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SI PLANT BIOTIC INTERACTIONS

Sugar flux and signaling in plant–microbe interactions

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SUMMARY

Plant breeders have developed crop plants that are resistant to pests, but the continual evolution of pathogens creates the need to iteratively develop new control strategies. Molecular tools have allowed us to gain deep insights into disease responses, allowing for more efficient, rational engineering of crops that are more robust or resistant to a greater number of pathogen variants. Here we describe the roles of SWEET and STP transporters, membrane proteins that mediate transport of sugars across the plasma membrane. We discuss how these transporters may enhance or restrict disease through controlling the level of nutrients provided to pathogens and whether the transporters play a role in sugar signaling for disease resistance. This review indicates open questions that require further research and proposes the use of genome editing technologies for engineering disease resistance.

Keywords: pathogen, symbiosis, sucrose, transport, nutrition, signaling, *Arabidopsis thaliana*, *Oryza sativa*, Triticum sp.

INTRODUCTION

Plant pathogens cause massive yield losses in all crops, and thus contribute to food insecurity and shortages (Oerke, 2006). Both full-blown diseases and subclinical infections (low-level infestation without major disease symptoms) cause substantial yield losses (Popp and Hantos, 2011). The health and economic consequences of food security cannot be overstated. Thus, the development of effective disease resistance within food crops is of fundamental importance to both subsistence farmers and agribusiness. A major task has to be the development of effective strategies to reduce disease losses and the associated social instability. This difficult task requires effective collaboration among diverse disciplines in order to develop new technologies. Bioengineering requires extensive knowledge gleaned from fundamental research in the field of plant–pathogen interactions (Jones and Dangl, 2006; Jones *et al.*, 2016). Many promising solutions are on the horizon, including greatly expanded accessibility to R genes and an improved understanding of disease susceptibility (Boutrot and Zipfel, 2017). Anecdotal examples and recent research indicate that the rational manipulation of host susceptibility can contribute to development of effective disease management strategies. This review focuses on recent groundbreaking discoveries regarding the role of

host sugar transporters in disease progression. We propose two hypotheses regarding the roles of sugar transporters in pathogen defense, which are not mutually exclusive, and can serve as guides for future research and engineering (subsequently referred to as 'pathogen-starvation' and 'apoplasmic sugar signaling' hypotheses).

SUTs, SWEETs and STPs: gate keepers of sugar allocation

The identification of the role that sugar transporters play in pathogen susceptibility should not come as a surprise, as it had been predicted 30 years ago (Patrick, 1989). At that time, none of the plant genes encoding sugar transporters was known. Since then, many of the transporters that distribute the carbon resources of a plant, including those for phloem loading and seed filling, have been identified at the molecular level (Chandran, 2015; Chen *et al.*, 2015a). Sugar uptake transporters, or SUTs, were the first sucrose transporters characterized (Riesmeier *et al.*, 1992, 1994). SUT1 homologs from a variety of species are now known to function as proton symporters, which use the proton gradient to import sucrose into the sieve element companion cell complex (SECC) for phloem loading (Boorer *et al.*, 1996; Carpaneto *et al.*, 2005). In Arabidopsis, corn and several solanaceous species, SUT1 has been shown to import sucrose into the SECC conduits from the cell wall space (Riesmeier *et al.*, 1994; Bürkle *et al.*, 1998; Gottwald *et al.*, 2000; Slewinski *et al.*, 2009). Since the discovery of SUT1, the search was on for the mechanism responsible for efflux of sucrose from the cytosol, where sucrose is made by photosynthesis, into the cell wall space. Genetically encoded FRET sensors proved pivotal to identifying proteins that had such properties, the so-called SWEETs (Chen *et al.*, 2010, 2012, 2015a,b). Each plant contains about two dozen SWEET paralogs, which predominantly transport hexoses or sucrose. Of note, several SWEETs play critical roles in the cellular efflux of sugars, in phloem (AtSWEET11, 12, ZmSWEET13a, b, and c; Chen *et al.*, 2012; Bezrutczyk *et al.*, 2017), seeds (AtSWEET11, 12 and 15; OsSWEET11 and 15; Chen *et al.*, 2015b; Yang *et al.*, 2017) and nectaries (AtSWEET9, BrSWEET9 and NtSWEET9; Lin *et al.*, 2014). In the context of pathogen susceptibility (discussed below), the efflux of sucrose in uninfected leaves by SWEETs appears to be limited to phloem parenchyma cells, at least in Arabidopsis. One may speculate that sugar release occurs in the few micrometers between phloem parenchyma and the SECC, and in close vicinity to the subsequent active uptake by SUTs in the SECC, potentially limiting the release of sucrose to a tiny interface in leaves. In one case, a hexose-transporting SWEET appears to be responsible for cellular uptake of hexoses to serve seed filling in corn (Sosso *et al.*, 2015).

A third class of sugar transporters that will be addressed in this review are STPs (sugar transport proteins, sometimes also MSTs), monosaccharide/H^+ symporters first described in Chlorella and Arabidopsis (Sauer and Tanner, 1989; Sauer *et al.*, 1990; Boorer *et al.*, 1994). As is the case with SWEET proteins, each plant contains multiple paralogs. STPs are 12-transmembrane domain transporters that play vital roles in sugar retrieval from the cell wall space (Lemonnier *et al.*, 2014; Yamada *et al.*, 2016).

