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Review Article

Physiological implications of SWEETs in plants and their potential applications in improving source–sink relationships for enhanced yield

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Summary

The sugars will eventually be exported transporters (SWEET) family of transporters in plants is identified as a novel class of sugar carriers capable of transporting sugars, sugar alcohols and hormones. Functioning in intercellular sugar transport, SWEETs influence a wide range of physiologically important processes. SWEETs regulate the development of sink organs by providing nutritional support from source leaves, responses to abiotic stresses by maintaining intracellular sugar concentrations, and host–pathogen interactions through the modulation of apoplastic sugar levels. Many bacterial and fungal pathogens activate the expression of *SWEET* genes in species such as rice and *Arabidopsis* to gain access to the nutrients that support virulence. The genetic manipulation of *SWEETs* has led to the generation of bacterial blight (BB)-resistant rice varieties. Similarly, while the overexpression of the *SWEETs* involved in sucrose export from leaves and pathogenesis led to growth retardation and yield penalties, plants overexpressing *SWEETs* show improved disease resistance. Such findings demonstrate the complex functions of *SWEETs* in growth and stress tolerance. Here, we review the importance of *SWEETs* in plant–pathogen and source–sink interactions and abiotic stress resistance. We highlight the possible applications of SWEETs in crop improvement programmes aimed at improving sink and source strengths important for enhancing the sustainability of yield. We discuss how the adverse effects of the overexpression of *SWEETs* on plant growth may be overcome.

Introduction

SWEETs are the most recently identified class of sugar transporters. SWEETs are present in all kingdoms of life, being conserved across prokaryotes and eukaryotes (Chen *et al.*, 2010; Jia *et al.*, 2017). The eukaryotic SWEET proteins are predicted to have seven transmembrane domains (Anjali *et al.*, 2020). Phylogenetically, plant SWEETs are divided into four clades (clades I, II, III and IV) (Chen *et al.*, 2010; Yuan and Wang, 2013). They function in the control of plant growth and defence, facilitating the long-distance sugar transport from source (leaves) to sink (such as seeds and flowers) organs, with crucial roles in, among others, senescence, nectar secretion, hormone signalling, pathogenesis and abiotic stress responses (Figure 1) (Breia *et al.*, 2021; Chardon *et al.*, 2013; Chen *et al.*, 2010, 2012; Jeena *et al.*, 2019; Mathan *et al.*, 2021a; Sosso *et al.*, 2015; Wang *et al.*, 2019a). Of the many functions of SWEETs in plant biology, their critical roles in partitioning photosynthates to sink organs such as seeds and in pathogenicity are perhaps the most important because they can directly influence crop yield.

The transport of photosynthates from source leaves to sink tissues is an essential feature of the whole-plant source–sink balance that requires both symplastic and apoplastic phloem loading mechanisms. It is widely assumed that the pre-phloem transport of photoassimilates from mesophyll cells to phloem parenchyma cells occurs predominantly through plasmodesmata, which create a symplastic route (Liesche and Schulz, 2012; Miras *et al.*, 2022; Schulz, 2015). In species such as maize, potato and *Arabidopsis* that use apoplastic phloem loading mechanism, sucrose from phloem parenchyma cells is exported out of the cytoplasm into the apoplast/cell wall space by SWEETs (Abelenda *et al.*, 2019; Bezrutczyk *et al.*, 2018a; Chen *et al.*, 2012). Sucrose is then actively taken up from the apoplast by sucrose/H^+ symporters known as sucrose transporters (SUTs, also called SUCs), which load sucrose into the sieve element–companion cells complex for translocation to distant sink tissues (Gottwald *et al.*, 2000; Riesmeier *et al.*, 1994; Slewinski *et al.*, 2009). SWEETs and SUTs also function in sugar unloading in sink organs such as seeds (Scofield *et al.*, 2002; Wang *et al.*, 2021; Yang *et al.*, 2018).

