter americanus (*C*Lam) and *Candidatus* Liberibacter africanus (*C*Laf) also cause disease in some areas (Bové, 2006; da Graca *et al*., 2016; Haapalainen, 2014). The characteristics of *C*Las insect transmission remain unclear; current evidence suggests that *C*Las is propagative in nymphs, but non-propagative in adults (Canale *et al*., 2017; Inoue *et al*., 2009; Pelz-Stelinski *et al*., 2010).

Candidatus Liberibacter (*C*L) genomes are small, and have microsyntenous orthologous regions with their plant endosymbiont relatives *Sinorhizobium meliloti*, *Bradyrhizobium japonicum* and *Agrobacterium tumefaciens* (Kuykendall *et al*., 2012). *C*Las is only able to metabolize a limited set of sugars, and probably uses exogenous carbon sources from phloem sap to generate energy. *C*Las also appears to be adapted to the microaerophilic environment of the phloem; its genome contains multiple components necessary for aerobic respiration (Duan *et al*., 2009; Wang and Trivedi, 2013). *C*Las has no restriction-modification system, and therefore contains multiple prophage regions integrated into its genome, which are differentially expressed in different *C*Las hosts (Fleites *et al*., 2014; Zhang *et al*., 2011). These prophage regions contain peroxidase genes that improve growth in culture and act as secreted effectors to counter host ROS, when expressed in the

Table 1 Pathogens and diseases discussed in this review.

Pathogen	Disease	Host	Vector	References
Walled phloem-limited bacteria				
Candidatus Liberibacter asiaticus, *Candidatus* Liberibacter *americanus*, *Candidatus* Liberibacter *africanus*	Citrus greening, Huanglongbing (HLB)	*Citrus* L. – all economically important citrus species, as well as close citrus relatives	Psyllids: *Diaphorina citri*, *Trioza eritreae*	Haapalainen (2014); Wang and Trivedi (2013)
Candidatus Phlomobacter fragariae	Marginal chlorosis of strawberry	*Fragaria* × *ananassa*	Planthopper: *Cixius wagneri*	Danet *et al*., (2003); Nourrisseau *et al*. (1993)
Candidatus Arsenophonus phytopathogenicus	Low-sugar syndrome ('Basses richesses') of sugar beet	*Beta vulgaris* ssp. *vulgaris*	Planthopper: *Pentastiridius leporinus*	Bressan *et al*. (2012); Sémétey *et al*. (2007)
Serratia marcescens	Cucurbit yellow vine disease	Cucurbitaceae sp.	Squash bug: *Anasa tristis*	Bruton *et al*. (2003); Rascoe *et al*. (2003)
Wall-less phloem-limited bacteria				
Candidatus Phytoplasma asteris/Aster Yellows Witches' Broom (AY-WB), Aster yellows 16SrI-A subgroup	Aster Yellows (AY)	*Daucus carota* ssp. *sativus*, *Allium sepa* L., *Lactuca sativa* L., *Apium graveolens*, Asteraceae	Leafhopper: *Macrosteles quadrilineatus*	Bai *et al*. (2006); Bertaccini *et al*. (2014)
Candidatus Phytoplasma asteris/Onion Yellows (OY), 16SrI-B subgroup	Onion Yellows (OY)	*Allium sepa* L., *Catharanthus roseus*, Asteraceae	Leafhopper: *Macrosteles striifrons*	Bertaccini *et al*. (2014); Miyahara *et al*. (1982)
Candidatus Phytoplasma vitis/ Flavescence dorée (FD), Elm Yellows 16SrV-C and 16SrV-D subgroup	Grapevine yellows: Flavescence dorée (FD)	*Vitis vinifera*	Leafhopper: *Scaphoideus titanus*	Bertaccini *et al*. (2014)*
Candidatus Phytoplasma solani/ Bois Noir (BN), Stolbur 16SrXII-A subgroup	Grapevine Yellows: Bois Noir (BN)	*Vitis vinifera*, wild hosts include *Convolvulus arvensis* L., *Urtica dioica* L.	Leafhopper: *Hyalesthes obsoletus* Signoret	Bertaccini *et al*. (2014)†
Candidatus Phytoplasma mali/ Apple proliferation (AP), Apple proliferation 16SrX-A subgroup	Apple proliferation	*Malus domestica*, *Prunus domestica*, *Prunus avium*, *Prunus armeniaca*, *Corylus* spp.; wild hosts include *Cynodon dactylon, Convolvulus arvensis*	Psyllids: *Cacopsylla costalis*, *C. mali*, *C. melanoneura*; Leafhopper: *Fiebierella florii*	Bertaccini *et al*. (2014)‡
Spiroplasma kunkelii	Corn stunt	*Zea* genus: *Z. maydis*, *Z. perennis*, *Z. mays mexicana*, *Z. diploperennis*, *Z. luxurians*	Leafhoppers: *Dalbulus maidis*, *D. eliminatus*, *Exitianus exitiosus*, *Graminella nigrifons*, *Stirellus bicolor*	Whitcomb *et al*. (1986)§
Spiroplasma citri	Citrus stubborn; Brittle root disease of horseradish	*Citrus* L., *Amoracia rusticana* *Brassica* spp., wild hosts include *Vinca rosea*, *Sisymbrium irio*, *Raphanus raphanistrum* L.	Leafhoppers: *Circulifer tenellus*, *C. haematoceps*, *Scaphytopius nitridus*, *S. delongi*	Fletcher *et al*. (1981); Saglio *et al*. (1973)
Phloem-limited viruses				
Citrus tristeza virus (CTV)	Citrus tristeza, Seedling Yellows	*Citrus* L. – all economically important citrus species	Aphids: *Toxoptera citricida*, *Aphis gossypii*, *Aphis spiraecola*, *Toxoptera aurantii*	Bar-Joseph *et al*. (1989); Moreno *et al*. (2008)
Potato leafroll virus (PLRV)	Potato leaf roll	Solanaceae including *Solanum tuberosum* spp.	Aphids: *Myzus persicae*	Taliansky *et al*. (2003)¶
Squash leaf curl virus (SLCV)	Squash leaf curl	Cucurbitaceae, Leguminosae, Solanaceae, Euphorbiaceae	Whitefly: *Bemisia tabaci*	Cohen *et al*. (1983)**