PLANT PHYSIOLOGY, ONE R GENE AT A TIME

SWEETs also play a role in pathogen susceptibility. The recessive *xa13* bacterial blight resistance locus was first described in 1987 in rice (Ogawa *et al.*, 1987). It took almost 20 years before the underlying gene was identified, and another 4 years until the function of Xa13 as a SWEET sucrose transporter became clear (OsSWEET11; Chu *et al.*, 2006; Yang *et al.*, 2006; Chen *et al.*, 2010). Chromatin-immunoprecipitation experiments demonstrated that the bacterial type III TAL (Transcription Activation-Like) effector PthXo1 from the *Xanthomonas oryzae* pv. *oryzae* (Xoo) strain PXO99 bound directly to the Xa13/OsSWEET11 promoter, providing us with the mechanism that explains the gene-for-gene susceptibility and recessive resistance (Chen *et al.*, 2010; Römer *et al.*, 2010).

Xa13 (also called *Os8N3*) was separately cloned by two independent groups – one comprised of Bing Yang, Akiko Sugio and Frank White, and the other of Shiping Wang and Jeff Bennetzen (Chu *et al.*, 2006; Yang *et al.*, 2006). Resistance due to *xa13* occurs only in the recessive homozygote, and is due to nucleotide polymorphisms in the promoter that prevents PthXo1-induction of the associated *Xa13* gene (Yang *et al.*, 2006). Xa13 is a homolog of nodulin number 3 (MtN3), which is induced during nodulation of *Medicago truncatula* roots (Gamas *et al.*, 1996).

More recently, other rice SWEETs were associated with host susceptibility, and other TAL effectors were found to target different promoter regions of several SWEET loci (Antony *et al.*, 2010; Yu *et al.*, 2011; Zhou *et al.*, 2015). In fact, artificial TAL effector-induced expression of any member of a subset of phylogenetically related SWEETs (clade III) with sucrose transport ability is able to trigger susceptibility to the bacterial pathogen, although only three of them have been observed as targets by natural *Xoo* field strains so far (Streubel *et al.*, 2013; Zhou *et al.*, 2015).

The characterization of *xa13*, the associated *OsSWEET11* locus, and the PthXo1 TAL effector stood the classical gene-for-gene paradigm for resistance on its proverbial head. In the conventional resistance gene model, bacterial type III effectors (avr genes) are associated with specific resistance (R) genes. Strains with a specific avr gene are considered races within a specific pathogen and can find a host in a plant lacking the corresponding R gene. While gene-for-gene resistance is a condition of an R gene/avr gene pair, in this case susceptibility is a condition of a susceptibility (S) gene and a virulence gene pair. A failure of

the SWEET gene to respond to the induction by the TAL effector confers resistance in rice to bacterial blight. At the moment, the recessive *xa13* is bred into elite rice lines as an effective R gene, particularly in India (Lore *et al.*, 2011; Mishra *et al.*, 2013; Laha *et al.*, 2016). However, the gene is only effective against strains of the bacterium that rely on the TAL effector PthXo1 for ectopic induction of *OsSWEET11* expression; strains that have other TAL effector genes that target *OsSWEET13* or *OsSWEET14* are still virulent. The *xa13* resistance locus represents a series of alleles that have arisen naturally. Importantly, it appears that *xa13* mutations cause little to no impairment of physiological function or yield. While the alleles of *xa13* are the only known SWEET promoter mutations that have been historically used in breeding efforts, screening of rice germplasm has revealed additional recessive alleles at *OsSWEET13* and *OsSWEET14* (Liu *et al.*, 2011; Hutin *et al.*, 2015). More recently, the recessive resistance gene *b6* in cotton has been associated with alterations of the GhSWEET10 promoter, which is targeted by the TAL effector Avrb6 of *Xanthomonas citri* subsp. *malvacearum*, the causal agent of cotton blight (Cox *et al.*, 2017). Originally, SWEET-based susceptibility had been thought to be a unique feature of a xylem pathogen. However, *X. citri* does not appear to be restricted to xylem in cotton. It remains to be determined if this case is possibly a violation to that concept or if it is a more widespread phenomenon. The fact that SWEETs are induced during many other plant–pathogen interactions also challenges the 'xylem pathogen' hypothesis.

Interference with the binding of the TAL effectors is a promising avenue for blocking the induction of SWEET genes. TAL effectors are prokaryotic transcription factors that bind to sequence-specific effector-binding elements (EBEs) of the eukaryotic host (Boch *et al.*, 2009; for review, see Bogdanove and Voytas, 2011). TAL effectors bind to the promoter regions, commonly the TATAA box itself, and direct expression of the respective downstream SWEETs (Antony *et al.*, 2010; Chen *et al.*, 2010; Römer *et al.*, 2010). Mutations involving the EBE reduce or eliminate effector binding, preventing *SWEET* gene induction. TALEN-mediated deletions directed at *OsSWEET14* and, more recently, CRISPR-Cas9-mediated mutations at *OsSWEET13* have produced plants that are resistant to strains of *Xoo* (Li *et al.*, 2013; Zhou *et al.*, 2015; Blanvillain-Baufumé *et al.*, 2017). Alteration of promoter mutations, either present in natural variants of *OsSWEET11/*Xa13 as well as those obtained by genome editing, prevent binding of the TAL effectors and their usurpation of SWEET gene regulation in infected cells, which leads to a recessive 'gain of function' resistance that does not noticeably impair normal SWEET function, and importantly has no negative effects on yield potential (Chen *et al.*, 2010). The discovery that plant SWEETs are co-opted during Xanthomonas infection revealed a step within the plant–pathogen dance that, as a target, can be engineered to trip up the pathogen.