Plant pathogens require a supply of sugars from the host cells to support their growth and proliferation. The SWEET proteins play a vital role in the virulence strategies of many bacterial and fungal pathogens in species such as *Arabidopsis*, rice and cotton (Chen *et al*., 2010; Chu *et al*., 2006; Cox *et al*., 2017). Bacterial and fungal pathogens activate the expression of specific *SWEETs* to facilitate sugar secretion from cells at the sites of infection and ensure propagation (Chen *et al*., 2010; Gupta *et al*., 2021). Many bacterial pathogens, e.g. *Xanthomonas oryzae pv. oryzae* (*Xoo*) and *X. citri subsp. Malvacearum*, attack hosts, such as rice and cotton, by secreting effector molecules known as transcription activator-like effector (TALE) proteins via the type III secretion system (TIIISS) (Antony *et al*., 2010; Cox *et al*., 2017; Zhou *et al*., 2015). TALEs are transcription factors that activate the expression of their cognate *SWEET* genes by binding to the effector-binding element (EBE) sites present in the promoters of the *SWEET* genes (Figure 2)(Antony *et al*., 2010; Boch *et al*., 2009; Chen *et al*., 2010; Moscou and Bogdanove, 2009).

Current concepts suggest that genetic manipulation of *SWEETs* can result in improved partitioning of photosynthates, which in turn can lead to increased yield and enhanced resistance to pathogens. However, recent reports concerning the overexpression of clade III *SWEETs* to increase photosynthate translocation to sink tissues have shown that plant growth is adversely affected (Abelenda *et al*., 2019; Eom *et al*., 2015; Fatima and Senthil-Kumar, 2021; Gao *et al*., 2018; Kim *et al*., 2020; Singh *et al*., 2021; Yuan *et al*., 2009). Surprisingly, the transgenic plants overexpressing the clade III *SWEETs* showed increased tolerance to pathogens, which are known to induce these *SWEET* genes (Fatima and Senthil-Kumar, 2021; Kim *et al*., 2020; Singh *et al*., 2021; Yuan *et al*., 2009). Such findings suggest that sugar transport and pathogenesis are tightly coupled via SWEETs, at least in cases where the same *SWEET* genes regulate both processes. Manipulation of SWEETs, therefore, has implications for plant growth as well as pathogen resistance.

Here, we review the role of SWEETs in plant pathogenesis and carbohydrate translocation in different tissues and their potential for improving source–sink relationships to enhance yield. We consider the emerging roles of SWEETs in abiotic stress tolerance, evolution of C4 photosynthesis and highlight the new knowledge gained from overexpression studies concerning how clade III SWEETs can simultaneously modulate plant growth and susceptibility to disease.

SWEETs in pathogenic and symbiotic interactions of plants

The rice genome contains 22 *SWEET* genes, which show distinct tissue-specific expression patterns (Wu *et al*., 2022; Yuan *et al*., 2014; Yuan and Wang, 2013). Of these, activation of six clade III *SWEETs*, which have sucrose transport activity, namely *OsSWEET11/Os8N3/Xa13*, *OsSWEET11b*, *OsSWEET12*, *OsSWEET13/Xa25*, *OsSWEET14/Os11N3* and *OsSWEET15*, results in the development of BB disease symptoms triggered by *Xoo*. Hence, these *SWEETs* are called 'susceptibility genes' for *Xoo* (Streubel *et al*., 2013; Wu *et al*., 2022). Only *OsSWEET11*, *OsSWEET13* and *OsSWEET14* are targeted by at least one of the TALEs secreted by *Xoo*, leading to infection (Antony *et al*., 2010; Yang *et al*., 2006; Zhou *et al*., 2015). Activation of the expression of the *OsSWEET11*, *OsSWEET13* and *OsSWEET14* genes by *Xoo* enhances sucrose efflux from phloem parenchyma cells to the apoplast, a process that enhances *Xoo* growth and multiplication (Eom *et al*., 2019; Oliva *et al*., 2019). In addition, the rice OsSWEET11 interacts with the copper transporters COPT1 and COPT5 to remove copper from the xylem vessels, which are the sites of *Xoo* multiplication and disease progression (Yuan *et al*., 2010). Copper is an essential plant micronutrient used in many pesticides to inhibit *Xoo* growth. Thus, removing copper from xylem vessels via OsSWEET11 and copper transporters is another *Xoo* strategy to evade plant defences and enhance virulence (Yuan *et al*., 2010).