This table is not intended to be exhaustive, and further host and vector species, as well as diseases, may be associated with these pathogens.

*CABI ISC datasheet 7642 (http://www.cabi.org/isc/datasheet/7642).

†CABI ISC datasheet 7642 (http://www.cabi.org/isc/datasheet/7642).

‡CABI ISC datasheet 6502 (http://www.cabi.org/isc/datasheet/6502).

§CABI ISC datasheet 50978 (http://www.cabi.org/isc/datasheet/50978).

¶Harrison, B.D. (1984) CMI/AAB Descriptions of Plant Viruses. *Potato leafroll virus* 291 (no. 36 revised) (http://www.dpvweb.net/dpv/showdpv.php?dpvno = 291).

**Duffus, J.E. and Stenger, D.C. (1998) CMI/AAB Descriptions of Plant Viruses, *Squash leaf curl virus* 358 (http://www.dpvweb.net/dpv/showdpv.php?dpvno = 358).

non-pathogenic and culturable *C*Las relative *Liberibacter crescens* (Jain *et al*., 2015). Multiple prophage regions have been observed in *C*Las, *C*Lam and *Candidatus* Liberibacter solanacearum, and it is thought that these regions allow gene rearrangement in *C*L species (Duan *et al*., 2009; Lin *et al*., 2011; Wulff *et al*., 2014).

Many of the candidate MAMPs identified in the *C*L genome are similar to known MAMPs from extracellular bacterial pathogenesis systems (Mott *et al*., 2014; Segonzac and Zipfel, 2011). On the basis of these studies, MAMP perception is generally thought to happen at the cell surface, but there is some evidence that *C*L MAMPs are recognized (Hao *et al*., 2013; Kim *et al*., 2009). Transcriptional analyses in citrus identified RLKs induced in *C*Las-infected plants, suggesting that citrus host cells might traffic *C*Las MAMPs to the cell surface or use an intermediate signalling molecule (Aritua *et al*., 2013; Mafra *et al*., 2013). *C*Las encodes known MAMPs, such as lipopolysaccharides (LPS) and flagellin (source of flg22). Transgenic expression of the *C*Las flg22 peptide resulted in callose deposition, but not cell death, making it a weaker MAMP than the flg22 of other plant pathogens (Zou *et al*., 2012). There is also a fimbrial low-molecular-weight protein (flp) pilus system, which is probably involved in tight adherence. Interestingly, the flp pilus is present in *C*Las, but not in *L. crescens* (Leonard *et al*., 2012).

Examination of the processes required for effector delivery showed that *C*Las lacks a type 3 secretion system (T3SS) (Duan *et al*., 2009; Galán and Wolf-Watz, 2006). Instead, *C*Las has a type 1 secretion system (T1SS), which is another one-step secretion system important for pathogenesis (Charkowski *et al*., 2012; Kanonenberg *et al*., 2013). Multiple ABC transporters have been identified in *C*Las, and are thought to be involved in outer membrane biogenesis, drug resistance and DNA excision (Li *et al*., 2012). One of these is a T1SS that may secrete serralysin, which has been shown to contribute to pathogenesis in many bacteria, including *Serratia marcescens* (Ishii *et al*., 2014; Li *et al*., 2012; Maeda and Morihara, 1995). *C*Las contains some components of T2SS and T4SS; type 4 pili are used by *Xylella* spp. to block xylem flow (Duan *et al*., 2009; De La Fuente *et al*., 2008). T5SS (autotransporters) have also been identified in *C*Las, and have been shown to localize to the cell surface (Hao *et al*., 2013). Bacterial effector candidates are often identified by the presence of a signal peptide domain, which directs the proteins to the secretory pathway. As it is unknown what delivery system *C*Las uses, the pool of proteins with putative secretion signals was computationally screened for potential effector candidates; one candidate was shown to cause cell death in *Nicotiana benthamiana* (Pitino *et al*., 2016).

HLB infection primarily affects source–sink relationships, hormone pathways and nutrient distribution within plants, which are all processes for which a functional phloem is essential (Martinelli *et al*., 2012; Zhao *et al*., 2013). There are no known resistant citrus varieties or scion–rootstock combinations, although some are more susceptible than others (Fan *et al*., 2013; Folimonova *et al*., 2009). Some tested citrus relatives are resistant to HLB, but it remains unclear whether this is a result of plant processes or non-colonization by HLB vectors (Ramadugu *et al*., 2016).