TWO HYPOTHETICAL MODELS FOR HOW SUGARS INFLUENCE PATHOGEN RESISTANCE

The two primary working models of sugar-mediated pathogen resistance are currently 'pathogen starvation' and 'sugar signaling'. The first hypothesis is the simplest: that pathogens infect plants with the primary goal of gaining access to the resources (sucrose) needed for reproduction, a process that proceeds from a few cells at the time of infection to billions of bacteria when symptoms become apparent. There is no doubt that host-derived sugars are transferred to the pathogen, at least in the case of fungi (Aked and Hall, 1993; Sutton *et al.*, 1999). One step of this is the ectopic induction of SWEETs, which results in leakage of sugars into the apoplasmic space. This hypothesis depends on the assumption that apoplasmic sugar pools are low, thereby limiting pathogen growth. An alternative is a 'sugar signaling' hypothesis, in which altered levels of sugar at the infection site trigger signaling cascades that result in salicylic acid (SA) pathway activation and defense gene upregulation, ultimately generating physiological changes that repel pathogens (Gebauer *et al.*, 2017).

The sugar transporters described earlier fit both hypotheses: SWEET sugar transporters can be upregulated during pathogen attack and export sugars out of cells into extracellular spaces, where pathogens are known to feed (Asai *et al.*, 2016); SWEETs could also be upregulated to help translocate sugars to infection sites to fuel the host defense metabolism (Tadege *et al.*, 1998). STPs, as proton hexose symporters, are known to take up hexoses from apoplasmic space and have been found to be induced during pathogen challenge (Lemonnier *et al.*, 2014), supporting the pathogen starvation hypothesis. On the other hand, sugars themselves can act as signals that induce defense genes (Herbers *et al.*, 1996; Herbers and Sonnewald, 1998; Gebauer *et al.*, 2017), supporting a 'sugar signaling' hypothesis.

One of the assumptions of the 'pathogen starvation' hypothesis is that plants do not volunteer sugars passively, so bacteria had to evolve elegant mechanisms to induce SWEETs and cellular efflux of sucrose (Figure 1). Given the complex defense machinery developed by plants to prevent and suppress infections, the host likely uses all possible means to restrict pathogen reproduction, including the limitation of resources for growth in the apoplasmic space. It is possible that the restriction of sugar transfer to the interface between phloem parenchyma and the SECC complex, deep inside the leaf, originally evolved to limit sugar availability in the cell wall space (Chen *et al.*, 2012). This hypothesis may explain the recessive nature of *xa13*-mediated resistance and, importantly, predicts elevated sugar flux towards the apoplasmic space during pathogen infection.