In addition to *Xoo*, *Rhizoctonia solani* infection induces the expression of *OsSWEET11* and *OsSWEET14* in rice leaves (Gao *et al*., 2018; Kim *et al*., 2020). The expression of a mutated inactive form of the protein (ossweet11) under the control of the *RUBISCO* promoter in rice leaves led to the formation of dysfunctional OsSWEET11 oligomers that lacked sugar transport activity. These transgenic rice plants showed improved resistance

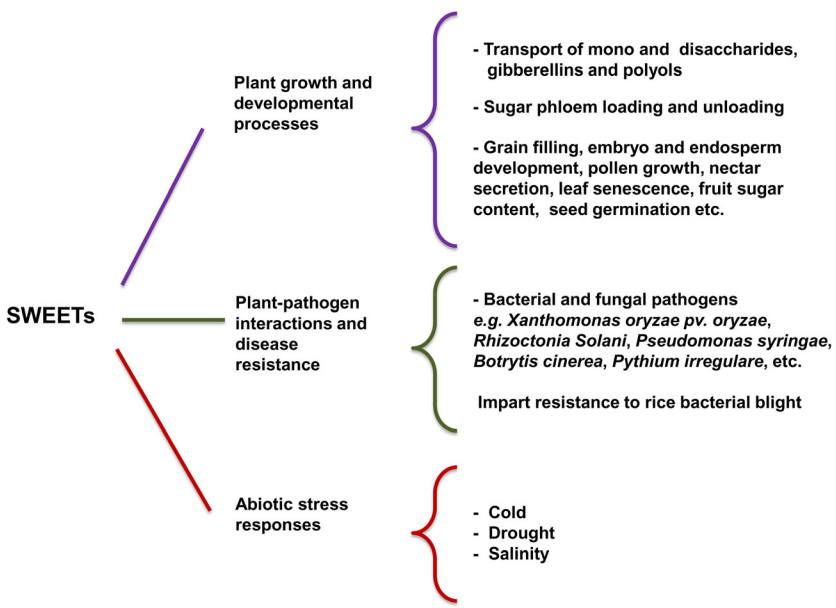

Figure 1 Different aspects of plant growth, development and physiology regulated by SWEETs.

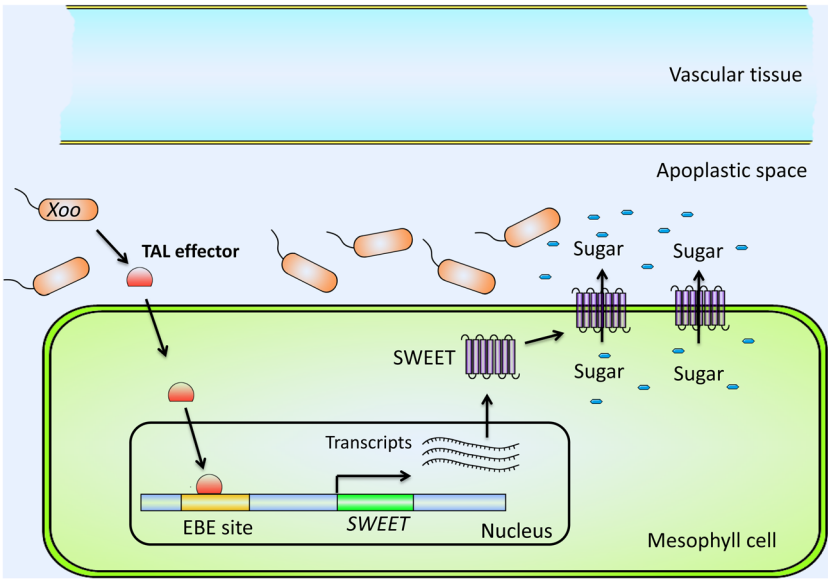

Figure 2 TAL effectors dependent activation of *SWEETs* by pathogenic bacteria. Pathogenic bacteria such as *Xanthomonas oryzae pv. oryzae* (*Xoo*), invading plant cells secrete transcription activator-like (TAL) effectors that bind to the effector-binding element (EBE) sites in the promoter regions of some *SWEET* genes to activate their expression. Increased expression of *SWEETs* results in enhanced efflux of sugars from cells to the apoplastic space that facilitates bacterial growth.

to *R. solani* with no yield penalty. The results suggest that *R. solani* induces *OsSWEET11* in rice leaves to acquire sugars for pathogenesis (Gao *et al*., 2018). Oligomerization of the SWEET proteins is necessary to form a functional pore to transport sugars. It has previously been shown that a mutated version of the SWEET protein can form oligomers with functional SWEET units and abolish sugar transport activity (Xuan *et al*., 2013).

