Sugar conundrum in plant-pathogen interactions: Roles of invertase and sugar transporters depend on pathosystems

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Highlight Available information on roles of sugar-related processes in plant-pathogen interactions comes from diverse plant species and types of pathogens with contradictory findings. We found that the specific roles of invertases and sugar transporters in plant-pathogen interactions are dependent on the lifestyle and infection strategies of pathogens.

Abstract

It has been increasingly recognized that CWIN (cell wall invertase), and sugar transporters including STP (sugar transport protein) and SWEET (sugar will eventually be exported transporters) play important roles in plant-pathogen interactions. However, the information available in the literature comes from diverse systems and often yields contradictory findings and conclusions. To solve this puzzle, we provided here a comprehensive assessment on the topic. Our analyses revealed that the regulation of plant-microbe interaction by CWIN, SWEET and STP is conditioned by the specific pathosystems involved. The evaluation indicates that: (a) Roles of CWINs in plant resistance are largely determined by the lifestyle of pathogens (biotrophs vs necrotrophs or hemibiotrophs), possibly through CWIN-mediated salicylic acid or jasmonic acid signaling and programmed cell death pathways; (b) upregulation of SWEETs and STPs may enhance or reduce resistance, depending on the cellular sites from which the pathogens acquire sugars from the host cells and (c) Plants employ unique mechanisms to defend against viral infection, in part, through a sugar-based regulation on plasmodesmatal development or aperture. Our appraisal further calls for an attention on the involvement of microbial sugar metabolism and transport in plant-pathogen interactions, which is an integrated but overlooked component of plant-pathogen interactions.

Keywords bacteria; fungi; invertase; pathogen; sugar metabolism; sugar transport; sugar signaling; STP; SWEET; virus.
**Introduction**

A significant progress has been made in understanding plant-pathogen interactions, which is essential for achieving sustainable crop production. Upon infection by pathogens including bacteria, fungi and virus, plants activate various defense systems to prevent or slow down pathogen proliferation (Berger *et al*., 2007). The defense responses may take place at multiple levels, ranging from cell wall thickening and callose deposition to generation of reactive oxygen species (ROS) and immunity phytohormones, namely salicylic acid, jasmonic acid and ethylene, as well as de novo biosynthesis of defense-related proteins and secondary metabolites such as phytoalexins and phenolics (Proels and Hückelhoven, 2014; Tauzin and Giardina, 2014; Rojas *et al*., 2014). To meet the intensive demand for energy, carbon nutrient and reducing agents that are required for defense responses, plant primary metabolism is reprogrammed during infection. This reprogram may include, for example, reduced photosynthesis, increased respiration and altered metabolism for nitrogen, lipid and carbohydrate (Reviewed by Bolton, 2009 and Rojas *et al*., 2014). To this end, sugars are the main source of energy and carbon skeleton for plant defense responses (Morkunas and Ratajczak, 2014). Pathogen-induced shut-down of leaf photosynthesis often leads to source-to-sink transition of the infected tissues (Bolton, 2009). The metabolic shift from source-to-sink status mandates sugar import to the infected tissue from the adjacent or distal healthy source leaves via long distance translocation in the form of sucrose (Suc).

Unsurprisingly, accumulating evidence reveals vital roles of Suc metabolism and transport in plant resistance or adaptation to biotic stresses (Koch, 2004; Ruan, 2014; Wang and Ruan, 2016). It has long been noted that plant-pathogen interactions are significantly influenced by the levels of soluble sugar in the host plants. For example, an increase in sugar level in tomato leaves enhanced resistance to foliar disease target spot caused by *Alternaria solani* (Horsfall and Dimond, 1957). Similarly, pretreatment of rice and Arabidopsis plants with exogenous Suc, glucose (Glc) or fructose (Fru) also increased resistance to fungus *Magnaporthe oryzae* and bacterial pathogen *Pseudomonas syringae* pv. tomato DC3000 (Pst DC3000), respectively (Gómez-Ariza *et al*., 2007; Qian *et al*., 2015), indicating an intimate involvement of sugars in plant-pathogen interaction.

Theoretically, sugar metabolism and transport may modulate plant-pathogen interaction in several ways: Firstly, sugars provide carbon (C) nutrients and energy to fuel defense. There is a dramatic increase in sugar demand for defense responses including cell
wall strengthening, biosynthesis of phytoalexins and induction of defense-related proteins, for example, pathogenesis-related (PR) proteins (Berger et al., 2007). Secondly, accumulated soluble sugars (especially hexose) themselves may activate the expression of defense-related genes such as various PR genes through sugar signaling (Herbers et al., 2000; Sonnewald et al., 2012; Gebauer et al., 2017; Ru et al., 2017). Lastly, soluble sugars, especially those in the extracellular matrix, often serve as a carbon source for the growth of pathogens, thereby increasing their virulence (Pommerrenig et al., 2020). Thus, sugars could exert positive or negative roles in plant defense against pathogen infection, depending on the outcome of tug-of-war between pathogens and plant cells competing for the sugar resource.

The apoplasm of plant cells forms the frontier to fight pathogens upon infection. This cell wall matrix is often enriched in nutrients including sugars and thus is the main battlefield for pathogens to compete with the host cells for resources required for colonization (Naseem et al., 2017). Suc degradation in the apoplasm and subsequent sugar transport across plasma membranes (PM) determine not only sugar levels and compositions in the apoplasm (Bezrutczyk et al., 2018), but also the partitioning of organic C between the host and the pathogens, and hence the outcome of plant-pathogen interaction (Lemonnier et al., 2014). Some aspects on the involvement of sugar metabolism, transport and signaling in plant-pathogen interaction have been recently reviewed (Naseem et al., 2017; El Kasmi et al., 2018; Pommerrenig et al., 2020). Those analyses highlighted that, to colonize plants successfully, bacterial and fungal pathogens typically hijack plant sugar transport systems to export sugars into apoplasmic space to fuel their growth, mainly by inducing the expression of host SWEETs (Sugars Will Eventually be Exported Transporter), a class of energy-independent uniporters for moving sugars across membranes (Chen et al., 2010). As a countermeasure, host cells up-regulate the expression or activity of energy-dependent STPs (Sugar Transport Protein) and SUTs (SUgar Transporter) to retrieve the apoplasmic sugars back into the cytosol of the plant cells, thereby starving the pathogens under many circumstances (Naseem et al., 2017; El Kasmi et al., 2018; and references therein). Pommerrenig et al (2020) pointed out that STP, but not SUT, is likely the major sugar transporter responsible for the reuptake of apoplasmic sugar to minimizing bacterial infection. Another countermeasure is the up-regulation of host CWIN upon pathogen infection. CWIN-derived hexose could act as signaling molecules to activate plant defense responses such as oxidative burst, hypersensitive response (HR) and cell wall biosynthesis, production of secondary metabolites, alteration of circadian clock and stomata aperture.
Despite of the progress as outlined above, many questions remain. First, current available studies show that CWINs, SWEETs and STPs appear to play contradictory or even contrasting roles in plant-pathogen interactions in different systems (as discussed in the following sections). The underlying basis and implications remain elusive. Second, while much attention has been paid to the roles of CWIN and sugar transporters in host response to bacterial and fungal attack (e.g. Pommerrenig et al., 2020), the potential roles of these proteins in response to viral infection seem overlooked. Third, little is known about the roles of pathogen-originated CWINs and sugar transporters in plant-pathogen interactions. Here, we addressed these issues by assessing the relevant information available and provided likely scenarios and insights to this sugar conundrum in plant-pathogen interactions. We then proposed several perspectives for future studies to improve our understanding on sugar-mediated plant defense.
Box 1. Role of CWIN and sugar transporters in plant defense against pathogens