Sieve tube occlusion appears to be a primary means of defence against HLB. Blocked sieve elements are thought to kill *C*Las cells (Trivedi *et al*., 2009), but this defence mechanism could also be the cause of the disrupted photoassimilate movement seen in *C*Las-infected plants (Fan *et al*., 2013; Kim *et al*., 2009; Koh *et al*., 2012). The P protein PP2 is induced by HLB, and callose deposition reduces sieve pore size in infected plants (Kim *et al*., 2009; Koh *et al*., 2012). Phloem transport is less affected in *C*Las-tolerant citrus varieties, even though susceptible and tolerant varieties have similar signs of HLB infection and defence responses (Fan *et al*., 2013). Transcriptome profiling shows increased expression levels of genes involved in callose deposition and cell wall breakdown in susceptible varieties, but tolerant varieties have increased expression levels of NBS-LRR, pathogenesis-related (PR) and RLK genes (Mafra *et al*., 2013; Wang *et al*., 2016). These findings could indicate that susceptible varieties establish callose defences too slowly to prevent pathogen spread, or that ETI is activated more rapidly in tolerant varieties. Induced defence processes in citrus do not appear to be able to restrict HLB spread throughout the plant, possibly because citrus is unable to effectively employ both MTI and ETI against *C*Las (Canales *et al*., 2016; Kim *et al*., 2009; Nwugo *et al*., 2013; Zou *et al*., 2012). Another hypothesis is suggested by the early presence of *C*Las in roots; this colonization may lead to a reservoir of pathogens that can no longer be controlled by plant defence processes (Johnson *et al*., 2014).

Multiple approaches have been attempted in order to grow *C*Las cells in the laboratory. For example, the addition of citrus juice, co-cultivation with insect feeder cells and co-cultivation with Actinobacteria from citrus have all been reported to improve *C*Las cultivation success (Davis *et al*., 2008; Fontaine-Bodin *et al*., 2011; Parker *et al*., 2014). One group developed Liber A agar medium, which includes potassium phosphate, citrus vein extract (CVE) and NADP. The *C*Las and *C*Lam colonies grown on Liber A were inoculated into young citrus plants, and caused HLB-like symptoms (Sechler *et al*., 2009). Although promising, this method has many precise requirements that are not yet understood well enough to enable large-scale culture of *C*L species.

***Arsenophonus* bacteria: from insect endosymbionts to plant pathogens**

Marginal chlorosis of strawberry and low-sugar syndrome of sugar beet are both caused by gammaproteobacteria in the *Arsenophonus* clade (Bressan, 2014; Sémétey *et al*., 2007) (Tables 1, S1). The disease-causing agents are *Candidatus* Phlomobacter fragariae (*C*Phfr, marginal chlorosis) and *Candidatus* Arsenophonus phytopathogenicus (*C*Arph, low-sugar syndrome), both of which are transmitted by ciixid planthoppers (Bressan *et al.*, 2009; Danet *et al.*, 2003; Zreik *et al.*, 1998). *C*Arph has also been associated with strawberry marginal chlorosis, and can be transmitted to sugar beet by the *C*Phfr insect vector. Both marginal chlorosis of strawberry and low-sugar syndrome of sugar beet can also be caused by stolbur phytoplasmas. Co-infection by *C*Phfr or *C*Arph and stolbur phytoplasmas has rarely been observed. It remains unclear what role these phytoplasmas play in natural infection systems, and whether they contribute host susceptibility to *C*Phfr or *C*Arph (Danet *et al.*, 2003; Sémétey *et al.*, 2007).

Both *C*Arph and *C*Phfr have low genetic diversity, indicating that they are recently emerged plant pathogens (Salar *et al.*, 2010). Other bacteria in the *Arsenophonus* clade are facultative or secondary insect endosymbionts, which are thought to help insects resist parasites and withstand heat stress (Montllor *et al.*, 2002; Oliver *et al.*, 2003). *C*Arph and *C*Phfr appear to have independently evolved the ability to infect plants (Bressan *et al.*, 2012; Sémétey *et al.*, 2007). The evolution of insect-associated bacteria to insect-vectored plant pathogens is thought to be one way in which phloem-limited pathogens arise (insect-first evolution) (Nadarasah and Stavrinides, 2011).