Like rice, pathogens modulate the expression of *SWEETs* in other plant species, either in a TALE-dependent or independent manner, to gain access to host carbon resources (Chen *et al*., 2010; Gupta *et al*., 2021; Veillet *et al*., 2017). Activation of the expression of the *GhSWEET10* gene by *X. citri* subsp. *malvacearum* and the *MeSWEET10a* gene by *X. axonopodis pv. manihotis* is associated with the progression of bacterial blight in cotton and with water-soaking symptoms in cassava, respectively, suggesting that bacteria exploit them for growth and disease progression (Cohn *et al*., 2014; Cox *et al*., 2017). The induced expression of *CsSWEET1* by *X. citri* subspecies *citri* (*Xcc306*), the causal agent for citrus bacterial canker, did not lead to the characteristic symptoms of pustule formation (Hu *et al*., 2014). Interestingly, *CsSWEET1* is a homologue of *OsSWEET11* and *OsSWEET14* in rice, which are disease-susceptibility genes (Hu *et al*., 2014). In addition to *CsSWEET1*, TALEs secreted from *Xcc306* induced the expression of the *CsLOB1* (*lateral organ boundaries 1*) transcription factor that causes the symptoms of citrus bacterial canker (Hu *et al*., 2014). CsLOB1 induces the expression of many downstream genes involved in cell expansion, which causes hypertrophy resulting in pustule formation (Hu *et al*., 2014). The bacterial spot disease of pepper is caused by *X. campestris pv. Vesicatoria* (*Xcv*). This pathogen induces the expression of many *UPA* (*up-regulated by AvrBs3 effector*) genes, including *UPA20* and *UPA16*, a SWEET family protein. Like *CsSWEET1*, *UPA16* activation is not associated with hypertrophy in pepper (Kay *et al*., 2009). Activation of *UPA20*, which is a bHLH (basic helix–loop–helix) transcription factor, causes hypertrophy via the transactivation of the expansin-encoding *UPA7* gene (Kay *et al*., 2007). These results suggest that *Xanthomonas*-induced hypertrophy in pepper and citrus depends on the activation of transcription factors and downstream genes that are either directly or indirectly involved in cell expansion. The *CsSWEET1* and *UPA16* genes in citrus and pepper, respectively, may be 'collateral targets' of *Xanthomonas* infection, with as-yet-unknown significance. However, the TALE-driven activation of *CsSWEET1* and *UPA16* indicates that bacterial virulence strategies are highly complex. It has been suggested that some *UPA* genes are involved in hypertrophy-unrelated functions. For example, they can have a role in disseminating *Xcv* between plants under field conditions (Kay *et al*., 2009).

The *Arabidopsis* genome contains 17 *SWEET* genes, most of which are induced upon exposure to either bacterial or fungal pathogens (Chen *et al*., 2010; Gupta *et al*., 2021). The expression of the clade III sucrose transporters *AtSWEET10*, *11*, *12* and *15* is significantly increased when the plants are challenged with bacterial or fungal pathogens (Chen *et al*., 2010). Infection of *Arabidopsis* plants by the protist *Plasmodiophora brassicae*, the causative agent of clubroot disease in *Brassica* crops, led to the phloem-specific accumulation of AtSWEET11 and 12 proteins at the site of infection, which facilitated the delivery of sugars to the pathogen (Walerowski *et al*., 2018). The *atsweet11* single- and *atsweet11;12* double-knockout mutants had impaired sugar distribution to pathogens and were found to be less susceptible to *P. brassicae*, as demonstrated by their slower gall formation compared to their respective wild types (Li *et al*., 2018; Walerowski *et al*., 2018). These reports suggest that pathogens exploit the AtSWEET11 and 12 sugar transporters to acquire sugars for growth and propagation.