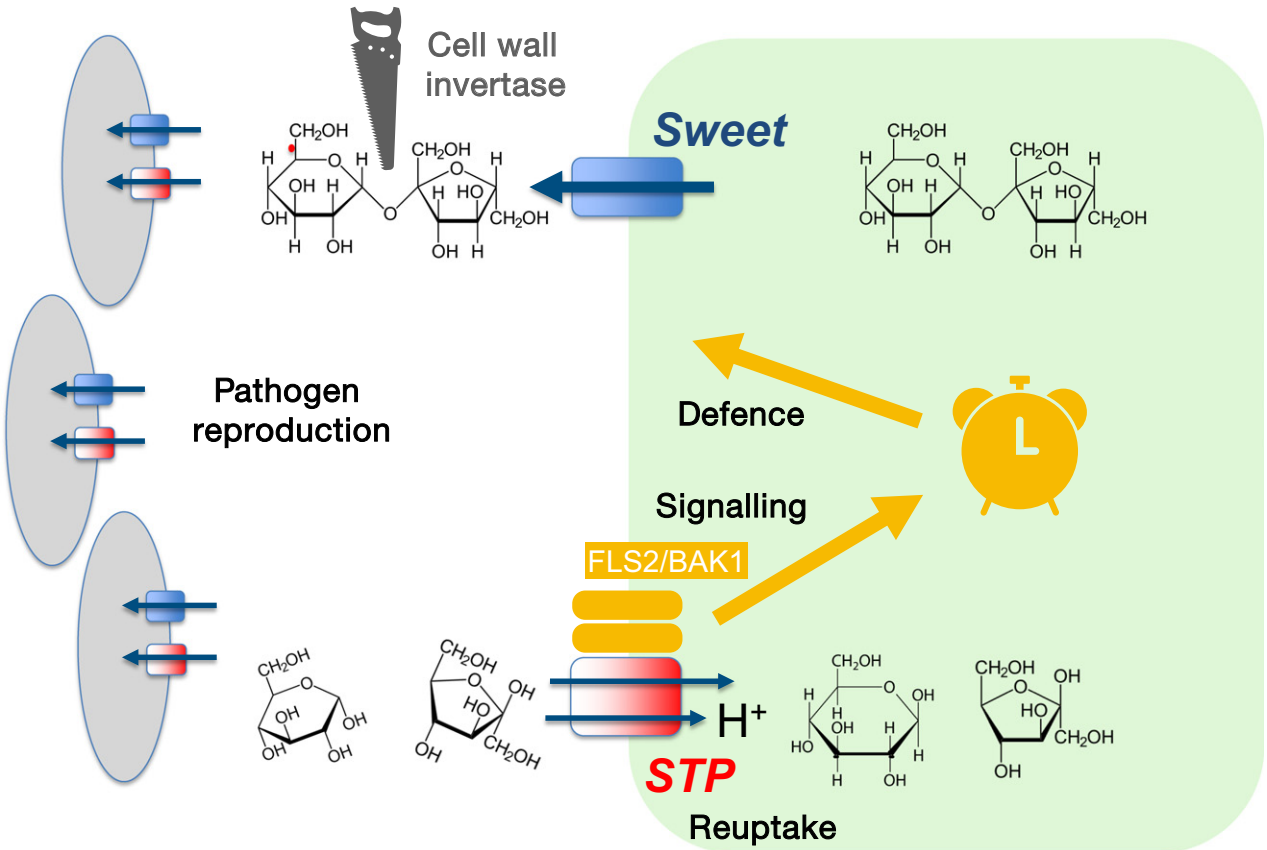

Figure 1. Cartoon illustrating two alternative pathways for SWEET- and STP-mediated pathogen susceptibility/resistance.
In the 'sugar starvation' hypothesis of disease resistance, the microbial pathogen induces SWEETs (sucrose uniporters) using effectors. In parallel, the plant recognizes the pathogen elicitors, which induce STPs (hexose/H^+ symporters). SWEET induction leads to secretion of sucrose into the cell wall space, where it is partially cleaved by cell wall invertases. The microbe uses sucrose and/or hexoses for nutrition/reproduction. STPs counteract the accumulation of sugars in the cell wall space by secondary active retrieval. In the 'sugar signaling' hypothesis of disease resistance, either the external accumulation of sugars or other signaling events, perhaps mediated via STPs by interaction with other proteins such as FLS2 and BAK1, signal an infection and trigger defense responses. These hypotheses are not mutually exclusive, and may function at the same or different times during the course of infection.

So far, experiments that test this hypothesis have not found elevated apoplasmic sugar levels, as measured by assays that typically detect sucrose and hexoses in leaves in the low millimolar range (Lohaus *et al.*, 2001). One explanation is that sugars may pass briefly from host cells to pathogens without accumulating substantially in the apoplasmic space. Flux can change without affecting pool sizes. Multiple Arabidopsis *SWEETs* are induced during Pseudomonas infection (Chen *et al.*, 2010), and higher hexose levels were not found in apoplasmic wash fluids despite induction of cell wall invertase activity (Yamada *et al.*, 2016). Cell wall invertase genes are induced in other some bacterial diseases, for example, cassava blight (Cohn *et al.*, 2014) and powdery mildew in wheat (Sutton *et al.*, 2007). Plants also respond to the bacterial pathogen-associated molecular pattern (PAMP) signals with induction of hexose/H^+ symporters, such as STP1, 4 and 13, that may counteract the SWEET-mediated secretion (Fotopoulos *et al.*, 2003; Yamada *et al.*, 2016), and thus limit apoplasmic sugar accumulation. STP13 appears to play such a role during infections with the fungus *Botrytis cinerea* (Lemonnier *et al.*, 2014).

The only method used for determining sugar pools in the cell wall space is based on infiltration of the apoplasmic space with solutions followed by centrifugation of the tissues (Lohaus *et al.*, 2001; Araya *et al.*, 2015). Potential issues with this apoplasmic wash technique could also be limiting the information on apoplasmic sugar accumulation: the technique has no temporal or spatial resolution, therefore cannot capture dynamics or local differences. It is generally assumed to measure the apoplasmic sugar pools. Pool size may also be less relevant than fluxes (Patrick, 1989). However, the technique is likely measuring also the efflux capacity of the tissues as the cells are exposed to medium that lacks sugars, creating an infinite gradient across the cell membranes. Incubation of cells in substrate-free medium is typically used to measure cellular efflux from the cytoplasm. Efflux of radiolabeled sugars was used to characterize efflux mediated by SWEETs when expressed in Xenopus oocytes (Chen *et al.*, 2010, 2012). Therefore,