- **CWINs exert different roles in plant resistance to pathogens with different lifestyles**
  
  Overexpression of CWIN gene *GIF1* in rice enhanced resistance to hemibiotrophic bacterial pathogen *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) and hemibiotrophic fungal pathogen *Magnaporthe oryzae* through increasing cell wall thickness, ROS accumulation and HR, and activated expression of PR genes including *PR1a, PR1b, PR3, PR10, WRKY45* and *NPR1* (Sun et al., 2014). However, silencing of CWIN gene *LIN8* in tomato increased, instead of decreased, leaf resistance to biotrophic bacterial pathogen *Xanthomonas campestris* pv. *vesicatoria* (*Xcv*) (Kocal et al., 2008). These findings indicate that CWIN may act as resistance and susceptibility factors in response to hemibiotrophic and biotrophic pathogens, respectively (see Table 1 for more examples and Fig. 1 for possible mechanisms).

- **Roles of STP in plant defense vary with the cellular sites from which pathogens acquire sugar nutrients**
  
  Mutation of *AtSTP13* resulted in reduced Arabidopsis resistance to necrotrophic fungi *B. cinerea* (Lemonnier et al., 2014). Similarly, double mutation of *AtSTP1/AtSTP13* in Arabidopsis increased susceptibility to bacterial pathogen Pst DC3000 (Yamada et al., 2016), implying that STP could enhance plant resistance by depriving bacteria and necrotrophic fungi of sugar supply in the apoplasm. In contrast, *Lr67res*, a mutation form of wheat homolog (*Lr67sus*) of *AtSTP13*, showed a broad-spectrum resistance to both biotrophic fungi including rust pathogens (*Puccinia triticina, P. striiformis* and *P. graminis*) and powdery mildew pathogen *Blumeria graminis* (Moore et al., 2015). Furthermore, knockdown of *TaSTP6* increased wheat resistance to *P. striiformis*, whereas an ectopic expression of *TaSTP6* reduced Arabidopsis resistance to powdery mildew (Huai et al., 2019). Different from bacteria and necrotrophic/hemibiotrophic fungi, biotrophic fungi acquire sugars not from cell wall apoplasm, but from specialized apoplasm named extrahaustorial matrix (EHMx). Sugar must be first imported into host cells by STP and subsequently exported into EHMx for the uptake by biotrophic fungi (See Fig. 2 for details and Table 3 for more examples).
Box1. Role of CWIN and sugar transporters in plant defense against pathogens
(continued)

- **CWIN and sugar transporters enhance resistance to virus possibly by inhibiting plasmodesmatal development or aperture**

  Different from bacteria and fungi, virus spreads from cell to cell within host plants through plasmodesmata (PD). In non-pathosystems, high expression of CWIN and sugar transporters commonly inhibits PD development or reduces PD aperture. For example, an ectopic expression of yeast INV in the apoplasm of tobacco leaves led to the arrest of PD development (Ding et al., 1993) and reduced viral infection (Herbers et al., 1996). Similarly, an increased expression of GhSUTs and clade III GhSWEETs correlated to a reduction in PD aperture (Zhang et al., 2017). Thus, CWIN and sugar transporters may block viron spread in plants via inhibiting PD development or aperture.

- **Microbial INVs and sugar transporters: the forgotten, yet important, players in shaping the outcome of plant-pathogen interaction**

  Similar to host plants, pathogenic microbes also possess their own sugar uptake and metabolic systems to facilitate their pathogenicity. For example, during an infection of sunflower by necrotrophic fungus *Sclerotinia sclerotiorum*, the protein level of host CWIN decreased, whereas that of microbial acid INV increased, indicating the rise of extracellular INV activity in the infected plant tissue may mainly derive from pathogenic microbes, instead of the host plants (Jobic et al., 2007). Furthermore, the silence of PsINV gene of biotrophic fungus *P. striiformis* inhibited fungal growth and reduced spore number and virulence (Chang et al., 2017). For biotrophic fungus *Ustilago maydis*, the deletion of Suc transporter UmSrt1, which is responsible for Suc uptake into fungus, reduced the virulence of *U. maydis* (Wahl et al., 2010; Wittek et al., 2017). Thus, microbial CWIN and sugar transporters play major roles in pathogenicity and must be taken into account in order to achieve a holistic understanding on sugar-modulated plant-pathogen interaction.
Activating and fueling defense by CWIN

In higher plants, sucrose synthase (Sus) and invertase (INV) are the two classes of enzymes that degrade Suc into hexose. Sus is a glycosyl transferase and reversibly converts Suc in the presence of UDP into UDP-Glc and Fru, whereas INV irreversibly hydrolyzes Suc into Glc and Fru. Based on their subcellular locations, INVs are further classified into cell wall invertase (CWIN), vacuolar invertase (VIN) and cytoplasmic invertase (CIN, Sturm, 1999; Wan et al., 2018). Up to date, studies on INV-mediated regulation of plant-pathogen interactions have been predominantly conducted on CWINs, as detailed below. This is not surprising since apoplasm is the main battle field between plant cells and pathogens competing for sugar resource and also a major cellular site eliciting sugar signaling for defense and development (Naseem et al., 2017; Liao et al., 2020).

In general, CWIN activity is induced or enhanced during pathogen infection (Joosten et al., 1990; Essmann et al., 2008; Bonfig et al., 2010), indicating its positive role in defense. Under pathogen attack, plants experience an increased sugar demand to trigger and sustain defense responses which are energy-costly (Engelsdorf et al., 2013 and references therein). The increased sugar level upon infection is largely attributed to the induction of CWIN activity, which enhances sink strength of infected tissues (Proels and Hückelhoven, 2014; Tauzin and Giardina, 2014). The buildup of soluble sugar may energize the local defense at the infection site. In addition, CWIN-derived hexose may activate defense responses via signaling. It has been suggested that some unknown sugar receptors localized on PM likely sense apoplastic hexose to prime plant defense responses (Bezrutczyk et al., 2018), although such a receptor is yet to be identified.

Dual role of CWIN in plant-pathogen interactions and the underlying basis

A number of studies have shown positive roles of CWINs in defense against pathogens. An expression of yeast INV in leaf apoplasm increased tobacco resistance to potato virus Y, probably owing to elevated hexose level in the leaves, activating systemic acquired resistance, including up-regulation of defense-related genes and peroxidase activities as well as enhanced synthesis of callose and salicylic acid (SA) (Herbers et al., 1996). More recently, CWIN-overexpressed rice lines displayed increased sugar levels (Suc, Glc and Fru) in leaves and enhanced resistance to bacterial pathogen Xanthomonas oryzae pv. oryzae (Xoo) and fungal pathogen Magnaporthe oryzae through increasing cell wall thickness and activating PR genes (Sun et al., 2014). Conversely, down-regulation of CWIN reduced tobacco
resistance to oomycete *Phytophthora nicotianae* due to decreases in callose deposition, H$_2$O$_2$ accumulation, and hypersensitive cell death (Essmann et al., 2008).