The *atsweet11;12* double-knockout mutants were resistant to the hemibiotrophic fungus *Colletotrichum higginsianum*. When the *atsweet11;12* mutants were exposed to *C. higginsianum*, the leaf starch, soluble sugars and salicylic acid (SA) contents increased (Gebauer *et al*., 2017). Reduced leaf sugar contents were negatively correlated with *C. higginsianum* infection in *Arabidopsis*. Moreover, the low availability of carbohydrates in starchless *Arabidopsis* knockout mutants of *phosphoglucomutase-1* and *ADP-glucose pyrophosphorylase1-1* resulted in reduced SA levels, which led to weakened SA-regulated defence responses and increased susceptibility to *C. higginsianum* (Engelsdorf *et al*., 2013). On the other hand, elevated carbon status of the *atsweet11;12* mutants correlated with high SA contents and the activation of SA-mediated

expression of pathogenesis-related (PR) defence genes, factors that led to increased *C. higginsianum* resistance (Gebauer *et al*., 2017). The expression of the grapevine glucose transporter *VvSWEET4* is strongly up-regulated upon infection with the necrotrophic fungus *Botrytis cinerea* (Chong *et al*., 2014). The *Arabidopsis atsweet4* knockout mutants (the closest homologue of *VvSWEET4*) were resistant to *B. cinerea* (Chong *et al*., 2014). These findings suggest that the infection-induced transcriptional activation of *VvSWEET4* increases glucose efflux from the cytoplasm to the apoplast to augment fungal growth (Chong *et al*., 2014). Overexpression of *VvSWEET4* in grapevine hairy roots conferred resistance to the necrotrophic pathogen *Pythium irregulare* (Meteier *et al*., 2019). The resistant phenotype was ascribed to the higher glucose levels in roots following infection, which provided energy for synthesizing flavonoids with antifungal properties. *VvSWEET4*-overexpressing hairy root lines had significantly higher flavanol contents than controls (Meteier *et al*., 2019).

SWEETs are bidirectional sugar transporters and can thus facilitate both the efflux and influx of sugars, depending on the sugar concentration on either side of the membrane. Expression of the tonoplast-localized glucose transporter *AtSWEET2* was induced by more than 10-fold in roots by infection with the soil-borne oomycete *P. irregulare* (Chen *et al*., 2015a). Higher levels of the AtSWEET2 protein inhibit the growth of *P. irregulare* because they can sequester more glucose in the vacuoles and limit glucose availability in the rhizosphere. The knockout mutants of *atsweet2* were more susceptible to the oomycete than the wild type and exhibited growth defects after infection (Chen *et al*., 2015a). Thus, the infection-induced activation of *SWEETs* can act either in favour or against the pathogen. In some species, such as tomatoes and bananas, down-regulation of *SWEETs* expression was observed during the pathogen attack (Asai and Kobayashi, 2016; Miao *et al*., 2017). Down-regulation of *SWEETs* might positively regulate plant defence responses by retaining and redistributing sugars for biochemical processes such as antioxidant defence reactions and producing secondary metabolites that are important under stress conditions. Decreased expression of *SWEETs* also reduces the flux of sugars to infection sites that inhibit pathogen growth. On the other hand, suppression of *SWEET* genes by pathogens might aid in their virulence as it can interfere with plant immune responses dependent on the sugar signalling defence pathway. SWEETs-mediated release of sugars can trigger signalling cascades that can induce defence genes (Bezrutczyk *et al*., 2018b). Some fungal pathogens secrete small RNA effectors that hijack the RNAi machinery of the host plant and so silence immunity-related genes (Weiberg *et al*., 2013). Further characterization of different SWEET mutants is required to understand how SWEETs modulate plant–pathogen interactions.

The activation of *SWEETs* is also observed in legumes that have nitrogen-fixing symbioses with soil bacteria (rhizobia) and with arbuscular mycorrhizal (AM) fungi, suggesting that these transporters play a role in facilitating the infection efficiency by providing sugars to the symbiotic microorganisms (Desrut *et al*., 2020; Kryukov *et al*., 2021; Manck-Götzenberger and Requena, 2016). The expression of *LjSWEET3* is up-regulated in *Lotus japonicus* following mycorrhizal or rhizobial infection (Sugiyama *et al*., 2017). Similarly, the expression of *MtSWEET1b* (a glucose transporter) and *MtSWEET11* (a sucrose transporter) is increased in *M. truncatula* root cells after contact with the AM fungus *Rhizophagus irregularis* and the soil bacterium *Sinorhizobium meliloti* respectively (An *et al*., 2019; Kryvoruchko *et al*., 2016). Overexpression of *MtSWEET1b* in *M. truncatula* roots stimulated the growth of the intraradical mycelium during AM symbiosis (An *et al*., 2019). This finding indicates that more glucose was transported to the roots of the *MtSWEET1b* overexpressors, which enhanced AM growth (An *et al*., 2019). However, mycorrhizal colonization levels were unchanged when MtSWEET1b sugar transport activity was disrupted (An *et al*., 2019). Similarly, impairment of the activities of the LjSWEET3 and MtSWEET11 transporters did not affect symbiotic N_2 fixation (Kryvoruchko *et al*., 2016; Sugiyama *et al*., 2017). These data suggest that there is functional redundancy in the sugar transporters or that alternatives of sugar supplies are available to the symbiotic root tissues.