Box 1 Some critical questions

- *Xoo* induces OsSWEET11 to extreme levels – are high SWEET activity levels necessary for infection and, if true, why are such high levels required?
- Only Clade 3 SWEETs are susceptibility loci for *Xoo* – why can only this subset fulfill the role and not the others?
- *xa13* (*OsSWEET11* promoter variant) has been used as a key resistance gene for many decades – can we generate robust resistance by combining SWEET promoter mutations?
- If we assume that *Xoo* does not require its SucX sucrose and GLT glucose transporters for pathogenicity, do they use a combination of sucrose and hexoses or are there other sugar uptake systems present in planta?
- SWEETs are also induced in other pathogen systems – are SWEETs critical in plant pathogen systems beyond Xanthomonas? If so, how do they induce SWEETs in the absence of TAL effectors? And, can we engineer resistance against a wide range of pathogens by restricting SWEET induction?
- If SWEETs serve predominantly in pathogen nutrition – what are the pools of sugars in the apoplasm, what are the fluxes, and what are the sources?
- Have plants evolved to limit apoplasmic sugar availability? Does the plant restrict access to nutrients by moving sugars predominantly via plasmodesmata and by restricting apoplasmic loading to the interface between phloem parenchyma and the sieve element companion cell complex (SECC)?
- Direct evidence for sugar movement through plasmodesmata is lacking – how can we test whether sugars traffic through plasmodesmata?
- What is the spatial distribution of sugars in the apoplasm of uninfected and infected plants?
- If the apoplasmic space contains substantial amounts of sugars – would these apoplasmic sugars be carried to the stomata by the water flux from xylem to stomata in leaves? Is there a retrieval system to avoid such issues?
- STP H^+-symporters could serve as hexose retrieval systems during infection – does the plant use STPs to counteract SWEET activity?
- The STP13 conundrum – why is the effect of inhibition of STP13 sugar transport activity the opposite in wheat rust compared with *Botrytis cinerea* infection of Arabidopsis?
- No one feeds on sugars alone – are transporters for other nutrients also required for susceptibility? In other words, can we block growth of pathogens by preventing access to nutrients in general?

there is a distinct need for better tools that have a high spatial resolution, the ability to separate cytosolic from apoplasmic concentrations, and the ability to measure dynamics in response to infection. Local changes in sugar availability have been predicted from photosynthesis imaging experiments in infected leaves (Siebke and Weis, 1995; Rolfe and Scholes, 2010). One potentially suitable technology may be the use of genetically encoded sensors (Okumoto, 2010) that can be expressed *in planta* to assess sugar flux during pathogen infection, or in the pathogen itself to visualize the nutritional status of the invading fungus or bacteria. Other methods such as mass spectrometry imaging, Raman spectroscopy or other tools not yet developed may help in addressing this important set of questions. Despite progress over the past decade, many questions remain open, a subset of which is summarized in Box 1.

SWEETs — SELECTIVE SUGARS TRANSPORTERS OR TRANSPORTERS OF OTHER SUBSTRATES?

During evolution, transporters have been optimized for the recognition of specific substrates. However, it is now evident that many, if not all, transporters can translocate many compounds, including natural and artificial drugs. For example, SUTs, which have a primary physiological role in importing sucrose into the SECC, can also transport a variety of glucosides such as helicin and salicin (Sun *et al.*, 2010). Another example is NTR1/PTR1, a transporter originally identified as a weak amino acid transporter, but this activity was later shown to likely be a side activity of a di- and tripeptide transporter that has no physiological relevance (Rentsch *et al.*, 1995). The related human peptide transporter PepT1 also transports a wide range of drugs (Brandsch, 2013). Recent findings indicate that the nitrate/peptide transporters mediate transport of compounds with highly diverse structures, such as nitrate, peptides, plant hormones and specialized metabolites (Kanno *et al.*, 2012; Nour-Eldin *et al.*, 2012; Chiba *et al.*, 2015). Of particular note in the context of this review, is that SWEETs transport gibberellins (Kanno *et al.*, 2016). Could gibberellin transport be key to the roles SWEETs play in pathogen resistance? Although this hypothesis does need to be tested, it must be noted that SWEET transport of sugars is well established, the physiological phenotypes of mutants are compatible with sugar transport function, and only

sucrose-transporting SWEETs have been shown to confer pathogen susceptibility.

Many SWEETs have been shown to transport glucose and/or sucrose, and even the bacterial ancestors are sugar transporters (Chen *et al.*, 2015a). SWEET mutant phenotypes are consistent with physiological roles in sugar transport during nectar secretion, phloem loading and seed filling (Chen *et al.*, 2012; Lin *et al.*, 2014; Sosso *et al.*, 2015; Bezrutczyk *et al.*, 2017; Yang *et al.*, 2017). However, Shiping Wang's lab indicated that a number of SWEETs did not complement a yeast sugar transport mutant (Yuan *et al.*, 2014). Negative results obtained with functional assays in heterologous systems can be due to a variety of issues. For instance, vacuolar SWEETs do not localize to the yeast plasma membrane and thus are unable complement the yeast mutant that rely on proper plasma membrane targeting of the heterologous transporters (Chardon *et al.*, 2013; Guo *et al.*, 2014; Chen *et al.*, 2015c). More generally, the detection of transport activity in any heterologous expression depends on adequate targeting of the proteins to the respective compartments in the host: however heterologous systems often fail to traffic sufficient numbers of transporters for example to the cell membrane (yeast, human cells, Xenopus oocytes). These negative results cannot definitively eliminate these proteins as functional transporters, as shown for the human glucose transporter GLUT1 in yeast (Kasahara and Kasahara, 1996). Different assays may be required to evaluate the transport properties of proteins that do not reach the cell membrane in the currently prevalent test systems. Moreover, some SWEETs preferentially transport sucrose over hexoses, rendering activity not testable in the hexose-deficient yeast strain (Wieczorke *et al.*, 1999).