However, emerging evidence also shows that CWIN could play negative roles in several pathosystems. For instance, silencing of CWIN gene LIN8 in tomato delayed the development of disease symptom in leaves infected by bacterial pathogen *Xanthomonas campestris* pv. *vesicatoria* (Xcv), although the bacterial growth *in planta* remained unchanged in the transgenic tomato (Kocal et al., 2008). Here, assessment of plant tolerance to pathogens is generally based on the development of symptom, instead of the growth or number of pathogenic microbes *in planta* (Kranz, 1988). Thus, it can be concluded that the silencing of LIN8 expression enhanced tomato tolerance to Xcv. Likewise, reduced CWIN activity through over-expression of a CWIN inhibitor gene increased Arabidopsis tolerance to fungal pathogen *Plasmodiophora brassicae*, which causes clubroot symptom (Siemens et al., 2011). The observations discussed above indicate contrasting roles of CWINs in plant defense.

According to their lifestyles, plant pathogens can be classified into two groups: biotrophs and necrotrophs/hemibiotrophs, which feed on living and dead plant tissues, respectively (Glazebrook, 2005, Spanu, 2012). Alterations in metabolism or signaling in the host appear to have opposite effects on resistance to these two groups of pathogens. For example, barley mutant *albostrians* with pale leaves due to blocked chloroplast development, showed decreased resistance to the hemibiotrophic fungus *Bipolaris sorokiniana* (Schäfer et al., 2004), but increased resistance to the biotrophic powdery mildew fungus *Blumeria graminis* (Jain et al., 2004). Similarly, the functional-loss of MLO, a PM-localized protein interacting with cytoplasmic calmodulin, led to broad-spectrum resistance in barley to all known isolates of biotrophic powdery mildew, but increased susceptibility to hemibiotrophic *Magnaporthe grisea* and necrotrophic *Bipolaris sorokiniana* (Jarosch et al., 1999; Kumar et al., 2001; Panstruga, 2005).

After evaluating a large number of cases on plant responses to different pathosystems, it appears clear that that CWINs could exert different roles in plant defense, depending on the lifestyle of a given pathogen involved. As summarized in Table 1, CWIN enhances plant resistance to hemibiotrophic pathogens such as oomycete *Phytophthora nicotianae* (Essmann et al., 2008), bacterial pathogen Xoo and fungal pathogen *Magnaporthe oryzae* (Sharma et al., 2013; Sun et al., 2014), but reduces host resistance to biotrophic pathogens including
fungal pathogen *Plasmodiophora brassicae* (Siemens *et al.*, 2011) and bacterial pathogen Xcv (Tamir-Ariel *et al.*, 2007; Kocal *et al.*, 2008). The model can be validated through further studies, by, for example, testing the roles of CWIN in response to biotrophic and necrotrophic/hemibiotrophic pathogens simultaneously using genome-editing to knockout the CWIN gene. It should be pointed out that the model does not appear applicable to virus, which exerts its virulence differently from pathogenic bacteria and fungus and thus will be discussed separately in the paper. Similar to CWIN-mediated sugar metabolism, nitrogen metabolism also shows contradicting roles in plant defense, depending on the lifestyle of the pathogen (As reviewed by Seifī *et al.*, 2013). For instance, a supply of high N to hydroponically cultivated tomato reduced or increased susceptibility to the necrotrophic *B. cinerea* and the biotrophic powdery mildew fungus *Oidium lycopersicum*, respectively (Hoffland *et al.*, 2000). It has been hypothesized that an earlier and more dramatic induction of CWIN increases plant resistance via hexose-signaling that triggers defense responses, whereas a late and moderate induction of CWIN benefits pathogen development through increasing sugar supply to the microbes (Scharte *et al.*, 2005; El Kasmi *et al.*, 2018). However, this postulation cannot explain why the roles of CWIN in defense vary with lifestyle of pathogens. Below, we proposed two possible scenarios underlying the contrast roles of CWIN in plant-pathogen interactions.

First, phytohormones, especially salicylic acid (SA) and jasmonic acid (JA), may involve in CWIN-mediated plant resistance. There are at least nine hormones identified in plants, including auxins (IAA), cytokinins (CK), gibberellins (GA), abscisic acid (ABA), ethylene (ET), brassinosteroids (BR), salicylates (SA), jasmonates (JA), and strigolactones (SL) (Su *et al.*, 2017). Among these, SA, JA and ET are well known for their regulatory roles in plant defense against pathogens and thus usually called as immunity hormones (Ma and Ma, 2016; Akhtar *et al.*, 2020). The other hormones traditionally considered as growth hormones (e.g. IAA, CK, GA and BR) have also been revealed to be involved in plant-pathogen interaction (Ma and Ma, 2016; Chanclud and Morel, 2016). Interestingly, contrasting roles (positive or negative) in plant defense have been reported for CK, in part depending on the dosage involved (Albrecht and Argueso, 2017; Spallek *et al.*, 2018; Akhtar *et al.*, 2020). CK signaling for leaf growth has been shown to be dependent on CWIN activity (Lara *et al.*, 2004). However, the reversal is not necessarily the case. For instance, an elevation of CWIN activity in tomato delayed leaf senescence but with no impact on CK level in leaves (Jin *et al.*, 2009). It remains unknown whether and how CWIN-mediated plant-
pathogen interaction involves in CK signaling. Similarly, while application of ET could affect CWIN gene expression or activity (Linden et al., 1996; Sun et al., 2021), it is unknown if changes in CWIN activity or expression may affect ET level and signaling during defence against pathogens.

Generally, SA-mediated signaling pathway promotes plant resistance to biotrophic pathogens, whereas JA/ET pathway enhances resistance to necrotrophic/hemibiotrophic pathogens (Thaler et al., 2004). There is antagonistic relationship between SA- and JA-mediated defense signaling pathways since SA and JA have opposite influence on the expression of many defense genes (Glazebrook, 2005). Here, CWIN appears to negatively interact with SA, but positively with JA signaling. For instance, in the maize mutant miniature with the loss of CWIN activity in grain, SA level was elevated by 10 folds (LeClere et al., 2008). Similarly, the inhibition of CWIN activity by application of acarbose, a chemical INV inhibitor, led to increased SA levels in Arabidopsis (Bonfig et al., 2010). On the other hand, silencing of CWIN gene LIN5 resulted in a reduction in JA levels in tomato (Zanor et al., 2009).

The different response of SA and JA to CWIN may explain why CWIN has contrast effects on plant resistance to pathogens with different lifestyles. Here, CWIN may reduce plant resistance to biotrophic pathogens possibly through inhibiting SA signaling pathway, but increase the resistance to necrotrophic/hemibiotrophic pathogens by activating JA signaling pathway (Fig.1). Up to date, however, studies on the roles of CWIN in plant-pathogen interaction have not reported potential changes in SA and JA levels (Kocal et al., 2008; Essmann et al., 2008; Siemens et al., 2011; Sun et al., 2014), whereas those studying the impact of CWIN on SA and JA levels were conducted out of the context of plant-pathogen interaction (LeClere et al., 2008; Zanor et al., 2009). Clearly, future efforts are needed to experimentally test the CWIN-SA and JA hypothesis during plant-pathogen interaction.