SWEET proteins for improved source–sink relationships

SWEETs in sink tissues

SWEETs in seeds and fruits

Understanding source–sink relationships is key to improving crop productivity, resilience and nutritional quality (Foyer and Galtier, 2017). More efficient photosynthate partitioning between photosynthesizing leaves (source) and heterotrophic sink tissues, such as seeds, stems, roots and flowers, is an agreed strategy to increase photosynthesis and yield (Ainsworth and Bush, 2011). In globally important food and oilseed crops such as rice, maize and soybean, SWEETs mediate sugar partitioning to seeds, thus determining seed carbohydrate, protein and oil contents, as well as seed size (Fei *et al*., 2021; Ma *et al*., 2017; Sosso *et al*., 2015; Wang *et al*., 2020; Yang *et al*., 2018). Early farmers and breeders selected larger seeds for their high caloric value, and thus SWEETs became selection targets inadvertently throughout crop domestication (Sosso *et al*., 2015). For example, the maize and rice transporter SWEET4, which mediates the transport of hexose sugars across endosperm membrane during grain filling, was selected during domestication for larger seed sizes. Knockout mutations in *zmsweet4c* and its rice orthologue *ossweet4* resulted in defective seed filling in both maize and rice, respectively, indicating impaired import of hexoses into the endosperm (Sosso *et al*., 2015). The superior alleles of *GmSWEET10a*, *GmSWEET10b* and *GmSWEET39*, which are expressed in seeds, were selected during domestication for increased seed size and oil contents in soybean (Miao *et al*., 2020; Wang *et al*., 2020). The *GmSWEET10a* and *10b* are expressed in the seed coat, and they transport both sucrose and glucose to the embryo during development. The CRISPR/Cas9-edited *gmsweet10a* and *gmsweet10b* knockout mutants produce seeds but are smaller in size with reduced oil contents than the wild-type controls. Double-knockout mutants of *gmsweet10a* and *gmsweet10b* had a significantly reduced seed size and oil content compared to the single-knockout mutants or wild-type plants, suggesting their functional redundancy (Wang *et al*., 2020). Conversely, overexpression of *GmSWEET10a* and *10b* by genetic transformation of their full-length genomic sequences increased seed size and oil contents in transgenic soybean plants, possibly by enhancing sugar transport to the embryo (Wang *et al*., 2020). Similarly, the inbred soybean lines possessing superior *GmSWEET39* alleles had higher oil contents than their parental accessions (Miao *et al*., 2020). Two soybean *SWEET* paralogues, *GmSWEET15a* and *15b*, regulate embryo and

seed development by mediating sucrose transport from endosperm to embryo (Wang *et al.*, 2019b). Overexpression of *GmSWEET15b* in soybean resulted in increased seed sucrose contents (Wang *et al.*, 2019b).

In *Arabidopsis*, *AtSWEET11*, *12* and *15* are expressed in the seed coat and endosperm to import sucrose into the embryo to support normal seed development (Chen *et al.*, 2015b). In comparison to the single- and double-knockout mutants of *atsweet11*, *12* and *15*, the *atsweet11;12;15* triple-knockout mutants had more severe phenotypes such as retarded embryo development and lower seed weight with reduced starch and lipid contents, suggesting their functional redundancy during seed development (Chen *et al.*, 2015b). Similarly, the rice *OsSWEET11*, *14* and *15* sucrose transporters, which show distinct expression profiles in seeds, are involved in carbohydrate import into the seeds. The *ossweet11*, *14* and *15* single-knockout mutants had reduced seed weight and lowered seed starch contents because of aberrant grain filling (Antony *et al.*, 2010; Fei *et al.*, 2021; Li *et al.*, 2021; Ma *et al.*, 2017; Yang *et al.*, 2018). Endosperm development and grain filling were much more severely affected in the *ossweet11;15* double-knockout mutants due to impaired sucrose transport in seeds, indicating their redundant roles in seed development (Yang *et al.*, 2018).