Another interesting angle in the alternate-substrate model comes from the work of Shiping Wang and colleagues. Wang's lab found that OsSWEET11 can interact with apparently non-functional members of the COPT copper transporter family (Yuan *et al.*, 2010, 2011). Using the yeast mutant MPY17, which only shows copper-dependent growth when grown on non-fermentable carbon sources (Puig *et al.*, 2002), copper auxotrophy was only complemented by co-expression of two COPT proteins with OsSWEET11. Because two COPT homologs are involved, OsSWEET11 may not contribute to copper transport itself: rather it could affect the growth phenotype of the yeast mutant in an indirect way, either by increasing the activity of the two COPTs in the complex or by importing trace amounts of soluble carbohydrates derived from the agar, which could partially relieve the conditional copper dependence of the mutant.

Wang's group proposes that Xanthomonas susceptibility in rice is due to the ability of a COPT–SWEET complex to remove copper from the xylem sap, which would otherwise be toxic to the bacteria. This reduction in copper toxicity specifically occurs during infection with the disease-causing strain PXO99, but not for other tested strains (PXO86 and PXO61, which depend on *OsSWEET14* for virulence; Yuan *et al.*, 2010, 2011). One interpretation of this result is that SWEETs transport copper; another is that SWEETs are required for COPT transporter complex function because sugars are needed for its assembly or another energy-consuming process.

Wang's hypothesis appears to be able to explain the susceptibility caused by *Xa13/OsSWEET11*, because PXO99 is particularly sensitive to copper. However, it has been shown that other *Xoo* strains target *OsSWEET11* paralogs like *OsSWEET13* and *14* with closely related TAL effectors (Antony *et al.*, 2010; Yu *et al.*, 2011; Zhou *et al.*, 2015). Notably, transgenic PXO99 carrying TAL effectors targeting *OsSWEET14* overcome the resistance (or copper toxicity) conferred by either *xa13* (mutated alleles of *OsSWEET11* promoter) or RNAi-silenced *OsSWEET13* (Yang *et al.*, 2006; Antony *et al.*, 2010). If copper homeostasis is the key to explaining resistance to each strain in a gene-for-gene manner, all five SWEETs must be able to contribute to copper transport in a similar way as they all can cause susceptibility (Streubel *et al.*, 2013) and all the strains that induce other SWEETs must also be hypersensitive to copper. More work will be required to determine the mechanisms of SWEET interaction with COPT transporters and of copper-mediated resistance: whether SWEETs transport copper or if the sugar that they transport is required for COPT function. These hypotheses are testable – by analyzing copper availability in cell wall space, by determining local copper levels with biosensors, by detailed and more direct characterization of the complex and its copper transport activity, by analysis of copper transport by SWEETs, and by analysis of copper susceptibility of the other strains. Also, copper resistance is a common trait of xanthomonads in fields where copper-based treatments are applied (Behlau *et al.*, 2013). Presumably, Xoo would only have to acquire copper resistance to regain virulence in the face of limited SWEET expression. Nonetheless, further support for this interesting hypothesis would shed new light on the multiple roles of transporters in disease resistance.

A CLOSER LOOK AT THE SUGAR SIGNALING HYPOTHESIS

Extensive co-adaptation has occurred between plant hosts and pathogens. The plant host recognizes a pathogen by molecular patterns at its surface or by its secreted compounds, some of which the pathogen has little freedom to change in order to avoid recognition. While most pathology work has concentrated on processes unrelated to metabolism, a series of studies examined how sugars could serve as potential signals during pathogen interactions. 'High sugar resistance' has been mentioned in a variety of systems (Horsfall and Dimond, 1957). Notably, addition of sucrose to rice plants led to increased

resistance to rice blast (Gómez-Ariza *et al.*, 2007). While supporting a sugar signaling model, the external application of sucrose is fundamentally different from local induction of transporters, thus this observation should be interpreted with care. Sonnewald's group put forward a 'priming' hypothesis, in which hexose sensing in the secretory pathway mediates the induction of defense genes (Herbers *et al.*, 1996). More recently, they showed that defects in phloem loading can trigger SA-mediated priming of defense during infection of Arabidopsis by *Colletotrichum higginsianum*, further supporting the 'sugar signaling' hypothesis (Gebauer *et al.*, 2017).

One way that sugar signaling could mediate resistance is through modulation of the ability of bacterial pathogens to inject effector molecules into the host via Type III secretion systems (TTSS). Sugars are known to affect the expression of TTSS, at least in Pseudomonas (Wengelnik *et al.*, 1996; Stauber *et al.*, 2012). It is apparent that sugar homeostasis in the plant apoplasm directly affects pathogen virulence (Figure 2). Scott Peck's group also showed that extracellular metabolites are necessary for the assembly of TTSS (Anderson *et al.*, 2014). Further exploration in this area could include testing if altered sugar levels in the apoplasm change the induction or assembly of TTSS components. Again, additional work is required to dissect the specific roles of the metabolites and ultimately differentiate between alternate hypotheses, i.e. the signaling and starvation models of plant resistance.