Second, CWIN may indirectly affect plant-pathogen interactions through impacting on PCD incidence. PCD is often induced during plant-pathogen interactions as part of the defense response (Gilchrist, 1998). There is compelling evidence that CWIN-mediated Suc degradation exerts important roles in the regulation of PCD. For example, the loss-of-function of CWIN in maize mutant mn1 led to PCD in placento-chalazal region of maize kernel (Kladnik et al., 2004). Consistently, an elevation of CWIN activity through silencing its inhibitor blocked heat stress-induced PCD, thereby alleviating tomato fruit abortion (Liu
et al., 2016) and increased CWIN activity through injection of Suc into stems sustained grain set in maize under drought also through, in part, reducing the incidence of PCD (Boyer and McLaughlin, 2007). It is well known that PCD impairs the development of biotrophic pathogens by blocking their colonization in living cells, but benefits that of necrotrophic/hemibiotrophic ones (Greenberg, 1997). Thus, it is plausible to hypothesize that the inhibition of PCD by CWIN could favour or block biotrophic and necrotrophic/hemibiotrophic infection, respectively (Fig.1).

**SWEETs: Factors of susceptibility or resistance in plant-pathogen interactions?**

CWIN-mediated Suc metabolism and signaling is tightly coupled with sugar transport across cell membranes for plant development and defense (Ruan, 2014; Gebauer et al., 2017; Liao et al., 2020). Thus, we next explored how sugar transport may modulate plant defense response by focusing on three main sugar carriers (Doidy et al., 2012; Pommerrenig et al., 2020): SWEET, STP/MST (Sugar Transport Protein/MonoSaccharide Transporter) and SUT/SUC (SUgar Transporter/SUcrose Carrier).

SWEETs passively transport Suc and/or hexose along sugar concentration gradient and thus function as bidirectional transporters, to exert multiple physiological functions such as seed filling, phloem loading and unloading, nectar secretion and plant-pathogen interaction (Chen et al., 2012; Eom et al., 2015; Jeena et al., 2019). SWEETs are phylogenetically classified into four clades (Chen et al., 2010; Chandran, 2015). Among them, Clade I and II exhibit preference for Glc over Fru, while Clade III and Clade IV predominantly transport Suc and Fru, respectively (Zhao et al., 2018). Apart from Clade IV SWEETs operating on tonoplasts, the other three classes of SWEETs mainly function on plasma membranes (Breia et al., 2021). During infection, SWEETs generally facilitate the export of Suc and/or hexose out of host cells as susceptibility factors, which increases sugar availability to pathogens in the apoplasm (Chen et al., 2015b; Pommerrenig et al., 2020 and Breia et al., 2021).

Early evidence on roles of SWEETs in plant-pathogen interaction mainly came from studies on Clade III members in rice (Li et al., 2013; Streubel et al., 2013). Through direct binding of secreted effectors to the promoters of SWEETs, the hemibiotrophic bacterial pathogen Xoo PXO99A hijacked and induced the expression of *OsSWEET11* and *OsSWEET14* in rice, both belonging to Clade III PM-located SWEETs, for its virulence by facilitating Suc efflux into apoplasm for the uptake by Xoo. Accordingly, RNAi repression of *OsSWEET11* increased rice resistance to Xoo (Chen et al., 2010). Besides bacterial pathogens, *OsSWEET11* also acts as a susceptible gene in rice when infected by the
necrotrophic fungal pathogen *Rhizoctonia solani* (Gao *et al*., 2018). Similarly, in cotton, silencing of *GhSWEET10*, an ortholog of *OsSWEET11*, enhanced resistance to hemibiotrophic bacterial blight pathogen *Xanthomonas citri* subsp. *malvacearum* (Xcm), most likely owing to reduced apoplastic Suc supply to Xcm since overexpression of *GhSWEET10* in *Nicotiana benthamiana* indeed elevated Suc level in the apoplastic fluid of the transgenic leaves (Cox *et al*., 2017). In addition, the phloem-localized Clade III transporters AtSWEET11 and AtSWEET12 also act as susceptibility factors in Arabidopsis during infection by the fungal hemibiotroph *Colletotrichum higginsianum* (*Ch*) since *sweet11/sweet12* double mutants showed increased resistance toward *Ch* (Gebauer *et al*., 2017). Apart from Clade III SWEETs, other clades of SWEETs also play negative roles in plant-pathogen interaction. For example, the knockout of *AtSWEET4*, encoding a Clade II Glc transporter, increased Arabidopsis resistance to necrotroph *B. cinerea*, implying AtSWEET4 may benefit fungal growth through facilitating acquisition of hexose from the host cells by the pathogen (Chong *et al*., 2014).

It is worth noting that some SWEETs could also function as resistance genes. In Arabidopsis, mutation in *AtSWEET2*, a Clade I SWEET, resulted in an increased susceptibility to root necrotrophic pathogen *Pythium irregulare* (Chen *et al*., 2015a). This is not surprising since *AtSWEET2* is responsible for Glc sequestration into vacuoles in Arabidopsis roots, as shown by the finding that the *Atsweet2* mutant displayed an increased Glc efflux from vacuole into cytoplasm and subsequently increased exudation of Glc into rhizosphere for uptake by *P. irregulare* (Chen *et al*., 2015a). Intriguingly, silencing of PM-localized *IbSWEET10*, a Clade III SWEET, resulted in susceptibility to hemibiotroph *Fusarium oxysporum* f. sp. *Batatas* in sweet potato, while its over-expression increased resistance (Li *et al*., 2017). These findings are clearly in contrast to those in rice and cotton (Chen *et al*., 2010; Cox *et al*., 2017), in which Clade III SWEETs contributed to susceptibilities.

In Arabidopsis, the Clade III AtSWEET11 and12 are specifically expressed in phloem parenchyma cells and xylem vessel-associated cells of floral stems (Chen *et al*., 2012; Le Hir *et al*., 2015). The double mutant of AtSWEET11 and AtSWEET12 showed not only reduced area of both phloem and xylem poles in floral stem, but also changed chemical composition of cell walls in vascular tissue, including reduced pectin and cellulose content, due to impaired sugar delivery from phloem to the adjacent vascular tissues (Le Hir *et al*., 2015). Considering that plants usually strengthen the cell wall as a defense strategy upon infection.
through the deposition of wall chemicals including callose, pectin and lignin (Rodriguez-Galvez and Mendgen, 1995), this finding from Arabidopsis (Le Hir et al., 2015) may help us to understand why IbSWEET10, an ortholog of AtSWEET11 or 12, could act as a resistance factor in sweet potato roots against to vascular pathogen Fusarium oxysporum, which usually penetrate the root vasculature and then spread upwards (Keane, 2012). It is possible that the down-regulation of IbSWEET10 could compromise cell wall integrity in the vascular tissues by reducing the deposition of pectin and cellulose, leading to reduced resistance to Fusarium oxysporum. Analyses of stem cross sections indeed showed that IbSWEET10-RNAi lines exhibited destroyed pith structure after infection, which did not happen in WT plants (Li et al., 2017).

Studies on the role of SWEETs in plant-pathogen interaction were largely carried on that with hemibiotroph/necrotroph, and little is known about the potential roles of SWEETs in response to biotroph infection (Table 2). Furthermore, the reported studies were mostly conducted on Clade III SWEETs with much less information on the involvement in pathogenicity of SWEETs from the other clades. Thus, there are huge potentials to explore along these lines.