Serratia marcescens: from generalist to specialist

Cucurbit yellow vine disease (CYVD) affects all cucurbits (Tables 1, S1), and is caused by the gammaproteobacterium *Serratia marcescens*, a generalist bacterium identified in environmental samples and as a pathogen of humans and insects (Mahlen, 2011). The causative agents, CYVD-causing strains of *S. marcescens* (CCS), are unable to use the same substrates as other *S. marcescens* strains, indicating that these strains are distinct and probably adapted to the phloem environment (Rascoe *et al.*, 2003). CCS is vectored by the squash bug *Anasa tristis*, which feeds on and damages multiple plant organs, including leaves, xylem and phloem (Beard, 1940; Bonjour *et al.*, 1991; Neal, 1993). These generalist feeding habits and large-scale damage to plant organs distinguish *A. tristis* from most phloem-localized pathogen vectors and, indeed, *A. tristis* was not known to vector plant pathogens before CCS was identified (Bruton *et al.*, 2003). It is unclear where in the vector CCS is maintained, and research has shown CCS can overwinter in dormant *A. tristis* (Pair *et al.*, 2004; Purcell and Finlay, 1979; Wayadande *et al.*, 2005). Other *S. marcescens* strains are also plant pathogens, but are not insect vectored or phloem limited (Gillis *et al.*, 2014; Ovcharenko *et al.*, 2010; Wang *et al.*, 2014). These strains, and the generalist nature of *A. tristis*, raise the intriguing possibility that CCS is an example in which a pathogen first infected plants before evolving to associate with an insect vector and becoming phloem limited (plant-first evolution) (Nadarasah and Stavrinides, 2011).

Genomic analysis of CCS revealed multiple genes contributing to surface structures that may be involved in pathogenesis. These include rhamnose synthesis pathway genes, which may play a role in adhesion, phosphatase AmsI, which is probably involved in producing extracellular polysaccharide, and surA isomerase, which is important for *Salmonella enterica* infection processes (Petersen and Tisa, 2013; Zhang *et al.*, 2005). In addition, CCS has type 1 fimbrial pilus genes, which appear to be part of a horizontally transferred genome island (Zhang *et al.*, 2005). Secreted proteases, such as serralysin, have been implicated in *S. marcescens* virulence, but have not been characterized in CCS (Ishii *et al.*, 2014; Petersen and Tisa, 2013). Similarly, biofilm formation using fimbrial genes and quorum sensing has been shown to be important for the pathogenesis of other *S. marcescens* strains in non-plant hosts (Labbate *et al.*, 2007; Shanks *et al.*, 2007). It is possible that CCS uses similar processes to adhere to phloem cells and block phloem sap flow.

Mobile genetic elements probably contributed to the acquisition of the aforementioned genes, a hypothesis supported by the over-representation of a transposase in CCS (Zhang *et al.*, 2005). In addition, an onion-infecting *S. marcescens* strain contains a potentially pathogenesis-promoting mobile genetic element (Ovcharenko *et al.*, 2010). These findings suggest that the versatility of *S. marcescens* strains is a result of mobile genetic elements, and that CCS could have specialized in this fashion.

WALL-LESS PHLOEM-LIMITED BACTERIA: *CANDIDATUS* PHYTOPLASMA AND SPIROPLASMA SPECIES

Mollicutes are a class of obligate parasitic bacteria distinguished from other bacteria by their lack of cell walls and small size; they have small genomes and limited metabolic capacities (Bai *et al.*, 2004b; Razin *et al.*, 1998; Woese, 1987). Within the Mollicutes, there are two major clades, referred to as the AAA clade and the SEM clade. Mollicutes live in and on a variety of animal and plant hosts, and many are pathogenic; for example, the human pathogen *Mycoplasma pneumonia* is a Mollicute. Many Mollicutes have a disproportionate number of repetitive elements for their genome size. These are used to vary cell surface antigens and promote pathogenesis in animal hosts (Bai *et al.*, 2006; Rocha and Blanchard, 2002). There are two groups of insect-transmitted plant-pathogenic Mollicutes: phytoplasmas and spiroplasmas (Ammar *et al.*, 2004; Gasparich, 2010; Orlovskis *et al.*, 2015). Phytoplasmas are a monophyletic genus (*Candidatus* Phytoplasma, *C*Ph) in the AAA clade, whereas spiroplasmas are a genus in the SEM clade (Bai *et al.*, 2004b).

*C*Ph species cause disease in hundreds of economically important plants, have many different shapes and are difficult to culture in laboratory settings (Bai *et al.*, 2006; Lee *et al.*, 2000). They can be transmitted by multiple insect species within the leafhopper, planthopper and psyllid hemipteran insect groups (Garnier *et al*., 2001; Orlovskis *et al*., 2015). *C*Ph species are grouped by their 16S rDNA sequence, which remains the sole identifier for many known phytoplasmal pathogens (Bertaccini *et al*., 2014). *C*Ph pathogens probably use a phytoplasma-specific pathway to generate energy that could play a role in pathogenesis (Bai *et al*., 2006; Kube *et al*., 2012; Saigo *et al*., 2014). They are thought to adhere to cell surfaces, like other mycoplasmas, and may move through the phloem passively, like viruses (Christensen *et al*., 2005; Lefol *et al*., 1993; Razin, 1999). Adhesion may involve actin, and appears to result in the rearrangement of ultrastructures within the sieve elements (Buxa *et al*., 2015; Musetti *et al*., 2016). The *C*Ph outer membrane is largely composed of immunodominant membrane proteins (IDPs) of largely unknown function (Kakizawa *et al*., 2006), although the IDP antigenic membrane protein (Amp) appears to be involved in uptake and internalization by the insect vector (Rashidi *et al*., 2015). Uniquely, *C*Ph plant pathogens are able to manipulate plant development to cause distinctive phenotypes, such as shoot proliferation and flower virescence. They do this via secreted effector proteins that are able to leave the phloem and target conserved plant transcription factor proteins (Bai *et al*., 2009; Hoshi *et al*., 2009; MacLean *et al*., 2011).