Proton symporters of the MST/STP (monosaccharide transporter/sugar transporter) family are induced during pathogen infection in many systems, from Pseudomonas and *B. cinerea* in Arabidopsis (Fotopoulos *et al.*, 2003; Lemonnier *et al.*, 2014; Yamada *et al.*, 2016) to multiple pathogens (causal agents of leaf, stripe and stem rusts; powdery mildew) in wheat (Moore *et al.*, 2015; White and Frommer, 2015; Ding and Jones, 2017). Several members of the MST family (STP1, 4 and 13) were induced during bacterial infections, most likely as part of the PAMP response (Fotopoulos *et al.*, 2003; Yamada *et al.*, 2016). STPs as proton symporters likely move hexoses from the cell wall into the cell. The most parsimonious hypothesis for sugar-mediated resistance is that STPs act as a defense system to counteract the hijacked SWEET sugar secretion by reimporting hexoses (derived from invertase-mediated hydrolysis of sucrose). Surprisingly, STP13 appears to interact with FLS2, the BAK1 complex and two other PRRs. Moreover, BAK1 phosphorylates STP13, which in turn alters STP13 glucose transport activity. Yamada *et al.* concluded that phospho-dependent regulation of STP13 activity changes apoplasmic sugar levels and thereby inhibits TTSS-mediated effector secretion from the bacteria (Figure 1). Remarkably, however, STP13 is also a key factor for resistance to fungal pathogens such as Botrytis (Lemonnier *et al.*, 2014). Arabidopsis plants overexpressing STP13 were more resistant, while knockout mutants were more susceptible, to Botrytis. Because at least one SWEET is also induced by Botrytis, STP13 could counteract SWEET-mediated sugar availability in the apoplasm (Chong *et al.*, 2014). In the case of the broad-spectrum fungal resistance caused by mutations in STP13 in wheat, transport-deficient STP13 confers dominant resistance in wheat (Moore *et al.*, 2015). Dominance of resistance has been linked to dominant negative inhibition of functional copies of STP13 by the mutated form.

In yeast, select homologs of the STPs can function as sugar sensors rather than transporters (Thevelein and Voordeckers, 2009). We had previously speculated that the Arabidopsis SUT2 may also function as a sensor (based on the presence of extended cytosolic domains, as found in yeast sugar sensors SNF3 and RGT2; Barker *et al.*, 2000). Because there is no convincing evidence so far, it is also pure speculation whether STPs or SWEETs may have additional activities. Over the past decade, other transporters have been identified that have sensor functions (Ho *et al.*, 2009; Thevelein and Voordeckers, 2009). Key evidence needed to prove transceptor activity is a separation of the two functions, as changes in nutrient levels generated by the transporter could act as signals. One would need to identify mutations that affect only the transport function to thereby uncouple transport from signaling. Testing such a hypothesis is substantially more feasible in single-cell organisms, where large numbers of mutations can be generated and tested rapidly to distinguish if additional activities other than transport are at work. Eventually, manipulation of STP13 function, whether in transport and/or signaling activities, may help the development of broad-spectrum resistance against bacterial and fungal pathogens.

PROVIDING NUTRITION FOR SYMBIONTS AND MICROBIOTA

Symbionts have co-evolved with their hosts to expand their range and supply nutrients. Rhizobia fix atmospheric N_2 and provide fixed N to their hosts, in return for carbon skeletons. The nodules in which they live require a constant supply of energy supplied either as carbohydrates or in the form of organic acids. Udvardi and Day showed that bacteroids in nodules take up organic acids preferentially, while transport of sugars is comparatively low and non-saturable for sucrose and glucose (Udvardi *et al.*, 1990). As already mentioned, SWEETs were first found as nodulins (genes induced during nodulation) and named MtN3 (*M. truncatula* nodulin number 3). Low-affinity transporters such as the SWEETs could mediate the above-mentioned, non-saturable uptake of glucose and sucrose. Alternatively, SWEETs could provide sugars to the nodule. Two studies recently demonstrated that multiple SWEETs capable of transporting either hexoses or sucrose are indeed

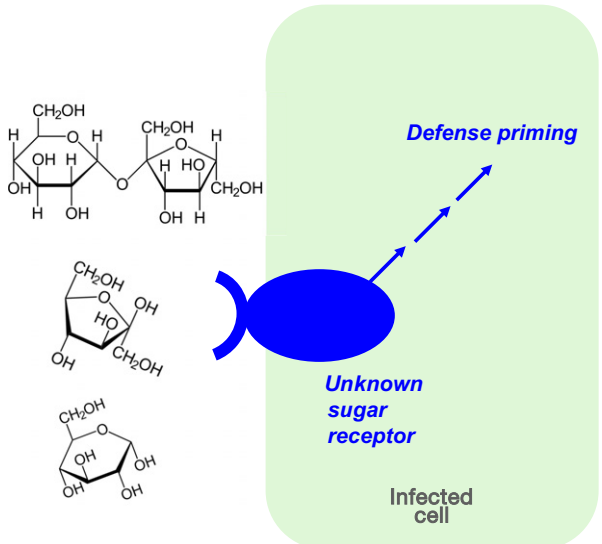

Figure 2. Hypothetical model for high sugar resistance.
Elevation of the levels of extracellular sugars, either through increased SWEET activity or through blockage of STP13, might be detected by a yet unknown sugar receptor that is somehow coupled to a signaling cascade that triggers defense priming (Gebauer *et al.*, 2017).