The watermelon hexose transporter, ClSWEET3, the most highly expressed SWEET sugar transporter in parenchymal cells (or storage cells) during fruit development, is involved in hexose uptake from the apoplast (Ren *et al.*, 2021). The expression level of *ClSWEET3* is positively correlated with the sugar content of watermelon fruit. Overexpression of *ClSWEET3* increased the sugar contents of watermelon fruit in transgenics compared to the wild type, whereas lack of ClSWEET3 activity reduced fruit sugar contents (Ren *et al.*, 2021). It has been suggested that during watermelon domestication and evolution, ClSWEET3 was selected with other sugar-metabolizing and transporting proteins such as ClAGA2 (*C. lanatus* alkaline alpha-galactosidase 2), ClVST1 (vacuolar sugar transporter 1) and ClTST2 (tonoplast sugar transporter 2) for higher sugar content and fruit size (Ren *et al.*, 2020a, 2021). The tomato sucrose transporter *SlSWEET15*, which functions in sucrose phloem unloading and its subsequent uptake into the storage parenchyma cells in fruits, is essential for fruit development (Ko *et al.*, 2021). The grape hexose transporters *VvSWEET10* and *VvSWEET15*, which are strongly expressed during fruit ripening, were shown to regulate the sugar contents of grape berries (Ren *et al.*, 2020b; Zhang *et al.*, 2019). The high expression of many *SWEETs* is associated with fruit development and the sugar contents of the fruits of other horticultural crops also, such as tomato, banana, loquat, apple, pineapple and litchi (Feng *et al.*, 2015; Guo *et al.*, 2018; Li *et al.*, 2020; Miao *et al.*, 2017; Xie *et al.*, 2019; Zhen *et al.*, 2018). Taken together, these reports show the potential of effectively targeting the import capacity of SWEETs allowing efficient unloading of sugars into harvestable sink organs, which may be used as an important strategy for crop yield improvements.

SWEETs in male and female reproductive organs

The glucose uniporters *AtSWEET1* and *AtSWEET8* (also known as *RPG1*, *ruptured pollen grain 1*) play a role in the nutrition of growing pollen tubes in *Arabidopsis* (Chen *et al.*, 2010). In addition, *AtSWEET8* is strongly expressed in male gametophytic tissues such as microspores and the tapetum (Chen *et al.*, 2010; Guan *et al.*, 2008; Yuan and Wang, 2013). The *atsweet8* knockout mutants are male sterile, suggesting a role for *AtSWEET8* in supplying glucose for pollen nutrition (Chen *et al.*, 2010; Guan *et al.*, 2008). The *AtSWEET8* gene is also expressed in the embryo sac of female gametophytes, suggesting a role in the development of female reproductive organs (Yuan and Wang, 2013). The *AtSWEET5* (also called *VEX1*), which transports glucose and galactose, shows high expression in vegetative pollen grains, where it may serve to supply sugar to the generative cells (Chen *et al.*, 2010; Engel *et al.*, 2005; Wang *et al.*, 2022b). The tomato *SlSWEET5* is expressed at high levels in stamens, where it functions in apoplastic hexose import for the development and maturation of pollen (Ko *et al.*, 2022). The *Arabidopsis* AtSWEET13 and 14 sucrose transporters are involved in gibberellic acid (GA) transport, which is an important factor in male fertility (Kanno *et al.*, 2016). The *atsweet13;14* double-knockout mutants with defective GA transport showed delayed anther dehiscence (Kanno *et al.*, 2016). Exogenous GA application restored the normal anther dehiscence phenotype in *atsweet13;14* double-knockout mutants. These mutants also exhibited reduced pollen viability, fertility and germination (Kanno *et al.*, 2016). Genetic complementation of *atsweet13;14* knockout mutant with AtSWEET9, which transports sucrose but not GA, fully restored the normal pollen viability and germination phenotypes, suggesting that sucrose limitation was responsible for defective pollens (Wang *et al.*, 2022a). These findings are validated by another study, in which the impaired pollen viability and germination phenotypes of *atsweet13;14* double-knockout mutants were rescued by the sucrose-selective AtSWEET13 structural mutant (that transported only sucrose) but not by the GA-selective AtSWEET13 mutant (high-capacity GA transporter) (Isoda *et al.*, 2022).