Spiroplasma species are one of the most widespread insect endosymbionts (Shokal *et al*., 2016). There are over 50 spiroplasma species, all of which have the characteristic spiral shape and are motile (Bové, 1997; Zhao *et al*., 2004). Endosymbiotic spiroplasmas alter insect immune responses, affect pathogen and endosymbiont titres and selectively kill male insects (Hayashi *et al*., 2016; Herren and Lemaitre, 2011; Shokal *et al*., 2016). There are only three known phytopathogenic spiroplasmas, all of which are vectored by leafhoppers (Davis *et al*., 1979; Orlovskis *et al*., 2015). Spiroplasmal genomes are less reduced than phytoplasmal genomes: they have more biosynthesis, transcriptional regulation, cell envelope and DNA-binding genes (Bai and Hogenhout, 2002). Although their genomes are less reduced, spiroplasmas are auxotrophs for sterols, fatty acids and phospholipids, and use a phosphotransferase system to import sugars (Bai *et al*., 2006; Razin *et al*., 1998).

We discuss two Mollicutes: a *C*Ph species with well-characterized effectors, and one spiroplasma that remains an agricultural problem.

Candidatus Phytoplasma asteris strains: pathogens that mould their hosts

The phytoplasma strain Aster Yellows Witches' Broom (AY-WB) is a member of the 16SrI-A subgroup of *Candidatus* Phytoplasma asteris (*C*Phas) (Tables 1, S1) (Bai *et al*., 2006; Lee *et al*., 2000; Zhang *et al*., 2004). Within *C*Phas, genome sizes vary widely, indicating a high degree of genome plasticity. AY-WB has a small genome without many metabolic processes, but with high repetitive DNA content (Bai *et al*., 2006). These repetitive regions contain membrane-targeted sequences involved in membrane-linked processes, and are probably used to vary the AY-WB cell surface in different hosts and environments (Bai *et al*., 2006). AY-WB has been shown to lengthen the lifespan and improve the fertility of its leafhopper vector (Beanland *et al*., 2000; Murral *et al*., 1996).

AY-WB secretes effectors, such as SAP11 and SAP54, into plant tissues beyond the phloem. SAP11 has a nuclear localization signal, and is found in the nuclei of non-phloem cells (Bai *et al*., 2009; Lu *et al*., 2014). In AY-WB-infected *Arabidopsis thaliana*, SAP11 binds to and destabilizes multiple class II TCP transcription factors, which affects the jasmonic acid (JA) synthesis pathway, weakening plant defences against the insect vector (Sugio *et al*., 2011, 2014). Destabilizing this set of transcription factors also affects leaf morphogenesis, causing some of the phytoplasma-induced developmental phenotypes (Lu *et al*., 2014; Sugio *et al*., 2011). SAP11 also appears to induce phosphate starvation pathways (Lu *et al*., 2014).

SAP54 is the AY-WB effector responsible for the altered flower morphology (virescence and phyllody) seen in infected *Arabidopsis* (MacLean *et al*., 2011). It degrades MADS-domain transcription factor family proteins, such as *APETALA1*, which are essential floral development regulators (Sugio *et al*., 2014). Plants with these leaf-flowers are more attractive to the AY-WB leafhopper vector, and improve phytoplasmal transmission (MacLean *et al*., 2014; Orlovskis and Hogenhout, 2016).

In plants infected by the *C*Phas strain Onion Yellows (OY), TENGU protein was found in apical buds, indicating that it is transported out of the phloem, like the SAPs. It acts to down-regulate auxin-responsive genes, including *AUXIN RESPONSE FACTOR 6* (*ARF6*) and *ARF8*, which regulate floral development and are linked to JA (Hoshi *et al*., 2009). This indicates that TENGU could regulate both auxin and JA, as well as play a role in the disease-related altered growth and floral development phenotypes (Minato *et al*., 2014). Phytoplasma-infected plants have been termed 'zombie plants', because extensive developmental and morphological changes render them sterile (MacLean *et al*., 2014).

A recent study used multiple complex media to grow phytoplasma strains, including a *C*Phas strain, from infected grapevine tissue. The strains were found to have highly specific growth requirements, including microaerophilic conditions, high salt concentration and a sterol-binding antifungal (Contaldo *et al*., 2016). As with the methods used to culture *C*L species, the growth requirements for *C*Ph species are not yet well understood. Further study on phloem-limited bacteria and Mollicutes might benefit from a simulated phloem environment, an approach which has been proven to be successful with uncultivatable environmental bacteria (Kaeberlein *et al*., 2002; Zengler *et al*., 2002).The ability to culture these microbes would facilitate advances in genomics, species classification and molecular manipulation of these pathogens.

Spiroplasma kunkelii: a Mollicute with high virulence and low genetic diversity

Spiroplasma kunkelii causes corn stunt disease, and is transmitted by leafhopper insects (Tables 1, S1) (Carloni *et al.*, 2011; Davis *et al.*, 1972; Whitcomb *et al.*, 1986). Extended maize growth periods and the ability of these vectors to overwinter mean that the pathogen can remain present throughout the year (Hruska *et al.*, 1996; Summers *et al.*, 2004). Maize varieties resistant to corn stunt have been bred, but this resistance is short lived. It is unclear why maize resistance is quickly overcome, as genomic analysis has shown that *S. kunkelii* isolates have low genetic diversity (Carpane *et al.*, 2013). Corn stunt is linked to magnesium metabolism: the symptoms are similar to magnesium deficiency, magnesium is involved in *S. kunkelii* localization and infected plants seem to be unable to process high magnesium concentrations (Nome *et al.*, 2009).