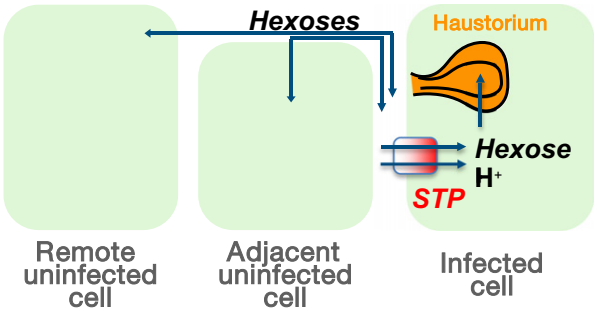

Figure 3. One possible model of the apparently different roles of STP13 in Arabidopsis and wheat.
During infection with a biotrophic pathogen that uses haustoria as feeding structures, STP13 expression and activity are induced as part of the defense response, thereby counteracting SWEET-mediated sugar accumulation in the apoplasm. In such systems, the pathogen has hijacked STP13 to import sugars into the haustorium or import sugars into the cell that feeds the haustorium with sugars provided from adjacent cells as part of the defense mechanism, thereby increasing the availability of sugars in the infected cell, which then can be used to feed the pathogen via the haustorium. This model is based on a concept presented by Yamada *et al.* (2016), but separates the source of sugars from the site of infection.

expressed in nodules, possibly providing sugars to the nodule (Kryvoruchko *et al.*, 2016; Sugiyama *et al.*, 2017). The presence of multiple SWEETs will require a careful analysis of all nodule-expressed members as well as the construction of mutant lines carrying knockouts of multiple family members in order to obtain clear insights into the roles of SWEETs in nitrogen fixation and nodule nutrition.

Mycorrhiza, with their fine hyphal networks, are thought to provide nutrients to their hosts in return for sugar supply (Schüssler *et al.*, 2006). Not surprisingly, SWEETs are also induced during mycorrhization and may thus be responsible for the sugar efflux that feeds the symbionts (Manck-Götzenberger and Requena, 2016).

Plants are colonized by complex communities of microbes, which colonize both their surface and apoplasm (Müller *et al.*, 2016; Andreote and Pereira E Silva, 2017). Presumably, these communities are fed by the plant host. The analysis of microbial communities in the gut and in plant roots provides circumstantial evidence that carbon availability may be important (Hacquard *et al.*, 2015). Could basal levels of SWEET expression provide sufficient nutrition to those that depend on sugars? If this is the case, could one strain take over during pathogenesis by using the available basal levels and outcompete the others without changing host supply? Computational approaches will have to be at the core of examining the effect of manipulation of nutrient secretion on these communities (Succurro *et al.*, 2017).

Microbes, whether symbionts or pathogens, need access to more than just sugars: they need to be supplied with all essential nutrients, and they likely prefer reduced forms. It is thus conceivable that many other host nutrient efflux systems, for example for amino acids, are manipulated by pathogens and symbionts in a similar fashion.

When we distinguish between the 'pathogen starvation' and 'sugar signaling' hypotheses, it is important to be aware that nutrient acquisition by symbiotic bacteria and the necrotrophic and biotrophic pathogens could differ in important ways. In its necrotrophic phase, *B. cinerea* causes cells to rupture and then feeds on the released nutrients (Lemonnier *et al.*, 2014), which is substantially different from the situation in extracellular appressoria-mediated feeding of, for example, corn smut *Ustilago maydis* (Wahl *et al.*, 2010) or the extrahaustorial-matrix feeding in the case of wheat stem rust *Puccinia graminis* (Voegele and Mendgen, 2003). Yamada *et al.* provided a possible model in which fungal pathogens that form haustorial feeding structures may use STP13 as a way to import sugars either into the haustoria or into the cells that contain the haustoria, possibly also explaining the differences observed for STPs in Botrytis and rust (Yamada *et al.*, 2016; Figure 3).

SUMMARY AND OUTLOOK

While there are many open questions (Box 1), the systematic identification of R genes has brought us substantially closer to being able to rationally engineer pathogen resistance in crop plants. Importantly, knowledge of the fact that different *Xoo* strains use different TAL effectors to induce particular SWEETs now allows the construction of elite rice lines that are resistant to particular *Xoo* isolates.

The combination of mutations in SWEET promoters may be a path towards broad-spectrum *Xoo* resistance. Because we are now able to rapidly identify which SWEETs are induced by a particular isolate, and can rapidly determine the TAL effector active in such a strain, it is conceivable that we can breed resistance towards newly emerging isolates more quickly than they can evolve and spread. Breeders have made extensive use of SWEET-based resistance, providing essentially proof-of-concept for approaches in which genome editing is used to engineer resistance. The approach is rather straightforward – TALEN or CRISPR technology is now effectively applied to obtain mutations in the effector molecule-binding sites in the SWEET promoters, thereby creating resistance without yield penalty (Bi and Yang, 2017). Advances in this field will rely heavily on collaborations between plant pathologists and physiologists. Moreover, the combination of different types of resistance mechanisms may help to increase the robustness of resistance as well as the spectrum. In addition to resistance to many diseases, subclinical infections (low-level infestation without major disease symptoms) also cause substantial yield losses (Popp and Hantos, 2011), thus there is an opportunity to even generate lines with increased yield.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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