**Elusive roles of STPs in plant-pathogen interactions**

In most cases, plant tissues accumulate soluble sugars in the infected regions (Kocal et al., 2008). However, pathogen-induced expression of CWINs and SWEETs generally does not accompany with an increase in apoplasmic sugar content (Yamada et al., 2016). One possible explanation is that the STPs are upregulated in parallel to retrieve apoplasmic sugars back to the host cells (Fotopoulos et al., 2003; White and Frommer, 2015; Ding and Jones, 2017).

STPs characterized thus far are all PM-localized H⁺/hexose symporters to facilitate energy-dependent hexose import into plant cells (Doidy et al., 2012; Pommerrenig et al., 2020). When compared to that in the WT Arabidopsis plants elicited by the flg22 peptide of bacterial flagellin, a higher apoplasmic Glc levels was observed in leaves of elicited stp1stp13 double mutant, which exhibited an aggravated susceptibility to bacterium Pst DC3000 (Yamada et al., 2016), demonstrating a role of STP in reducing apoplasmic sugar level and in conferring resistance. Further, an over-expression of AtSTP13 enhanced Arabidopsis resistance to necrotrophic fungus B. cinerea, whereas the mutation of AtSTP13 resulted in an opposite effect, implying that STP13 may improve resistance by fueling plant defense response and depriving the fungus of sugar nutrient (Lemonnier et al., 2014).

However, STPs could also play a negative role in defense against biotrophic fungi. For example, Lr67res is a protein derived from the mutation of its wild-type version Lr67sus, a
STP13 homolog from wheat, in two amino acids (Arg144Gly and Leu387Val) and showed the loss of Glc uptake activity in yeast cells (Moore et al., 2015). Wheat lines with Lr67res had a broad-spectrum resistance to both biotrophic fungi including rust pathogens (i.e. leaf rust Puccinia triticina, stripe rust P. striiformis and stem rust P. graminis) and powdery mildew pathogen Blumeria graminis. This broad resistance is potentially resulted from triggering a plant defense response via an increased sugar signaling due to Glc accumulation in leaf apoplasm (Moore et al., 2015). A recent study from the same team further shown that an ectopic over-expression of wheat Lr67res in barley (Hordeum vulgare) increased resistance to leaf rust (Puccinia hordei) and powdery mildew (Blumeria graminis) due to higher expression of PR gene (Milne et al., 2019). Consistently, knockdown of TaSTP6, another STP member in wheat, increased resistance to rust pathogen P. striiformis, whereas an ectopic expression of TaSTP6 in Arabidopsis raised susceptibility to fungal pathogen powdery mildew (Huai et al., 2019). Overall, these findings indicate that plant STPs generally promote proliferation of biotrophic fungi during infection (Fig 2; Table 3).

Possible involvement of SUTs in plant-pathogen interactions

Most of SUTs function as H+-coupled symporters to move Suc across plasma membranes into cytosol (Doidy et al., 2012). Similar to STPs, the expression of SUTs is also generally up-regulated by pathogen infection e.g. in maize infected by Colletotrichum graminicola (Vargas et al., 2012) and cucumber against cucumber mosaic virus (CMV) (Gil et al., 2011). However, the exact roles exerted by SUTs in plant-pathogen interaction remain unclear. It was proposed that SUT is unlikely the main transporters responsible for the retrieval of apoplastic Suc due to (i) the energy-expansive but seemingly futile cycle of Suc uptake and release actioned by SUT and SWEET, and (ii) its low affinity to Suc and acidic pH optimum (pH 5-6), when considering the alkalized apoplastic environment (pH>6) during infection (see Pommerrenig et al., 2020). However, a study on arbuscular mycorrhiza fungi indicates that transgenic tomato with reduced expression of SISUT2 exhibited an increased mycorrhization owing to the weakened Suc retrieval from the apoplasm back to the host cells (Bitterlich et al., 2014), implying that SUT may act like STPs to regulate plant-pathogen interaction by modulating Suc availability in the host apoplasm.
Roles of sugar transporters in defense are dependent on the ways pathogens obtain sugars

It is clear that sugar transporters influence the outcome of plant-pathogen interaction primarily through mediating sugar allocation between host plants and pathogens (Huai et al., 2019). Delivery of sugars to the absorbing site of pathogens would inevitably benefit pathogen proliferation. Bacteria (regardless of their lifestyles) and necrotrophic/hemibiotrophic fungi mainly uptake sugar from host apoplastic space (Lemoine et al., 2013; Xin et al., 2016). Thus, it is not surprising that plant sugar importers (STPs and Clade I SWEET) and exporters (Clade II and III SWEETs) act as resistance and susceptibility factors, respectively, during infection by bacteria and necrotrophic/hemibiotrophic fungi through reducing or increasing sugar availability in the apoplasms accordingly (Table 2 and 3; Fig. 2).

Different from pathogenic bacteria and necrotrophic/hemibiotrophic fungi, biotrophic fungi such as powdery mildew, rust fungi and Ustilago maydis acquire sugar not from host cell apoplast, but from specialized apoplast named extrahaustorial matrix (EHMx) via haustoria (Roberts et al., 1993; Wahl et al., 2010; Chang et al., 2017). EHMx is bordered by haustorial and host plasmalemma and separated from bulk apoplast due to the physical fusion of both plasmalemma at ‘neckband’ (Chang et al., 2017; Fig. 2). Before entering pathogenic cells, sugar must be first transported into host cells and then released into EHMx for the uptake by microbes (Bezrutczyk et al., 2018). In this scenario, plant PM-localized sugar importers (STPs) may act as susceptibility factors to biotrophic fungi through facilitating sugar accumulation in the intracellular space of infected host cells, where sugars are subsequently exported into EHMx for the uptake by the pathogen (Table 3 and Fig. 2). This model explains why sugar importer STPs act as resistance factors to bacteria and necrotrophic/ hemibiotrophic fungi, but as susceptibility factors to infection by biotrophic fungi.

Overall, the available evidence shows that specific roles of sugar transporters in plant-pathogen interaction are dependent on their cellular location in sugar partitioning between pathogens and host cells. If it helps pathogen to gain sugar nutrient, these sugar transporters act as susceptibility factors. Otherwise, they contribute to resistance (See the model depicted in Fig. 2). This model accommodates almost all available published studies, with one exception in which the silence of IbSWEET10 by RNAi technique, a putative PM-localized Clade III Suc exporter, reduced, rather than increased, the resistance to hemibiotrophic
fungus *Fusarium oxysporum* (Li *et al*., 2017; Table 2) that resides at vascular tissues (Yadeta and Thomma, 2013). The decreased resistance can be explained by the blocked development of vasculature in the RNAi plants as revealed by analyses on the stem cross sections (Li *et al*., 2017), possibly due to reduced sugar delivery from phloem to the surrounding vascular tissue by decreased SWEET expression (Le Hir *et al*., 2015). Although, one cannot exclude the possibility that the RNAi-mediated silencing may also inhibit the growth of *Fusarium oxysporum*, the available evidence suggests that the decreased resistance in the RNAi sweet potato more likely results from compromised vascular development in the host than that on the fungal growth. It remains to be verified if this is the case and whether it is a general phenomenon for SWEETs to act as resistance factors in plant defense against vascular pathogens.