Two *S. kunkelii* genes probably involved in insect transmission or plant pathogenicity were identified in a comparative study using AY-WB: (i) PNPase, a virulence factor regulator in *S. enterica*; and (ii) CBF, a plasmid replication enhancer (Bai *et al.*, 2004b). The PNPase could be involved in the alteration of gene expression depending on the host environment, whereas CBF could regulate plasmids that may contain virulence factors (Oshima *et al.*, 2002; Razin *et al.*, 1998). One such plasmid (pSKU146) in *S. kunkelii* carries an adhesin (SARP1), parts of a T4SS and may be involved in genetic exchange (Davis *et al.*, 2005). In *Spiroplasma citri*, SARP1 acts to attach the pathogen to the insect gut, and contains a conserved Mollicute adhesion motif important in *C*Phas strain adhesion (Berg *et al.*, 2001; Neriya *et al.*, 2014). *Spiroplasma citri* probably uses membrane proteins to adhere to insect cells, and has undergone large-scale genome rearrangement that allows it to be transmissible (Fletcher *et al.*, 1998). Four *traE* genes are present in *S. kunkelii*, and their protein sequences are highly similar to the VirB4 domain involved in T4SS pathways (Bai *et al.*, 2004a; Censini *et al.*, 1996; Zatyka and Thomas, 1998). *Spiroplasma kunkelii* also has fimbriae and pili, and may have morphologically distinct tips that could also be involved in orientation and attachment to host surfaces (Ammar *et al.*, 2004; Özbek *et al.*, 2003). Furthermore, analysis of the *S. kunkelii* genome sequence found multiple ABC systems, which contribute to virulence in bacterial and fungal pathosystems (Zhao *et al.*, 2004).

PHLOEM-LIMITED VIRUSES

Viruses use the vasculature to systematically infect the plant, and PD to move between cells. Viral movement is promoted by movement proteins (MPs) and coat proteins (CPs) (Hipper *et al.*, 2013). MPs have several functions within the host plant, including the modification of PD to permit viral genomes and proteins to move between cells. Viruses can move as encapsidated particles or ribonucleoprotein complexes, and many viruses move in multiple forms (Oparka and Cruz, 2000; Solovyev *et al.*, 2012; Verchot-Lubicz *et al.*, 2010). Although viral replication is tightly linked with movement of the virus (Heinlein, 2015), we focus on viral movement because it appears to play a more important role in restricting viruses to the phloem.

Viral cell-to-cell movement through the PD allows the virus to move from the initial site of infection to adjacent cells, and then eventually to the vasculature (long distance) (Heinlein, 2015; Hipper *et al.*, 2013; Oparka and Cruz, 2000). Long-distance movement through the phloem follows the normal source-to-sink movement of sugars, and allows viruses to be trafficked in all directions from the point of entry. Virus loading appears to be possible in all vein classes, whereas virus unloading seems to be limited to major veins in sink tissues (Hipper *et al.*, 2013). Host factors can facilitate or block viral movement, but the mechanism of these processes is not well understood (Ueki and Citovsky, 2007; Wang, 2015). The difficulty of studying phloem-specific processes has meant that long-distance viral movement remains poorly characterized. Indeed, many aspects of viral movement are not fully elucidated, and much of what is known only applies to specific systems.

Viral defence processes in plants include RNAi and HR, both of which limit viral movement. Many viral proteins first thought to be involved in systemic spread, including the potyviral HC-Pro, are, in fact, RNAi suppressors (Taliansky *et al.*, 2008; Ueki and Citovsky, 2007). These suppressors have also been shown to disrupt plant signalling systems, perhaps preventing the activation of systemic viral defences (Alvarado and Scholthof, 2012; Melnyk *et al.*, 2011).

Phloem-restricted viruses are able to move long distances, but appear to be unable to leave the vasculature and to move cell to cell. The mechanism of this limitation remains unclear, although it is probably a result of a combination of host and viral factors. Plants can be fully resistant to some phloem-limited viruses, indicating that these pathogens are more readily perceived or controlled than other phloem-limited pathogens.

We discuss *Potato leafroll virus*, which has been developed as a model system to study the movement processes of phloem-restricted viruses. We also discuss *Citrus tristeza virus*, a phloem-limited pathogen that citrus is able to resist.

Potato leafroll virus: limiting its own movement

Potato leafroll virus (PLRV) is a positive-sense RNA *Polerovirus* (family *Luteoviridae*) that forms icosahedral virids (Tables 1, S1). Luteovirids are all transmitted by aphids and retained in the phloem. They can move locally and long distance in the phloem, but not between non-vascular cells or from non-vascular cells into vascular cells (Taliansky *et al.*, 2003).