**Sugar-mediated plant response to viral infection**

In comparison with plant-bacterial and -fungal interactions, host response to viral infection exhibited some similarities as well as differences. For instance, apoplastic expression of yeast-derived INV increased tobacco resistance to potato virus Y (Herbers *et al*., 1996). Pertinently, silence of hexose/H⁺ symporter *LeHT1*, a PM-located STP in tomato (McCurdy *et al*., 2010), increased susceptibility to Tomato Yellow Leaf Curl Virus (TYLCV, Eybishtz *et al*., 2010; Sade *et al*., 2013). The cases above suggest positive roles of CWIN and STP in resistance to virus (Table 1 and 3). Like biotrophic fungi, virus also feeds on living plant tissue and can be considered as obligate biotrophs (Shapiro *et al*., 2013; Gullner *et al*., 2017). However, these findings do not appear to fit the hypothesis discussed previously that CWINs and STPs promote the growth of biotrophic fungi and bacteria (Table 1 and 3).

Different from pathogenic bacteria, fungi or oomycete which mainly reside at intercellular space, virus lives within the cytoplasm of the host cells and spreads from cell to cell through plasmodesmata (PD), an intercellular and membrane lined cytoplasmic channel (Eybishtz *et al*., 2010; Nassem *et al*., 2017). In this scenario, it is unlikely for STPs to block virus infection by sequestering sugars to starve virus as they do in dealing with fungal and bacterial infection. Thus, different mechanisms must be employed by CWINs and STPs to mediate resistance to virus.

Several studies indicate an inverse relationship between PD opening (symplasmic pathway) and the expression/activity of sugar transporters. For example, in the single-celled cotton fiber, there was little or no expression of GhSUTs and Clade III GhSWEETs when PD was open early in elongation, while an increased expression of these transporters was
observed when PD was closed during the late stage of fiber elongation (Ruan et al., 2001; Zhang et al., 2017). Furthermore, callose-induced closure of PD led to an increased and prolonged expression of GhSUTs and Clade III GhSWEETs (Zhang et al., 2017). An inverse correlation has also been observed between CWIN activity and PD gating. During fruit development of Chinese jujube, for instance, phloem unloading occurs apoplasmically at both early and late stage, but symplasmically at the middle phase, which correlates with high, low and high CWIN activity in the respective stages (Nie et al., 2010). Transgenic evidence also supports this inverse relationship in other systems. An ectopic expression of yeast INV in the apoplasm of tobacco led to the arrest of PD development in mature leaves (Ding et al., 1993). Thus, it appears that higher expression of CWINs and sugar transporters (STP) may block virus infection by disrupting PD development or function, which could explain why CWIN and STP play positive, rather than negative roles, in plant resistance to virus (Fig. 1). The molecular basis underlying CWIN- or STP-mediated regulation over PD in response to viral infection remains to be determined. One possibility is that enhancing CWIN and STP activity could generate more Glc for callose deposition to block PD aperture and hence the cell-to-cell spread of virus.

**The forgotten side: roles of microbial INV and sugar transporters**

The final outcome of plant-pathogen interaction is determined by factors from both sides. However, studies on roles of sugars in response to pathogen attack have mostly focused on the host with little attention paid to the pathogen side as how the latter may manipulate their own sugar uptake and metabolic systems to win the tug-of-war with the host for sugar resource.

Most pathogens absorb sugars from the host apoplasm in the form of hexose (mainly Glc), rather than Suc (Tetlow and Farrar, 1992; Bisson et al., 1993; Sutton et al., 1999; Talbot, 2010; Veillet et al., 2016; Julius et al., 2017). To facilitate the utilization of SWEET-exported Suc, many pathogenic microbes secrete INV into the host cell wall to hydrolyze Suc into hexose, which is then taken up by pathogens through their own hexose transporters (HXTs, Parrent et al., 2009). INV gene in biotrophic pathogens was first identified from rust fungus *Uromyces fabae* (Voegle et al., 2006), in which Suc derived from the host cells is hydrolyzed by the rust INV, INV1p, in the EHMx followed by the uptake of the resultant Glc and Fru by fungal HXT localized in haustoria (Voegle et al., 2001; Voegle and Mendgen, 2011). The fungal biotroph *P. striiformis*, the causal agent of wheat stripe rust, secretes abundant INV (PsINV) into the host apoplasm during its invasion, and silence of
PsINV gene inhibited fungal growth, hence reducing virulence (Chang et al., 2017). Given that *P. striiformis* only express HXT, but not Suc transporter (Cantu et al., 2011; Zheng et al., 2013), it can be inferred that PsINV plays major roles in the fungal pathogenicity by hydrolyzing Suc into hexose for uptake by the fungal HXT (Chang et al., 2017).

INV and HXT genes are also expressed in necrotrophic/hemibiotrophic fungi. For example, necrotroph *B. cinerea* has one extracellular INV gene and three HT genes, which are induced during their infection to Arabidopsis (Veillet et al., 2016). Five HXTs (CgHXT1 to 5) have also been identified in hemibiotrophic fungus *Colletotrichum graminicola* causing stem rot and leaf anthracnose in maize. Among them, the expression of CgHXT1 and CgHXT3 were induced at the biotrophic stage of its infection, whereas CgHXT2 and CgHXT5 were up-regulated at its necrotrophic stage (Lingner et al., 2011). In some cases, induced extracellular INV activity in the infected plant tissue is entirely attributable to the necrotrophic fungus, rather than the host plant (Jobic et al., 2007; Box 1).

Similar to fungi, many pathogenic bacteria also express extracellular INV and sugar transporters (Ziegler and Albersheim, 1977; Vásquez-Bahena et al., 2006). However, bacteria appear very different from the fungal counterpart in their mode of obtaining sugars from the host. Some transcriptome analyses indicate no induction of bacterial INVs and sugar transporters during invasion into host plants, for example, in the interactions of *Dickeya dadantii* and Arabidopsis and *Xanthomonas axonopodis* and soybean (Chapelle et al., 2015; Chatnaparat et al., 2016). These observations suggest that pathogenic bacteria may obtain sugars for their growth not through changing their own Suc degradation and sugar transport system, but possibly through modifying or hijacking the counterparts of the host cells. For instance, pathogenic bacterium Xcv secretes T3SS-dependent effector (XopB) to block the induction of host CWIN for its virulence (Sonnewald et al., 2012). In rice, as discussed earlier, Xoo secretes T3SS-dependent effector (PthXo1) to bind the promoter of Clade III SWEETs OsSWEET11 and OsSWEET14 to activate their transcriptional activity for provision of Suc to fuel its infection (Chen et al., 2010). Indeed, the type III secretion mutant (ΔhrcU) of Pst DC3000 failed to induce the expression of three *AtSWEETs* in Arabidopsis, thereby reducing pathogenicity (Chen et al., 2010).
There are a few of pathogens that can directly uptake and utilize Suc as the major carbon source without the need of Suc degradation into hexose by plant and/or microbial INV in apoplasm. Biotrophic fungus *Ustilago maydis*, causing corn smut disease in maize, expresses a Suc-specific sugar transporter UmSrt1, which is PM-localized and expressed only after successful invasion of the maize tissues (Wittek et al., 2017, Fig 2); UmSrt1 shows a higher affinity to Suc than maize Suc transporter ZmSUT1 and thus possibly outcompetes ZmSUT1 during the battle for limited intercellular Suc (Wahl et al., 2010; Wittek et al., 2017). Deletion of UmSrt1 using a PCR-based gene replacement system strongly reduced the virulence of *U. maydis*, indicating a central role of this fungal protein in maize/*U. maydis* interaction (Wahl et al., 2010). For Suc-favoring pathogens, it might be advantageous for them to uptake Suc as carbon source, as this step bypasses Suc hydrolysis, thus potentially blocking the activation of plant defense responses, since it is generally the hexose, not Suc, that triggers plant defense response (Wahl et al., 2010). Under this situation, manipulation of the host CWIN activities may differentially affect the proliferation of Suc-favoring or hexose-favoring pathogens through modulating the availability of apoplastic Suc and hexose. It is clear that more investigations on the mode of action of microbial CWINs and transporters are necessary for better understanding how sugar metabolism and transport from each side determine the final outcome of plant-pathogen interactions.

**Conclusions and future directions**

Our analyses showed that specific regulations of plant-microbe interaction by CWIN, SWEET and STP are conditioned by a given pathosystem involved. Here, the roles of CWIN in host response to pathogen attack are largely dependent on the lifestyle of pathogenic fungi and bacteria. Similarly, the nature of SWEET/STP-mediated plant-pathogen interaction varies, depending on the cellular sites from which pathogens acquire sugar nutrients. Furthermore, CWIN and SWEET/STP modulate plant defense against virus spread through, at least in part, impacting on PD formation or aperture.
Finally, we call an attention to much needed research on the pathogen-originated CWINs and sugar transporters as these microbial players could exert significant influences on plant-pathogen interactions and thereby shaping the final outcome of the interaction.

Looking ahead, while extensive studies have been performed to investigate how CWINs affect plant-pathogen interaction, little is known about effects of the other Suc-degrading enzymes (i.e. VIN, CIN and Sus) on plant defense. It will also be of significance to determine whether it is a general phenomenon for SWEETs to act as resistance factors, instead of susceptibility factors, in defense against vascular pathogens (Li et al., 2017; Table 2). Equally, there is a lack of studies on the roles of SWEETs in plant-biotroph interactions, despite available information on their roles in responding to hemibiotrophs/necrotrophs (Table 2). Most notably, although sugar signaling has long been proposed to be involved in defense response against pathogens (Rolland et al., 2006; Wingler and Roitsch, 2008), the potential signaling roles of CWIN and sugar transporters in this complex interaction remain elusive. One challenge is to experimentally dissect their roles in signaling from that of provision of C nutrients. Using reporter genes or sensors for sugar status, coupled with tissue or cell-specific expression analyses may be a promising approach to tackle this issue as recently demonstrated on CWIN-mediated signaling role in ovule initiation (Liao et al., 2020) and on control of cytosolic sugar homeostasis by tonoplast sugar transporters (Zhu et al., 2021).

Plant defence against pathogen attack is further complicated by abiotic stresses such as drought, heat (Pandey and Senthil-Kumar, 2019) and an increased CO₂ concentration (Zhang et al., 2015). The impact of these factors on defence is dependent on the pathogen involved and the frequency and the intensity of individual abiotic stress that the host plants encounter. Noteworthy is that the effects of combined abiotic stresses on plant-pathogen interaction appear to be more dramatic than single abiotic stress. For example, combined stress of heat and drought made
Arabidopsis plants more susceptible to infection by *Turnip mosaic virus* (TuMV) as compared to that under the single stress of either heat or drought (Prasch and Sonnewald, 2013). To this end, elevation of CWIN activity by silencing its inhibitor gene (Jin *et al*., 2009) activated the expression of PR genes in tomato ovaries (Ru *et al*., 2017) and improved fruit set under heat stress (Liu *et al*., 2016), indicating potentials in improving tolerance to both abiotic and biotic stresses by manipulating sugar metabolism and signaling. It remains to be elucidated how INVs and sugar transporters may regulate plant-pathogen interactions differently under abiotic stresses such as heat, cold and drought or a combination of them, as compared to that under optimal condition. With the increasing atmospheric CO₂ level, global warming-associated incidents of abiotic stresses are predicted to be more frequent and severer. It has thus become increasingly urgent to study plant-pathogen interaction in the context of abiotic stress, which will provide valuable insights for improvement of crop performance amid Climate Change.

Finally, although beyond the scope of this review, it is recognized that sugar allocation is also central to plant defence against pests (Rehill and Schultz, 2003; Zinkgraf *et al*., 2016). In this context, transgenic evidence suggests that upregulation of INV may enhance plant tolerance to insect herbivores. For instance, suppression of CWIN activity in tobacco compromised tolerance to simulated herbivory (Ferrieri *et al*., 2015), with similar phenotype observed in VIN- or CIN- knockout Arabidopsis mutants (Siddappaji *et al*., 2015). More recently, VST1, a phloem-expressed tonoplast transporter for unloading of Suc and Glc in watermelon was found to be induced by aphids and loss of VST1 via genome editing reduced aphid setting and honeydew production in young leaves of the mutant through blocking sugar supply in phloem sap to aphids (Li *et al*., 2021, Preprint). Clearly, great potentials exist to better understand sugar metabolism and transport for increasing resistance to not only pathogens but also pests.
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Author contribution

YHL and YLR conceived the project. YHL and YLR wrote the manuscript with inputs from YHS.

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Table 1: Contrasting roles of cell wall invertase (CWIN) in plant resistance to pathogens with different lifestyles

| Pathogen                        | Lifestyle  | Role in plant defense | Host                | Reference          |
|---------------------------------|------------|-----------------------|---------------------|--------------------|
| *Phytophthora nicotianae* (Oomycete) | hemibiotrophic | positive              | Tobacco source leaf | Essmann *et al.*, 2008 |
| *Xanthomonas oryzae pv. oryzae* (Xoo, Bacterium) | hemibiotrophic | positive              | Rice source leaf | Sun *et al.*, 2014 |
| Magnaporthe oryzae (Fungus)    | hemibiotrophic | positive              | Rice source leaf | Sun *et al.*, 2014 |
| Plasmodiophora brassicae (Fungus) | biotrophic | negative              | Arabidopsis root | Siemens *et al.*, 2011 |
| Xanthomonas campestris pv. vesicatoria (Xcv, Bacterium) | biotrophic | negative              | Tomato source leaf | Kocal *et al.*, 2008 |
| *Potato virus Y* (Virus)        | biotrophic | positive              | Tobacco source leaf | Herbers *et al.*, 1996 |

*CWINs may employ unique plasmodesmata-related mechanisms to regulate plant resistance to virus.*
### Table 2 Roles of SWEETs in defense are coupled with the ways pathogenic microbes absorb nutrients

| Pathosystem                        | Sugar absorbing site | Sugar transporter | Roles in defense | Function of SWEETs | References                        |
|-----------------------------------|----------------------|------------------|------------------|-------------------|----------------------------------|
| **Necrotrophic/hemibiotrophic fungi** |                      |                  |                  |                   |                                  |
| *Botrytis cinerea* /Arabidopsis leaf | apoplasm             | **AtSWEET4** (Clade II, PM) | negative         | Glc exporter      | Chong *et al*., 2014            |
| *Rhizoctonia solani* /Rice sheath | apoplasm             | **OsSWEET11** (Clade III, PM) | negative         | Suc exporter      | Gao *et al*., 2018              |
| *Colletotrichum Higginsianum* /Arabidopsis leaf | apoplasm             | **AtSWEET11/12** (Clade III, PM) | negative         | Suc exporter      | Gebauer *et al*., 2017           |
| *Fusarium oxysporum* /Sweetpotato root | apoplasm (vascular vessel) | **IbSWEET10** (Clade III, PM) | positive         | Suc exporter      | Li *et al*., 2017                |
| *Pythium irregulare* /Arabidopsis root | apoplasm             | **AtSWEET2** (Clade I, tonoplast) | positive         | Glc importer      | Chen *et al*., 2015a            |
| **Hemibiotrophic Bacteria**       |                      |                  |                  |                   |                                  |
| *Xanthomonas oryzae* pv. oryzae (Xoo) /Rice leaf | apoplasm             | **OsSWEET11/13/14** (Clade III, PM) | negative         | Suc exporter      | Chen *et al*., 2010; Zhou *et al*., 2015; Blanvillain-Baufumé *et al*., 2017 |
| *Xanthomonas citri* subsp. malvacearum (Xcm) /Cotton leaf | apoplasm             | **GhSWEET10** (Clade III, PM) | negative         | Suc exporter      | Cox *et al*., 2017              |