PLRV encodes a 17-kDa MP (MP17/P4) that can localize to PD in some cell types, suggesting that it assists in the movement of PLRV through PD (Link *et al.*, 2011; Vogel *et al.*, 2007). Without MP17, PLRV is either unable to systemically infect or has severely reduced systemic infection ability, confirming that MP17 contributes to viral movement (Lee *et al.*, 2002). The constitutive expression of MP17 at low levels in *Arabidopsis* increases sucrose efflux from source leaves, as well as overall biomass production, but the expression of MP17 at high levels impairs sucrose efflux, leading to high accumulation in source leaves and reduced vegetative growth (Hofius *et al.*, 2001; Kronberg *et al.*, 2007). These results indicate that MP17 interferes with PD transport, although its effects could be caused by defence processes in response to the presence of MP17 at PD rather than a direct effect on the source–sink system (Rinne *et al.*, 2005).

Two hypotheses for the phloem limitation of viruses have been proposed: (i) host silencing machinery outside the vasculature prevents the virus from leaving; or (ii) the virus does not encode MPs that allow the virus to leave. The first hypothesis was tested using plants expressing the strong RNAi suppressor HC-Pro. In these plants, the number of PLRV-infected cells increases, but PLRV is still physically restricted to the phloem (Savenkov and Valkonen, 2001). This suggests that phloem limitation of PLRV is not caused by host silencing. The second hypothesis is supported by co-infection experiments with PLRV and the potyvirus *Potato virus A* (PVA), which is not restricted to the vasculature. Co-infection allows PLRV to exit the phloem and infect all leaf types, indicating that MPs in PVA can complement the movement deficiencies of PLRV. Moreover, these findings indicate that certain co-infections can remove phloem limitation, a process not seen with other phloem-limited pathogens (Savenkov and Valkonen, 2001).

Recent work has conclusively established that the phloem-limiting factor in PLRV is a result of the features of another PLRV MP. PLRV is able to move through the phloem without MP17, instead using its CP and a translational readthrough product (RTP or P3/P5) (Kaplan *et al.*, 2007; Peter *et al.*, 2008). The RTP produces a protein fusion of CP with ORF5, one portion of which is necessary for aphid transmission, and another portion of which is necessary for phloem retention (DeBlasio *et al.*, 2015; Peter *et al.*, 2009). Deletion or mutation of key sections of the RTP portion required for phloem retention allows PLRV to exit the phloem and establish infection in mesophyll tissues (Chavez *et al.*, 2012; Kelley *et al.*, 2009; Peter *et al.*, 2009). Mutated RTPs in the related luteoviruses *Beet western yellows virus* (BWYV) and *Barley yellow dwarf virus* (BYDV-PAV) have reduced viral movement, reduced systemic infection efficiency and accumulate to lower titres (Brault *et al.*, 1995; Chay *et al.*, 1996; Mutterer *et al.*, 1999). RTP has two forms: (i) a non-incorporated form, which seems to restrict PLRV to the phloem; and (ii) an incorporated form, which replaces CP subunits, protrudes from virions and appears to be necessary for movement into mature tissues (DeBlasio *et al.*, 2015; Peter *et al.*, 2009).

The pathogenic processes of PLRV are less well characterized. Comparison of wild-type and mutant PLRV strains in *N. benthamiana* plants did not show altered host protein stability or expression level, indicating that PLRV proteins do not significantly modulate host protein processes during infection (DeBlasio *et al.*, 2015). Multiple wild potato relatives have PLRV resistance loci, for example *Solanum tuberosum* (Kelley *et al.*, 2009; Marczewski *et al.*, 2004; Novy *et al.*, 2007). In *Solanum tuberosum* ssp. *andigena*, resistance was mapped to the upper arm of chromosome V, which contains a known cluster of disease resistance genes (Velásquez *et al.*, 2007). This resistance locus was subsequently identified in other potato varieties (Mihovilovich *et al.*, 2014).

Citrus tristeza virus: recognized by the citrus immune system

Citrus tristeza virus (CTV) is a filamentous, single-stranded, positive-sense RNA virus (Moreno *et al.*, 2008) (Tables 1, S1). CTV encodes 12 open reading frames (ORFs) with poorly defined functions. Genetic approaches deleting one or several of these ORFs have demonstrated that full CTV virulence requires proteins for replication, movement and suppression of the host RNAi machinery (Albiach-Marti, 2013; Pérez-Clemente *et al.*, 2015). The gene p33 may be an MP, and is required for systemic infection in some citrus species, together with p18 and p13 (Bak and Folimonova, 2015). These three genes appear to be unique to CTV, and may have played a role in increasing the CTV host range (Bak and Folimonova, 2015; Tatineni *et al.*, 2008). The p33 protein is also required for superinfection exclusion (SIE), in which an established viral infection interferes with later infection by closely related viruses (Folimonova, 2012). This process leads to complex spatial and temporal viral infection patterns, which could be important in field infection systems. The p33 protein is involved in systemic SIE, but not cellular SIE (Bergua *et al.*, 2014), and this distinction between cellular and systemic SIE has been seen with human immunodeficiency virus (HIV) in animals (Nethe *et al.*, 2005). These results provide evidence that SIE is a virus-controlled process, and could be used in the development of viral management strategies. Other genes potentially involved in CTV movement include p6, p20 and the protein components of CTV particle coats (Dolja *et al.*, 2006; Tatineni *et al.*, 2008).