PM: Plasma membrane;
Table 3 Roles of hexose importer STPs in defense are dependent on the ways pathogenic microbes acquire nutrients

| Pathosystem                              | Sugar absorbing site | Sugar transporter | Roles in defense | References          |
|------------------------------------------|----------------------|------------------|------------------|---------------------|
| **Necrotrophic/hemibiotrophic fungi**    |                      |                  |                  |                     |
| *B. cinerea* /Arabidopsis leaf           | apoplasm             | AtSTP13          | positive         | Lemonnier *et al*., 2014 |
| **Bacteria**                             |                      |                  |                  |                     |
| *Pst DC3000* /Arabidopsis leaf           | apoplasm             | AtSTP1/13        | positive         | Yamada *et al*., 2016 |
| **Biotrophic fungi**                      |                      |                  |                  |                     |
| **Rust** (*P. triticina, P. striiformis, P. graminis*) and powdery mildew *B. graminis* /Wheat leaf | EHMx                 | TaSTP13          | negative          | Moore *et al*., 2015 |
| **Rust** *P. hordei* and powdery mildew *B. graminis* /Barley leaf | EHMx                 | TaSTP13          | negative          | Milne *et al*., 2019 |
| **Stripe rust** *P. striiformis* /Wheat leaf | EHMx                 | TaSTP6           | negative          | Huai *et al*., 2019 |
| **Virus**                                |                      |                  |                  |                     |
| Tomato yellow leaf curl virus (TYLCV) /tomato leaf | N/A                  | LeHT1            | positive          | Eybishtz *et al*., 2010 |

EHMx: Extrahaustorial matrix; PM: Plasma membrane;
Figure legend

Figure 1. A hypothetical model illustrating how cell wall invertase (CWIN) and sugar transport protein (STP) differentially regulate plant resistance to different pathogens.

Plant CWINs inhibit PCD incidence and SA signaling, and simultaneously promote JA signaling, which collectively contributes to susceptibility to biotrophic pathogens but increases plant resistance to necrotrophic/hemibiotrophic pathogens. Similar to biotrophic fungi and bacteria, virus also feeds on living tissues. However, in response to viral infection, CWINs and sugar transporters (SWEETS, STPs and SUTs) appear to enhance resistance to virus, possibly through inhibiting the formation or aperture of plasmodesmata (PD) via modulating callose deposition around PD.

Figure 2. A schematic model on different roles of plant sugar transporters in response to pathogen infection and the involvement of microbial INV and sugar transporters in plant-pathogen interaction.

Clade II and III SWEETs export Glc and Suc into plant apoplasm, respectively. Glc is then directly taken up into bacteria and necrotrophic/hemibiotrophic fungi during the initial infection phase via their own plasmalemma-localized hexose transporters (HXT), whereas Suc is firstly hydrolyzed into Glc and Fru by plant CWIN or pathogen-secreted INV before being imported into the pathogens. Consequently, these SWEETs promote bacterial and necrotrophic/hemibiotrophic fungal growth in the apoplasmand. On the contrary, Clade I SWEETs could sequestrate cytosolic Glc into plant cell vacuoles, thereby reducing Glc availability in the apoplasmand, which starves necrotrophic fungi.

For the plant STPs, they facilitate hexose uptake into plant cells, which is subsequently released into extrahaustorial matrix (EHMx) for the uptake by biotrophic fungi via fungal HXT and thus promoting fungal
infection. On the other hand, however, STPs reduce Glc level at apoplasm, which inhibits the development of bacteria and necrotrophic/hemibiotrophic fungi. Plant SUTs uptake apoplastic Suc into plant cells and are commonly induced by pathogen infection. Studies from mycorrhiza fungi indicate that SUT (i) may promote the development of biotrophic fungi through increasing intracellular sugar pool for subsequent import to EHMx and uptake by Suc transporters such as UmStrt1 (ii) could inhibit the development of bacteria and necrotrophic or hemibiotrophic fungi by limiting Suc availability in the apoplasm of the plant cells. Note: NB, neckband.

Data availability statement

All data supporting the findings of this study are available within the paper and the literatures cited therein.
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Figure 1. A hypothetical model illustrating how cell wall invertase (CWIN) and sugar transport protein (STP) differentially regulate plant resistance to different pathogens.

Plant CWINs inhibit PCD incidence and SA signaling, and simultaneously promote JA signaling, which collectively contributes to susceptibility to biotrophic pathogens, but increases plant resistance to necrotrophic/hemibiotrophic pathogens. Similar to biotrophic fungi and bacteria, virus also feeds on living tissues. However, in response to viral infection, CWINs and sugar transporters (SWEETS, STPs and SUTs) appear to enhance resistance to virus, possibly through inhibiting the formation or aperture of plasmodesmata (PD) via modulating callose deposition around PD.
Figure 2. A schematic model on different roles of plant sugar transporters in response to pathogen infection and the involvement of microbial INV and sugar transporters in plant-pathogen interaction.

Clade II and III SWEETs export Glc and Suc into plant apoplast, respectively. Glc is then directly taken up into bacteria and necrotrophic/hemibiotrophic fungi during the initial infection phase via their own plasmalemma-localized hexose transporters (HXT), whereas Suc is firstly hydrolyzed into Glc and Fru by plant CWIN or pathogen-secreted INV before being imported into the pathogens. Consequently, these SWEETs promote bacteria and necrotrophic/hemibiotrophic fungal growth in plant apoplast. On the contrary, Clade I SWEETs could sequestrate cytosolic Glc into plant vacuoles, thereby reducing Glc availability in the apoplast, which starves necrotrophic fungi.

For the plant STPs, they facilitate hexose uptake into plant cells, which is subsequently released into extrahaustorial matrix (EHMx) for the uptake by biotrophic fungi via fungal HXT and thus promoting fungal infection. On the other hand, however, STPs reduce Glc level at apoplasm, which inhibits the development of bacteria and necrotrophic/hemibiotrophic fungi.

Plant SUTs uptake apoplasmic Suc into plant cells and are commonly induced by pathogen infection. Studies from mycorrhiza fungi indicate that SUT (i) may promote the development of biotrophic fungi through increasing intracellular sugar pool for subsequent import to EHMx and uptake by Suc transporters such as UmSrt1 (ii) could inhibit the development of bacteria and necrotrophic or hemibiotrophic fungi by limiting Suc availability in the plant apoplast.

Note: NB, neckband.