CTV pathogenesis varies depending on the genotype of the host (Dawson *et al.*, 2013). Some citrus species are fully resistant to CTV, unlike *C*Las, and may achieve resistance by specifically inhibiting viral movement (Albiach-Marti *et al.*, 2004). One region conferring resistance has been characterized, and found to contain

R genes and many retrotransposons, indicating that CTV resistance could function using canonical ETI processes (Bernet *et al*., 2004; Rai, 2006). Citrus resistance to CTV has been shown to involve both salicylic acid signalling and RNAi, both of which are suppressed by the CTV genes p20 and p23 (Gómez-Muñoz *et al*., 2016).

CONCLUSIONS/EMERGING THEMES

The unique environment they inhabit shapes phloem-limited pathogens. Within the phloem, pathogens have access to the entirety of the plant, including its metabolic output and its means of limiting damage. Insect vectors are key to the access of this central hub, because they directly transmit phloem-limited pathogens into it. Pathogen, plant and vector form a complex tritrophic system that is difficult to study in its entirety.

Although each phloem-limited pathogen is unique, the symptoms caused by phloem-limited pathogens are similar (Table S1). As the diseases caused by phloem-limited pathogens progress, characteristic symptoms, such as chlorotic leaves and small, bitter fruits, become evident. In most cases, the causal links between the virulence strategies of phloem-limited pathogens and disease symptoms are not well understood.

Plant hosts of phloem-limited pathogens can become aware of their presence from the moment the insect vector begins to feed. Insect saliva and wounding can result in phloem blocks and SWR, which the insect will attempt to counter with its own effectors. Phloem-limited pathogens can also elicit plant defence responses, including MTI, ETI and SAR. Although the phloem is the conduit for many defence-related compounds, it is unclear how pathogen recognition within the phloem would occur; some studies indicate that Ca^{2+} signalling could play an important role. Similarly, intracellular pathogen recognition remains poorly characterized in plants. It is possible that phloem-localized pathogens are able to evade most plant defences merely by being delivered intracellularly. Some of these aspects could be the cause of the slow progression of disease for most phloem-limited pathogens.

The interaction between phytoplasmas and host defences is of particular interest, because multiple plant species are able to spontaneously recover from phytoplasmal infection. The phytoplasma bois noir (BN) in grapevine (Tables 1, S1) establishes a carbohydrate sink at its infection site, potentially by co-regulating sucrose transport and cleavage (Santi *et al*., 2013a). Spontaneously recovered grapevines appear to have restored carbohydrate allocation and increased capacity for both sucrose transport and defence signalling (Santi *et al*., 2013b). A system using Flavescence dorée phytoplasma (FD) in beans (*Vicia faba*) showed that phytoplasmas trigger Ca^{2+} signalling, which, in turn, leads to sieve tube occlusion via forisomes (Musetti *et al*., 2013). When apple trees spontaneously recover from apple proliferation (Tables 1, S1), symptoms are no longer seen in the crown, but the pathogen is still present in the roots. These recovered trees have higher levels of Ca^{2+} and H_2O_2 in the phloem, as well as increased callose and phloem protein accumulation, which could inhibit re-colonization of the aerial tissues (Musetti *et al*., 2004, 2010). These studies indicate that spontaneous recovery involves both the re-establishment of the sink–source system and the use of plant defence mechanisms effectively.

In field settings, many phloem-limited pathogens can co-infect plants, which can produce complex infection dynamics and result in genetic exchange. Genomic analysis of phloem-limited pathogens consistently shows hallmarks of gene transfer and rearrangement, which are facilitated by repetitive regions and plasmids (Bai *et al*., 2006; Saillard *et al*., 2008). Phytoplasmas and spiroplasmas can co-infect both insect and plant hosts, and it has been suggested that they horizontally transfer virulence genes (Bai *et al*., 2004b; Davis *et al*., 2005). In viruses, genetic exchange can lead to the production of infectious viral reassortants, such as in the case of the geminiviruses *Cucurbit leaf curl virus* and *Squash leaf curl virus* (Brown *et al*., 2002). Phloem-limited pathogens can also interact with non-pathogenic species in their insect vectors; for example, *C*L species have been shown to acquire genes from *Profftella* endosymbionts in the psyllid *Diaphorina citri* (Nakabachi *et al*., 2013). Genetic exchange has the potential to alter infectivity, increase host and vector range, and could be an important driver of pathogenesis for phloem-limited pathogens.

Continually improving techniques and analyses have given us more information on these pathogens than ever before. By focusing on commonalities between these pathogens, and on the unique environment that these pathogens share, we will be able to make more progress in the management of these diseases. For example, the development of methods to maintain high rates of phloem transport in infected plants, by disrupting host defences that have evolved to restrict phloem transport around infections, could help to combat many of the phloem-limited pathogens described in this review. Another useful approach would be to develop tractable systems for each of these pathogen categories. Although some progress on this has been made, well-understood models would enable more rapid progress to be made with newly emergent pathogens. With these diseases becoming more prevalent worldwide, disease containment focusing on population management is no longer sufficient. New research approaches across traditional boundaries will be needed to develop disease treatments for the modern era.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Symptoms of the diseases discussed in this review.

Table S2 Management strategies for the diseases discussed in this review.