The rice *OsSWEET11* has a role in pollen development. The RNAi mutants of *ossweet11* were shown to be defective in pollen development (Chu *et al.*, 2006; Yang *et al.*, 2006). However, CRISPR/Cas9-generated knockout mutants of *ossweet11* had normal pollen development and viability (Kim *et al.*, 2019; Yang *et al.*, 2018). Recently it has been shown that, unlike the single-knockout mutants, the double-knockout mutants of *ossweet11-a;11b* (*OsSWEET11* is referred to as *OsSWEET11a* after the discovery of *OsSWEET11b*) are male sterile (Wu *et al.*, 2022). The rice *OsSWEET11a* and *11b* genes are expressed in the anther peduncle and the anther veins respectively. Simultaneous mutations in *OsSWEET11a* and *11b* resulted in an insufficient supply of sugars to the pollen and lower pollen starch contents, together with defective pollen development (Wu *et al.*, 2022). Reduced male fertility was also observed in *ossweet11* RNAi mutants (Yang *et al.*, 2006). This observation is suggested to be caused by co-suppression of *OsSWEET11b* by the hairpin RNAi targeted against *OsSWEET11* (Wu *et al.*, 2022).

SWEETs in senescing and developing leaves

The expression of SWEETs in senescing leaves is associated with the remobilization of sugars from them to other sink tissues, which is vital for the reutilization of carbon resources in other plant organs. The *Arabidopsis AtSWEET15* (*SAG29 – senescence-associated gene 29*) gene and its homologue *PbSWEET4* in pear are abundantly expressed in senescing and older leaves, respectively, suggesting a role in the remobilization of carbon resources to sink organs through these sugar exporters for their re-assimilation in different plant tissues (Chen *et al.*, 2010; Ni *et al.*, 2020; Seo *et al.*, 2011). Overexpression of *PbSWEET4* is associated with accelerated leaf senescence and reduced sugar concentrations in leaves (Ni *et al.*, 2020). The rice galactose

transporter *OsSWEET5*, expressed in senescing leaves and other organs such as flowers and roots, has been suggested to control plant growth and senescence through crosstalk with auxin signalling (Zhou *et al*., 2014). Imbalances in sugar metabolism and transport led to stunted growth and premature senescence in *OsSWEET5* overexpressors (Zhou *et al*., 2014).

The *Arabidopsis* glucose and fructose transporter, *AtSWEET4*, is expressed in the veins of leaves, where it is thought to be involved in sugar unloading and import into leaves (Liu *et al*., 2016). The RNAi *atsweet4* lines were shorter in size and had lower levels of hexoses in the leaves than in the wild type. In contrast, the overexpression lines had greater biomass and accumulated higher glucose and fructose levels, suggesting that AtSWEET4 is involved in the import of hexose sugars to sink tissues (Liu *et al*., 2016). The tomato glucose transporter SlSWEET1a is involved in phloem unloading. It imports glucose into the phloem parenchyma cells from the apoplast of developing leaves (Ho *et al*., 2019). Silencing *SlSWEET1a* reduced the hexose contents of young leaves by 50%, with a concomitant increase in the hexose levels of mature source leaves (Ho *et al*., 2019). The fructose content of *Arabidopsis* leaves is dependent on the activity of a tonoplast-localized fructose transporter called AtSWEET17 (Chardon *et al*., 2013). The leaves of the *atsweet17* knockout mutants accumulate fructose to high levels compared to the wild type, confirming that AtSWEET17 is required to export fructose out of the vacuoles (Chardon *et al*., 2013).

SWEETs in flowers, stems and roots

Nectaries and tubers are important sink and storage organs for sugars derived from photosynthesis. The presence of chloroplasts in nectary parenchyma cells suggests that this tissue is capable of photosynthesis. Nectaries release a variety of sugars in the apoplastic space in order to attract pollinators. The sucrose synthesized from starch stored in *A. thaliana*, *Brassica rapa* and *Nicotiana attenuate* nectaries is secreted into the apoplast via the SWEET9 sucrose transporter (Lin *et al*., 2014). The petunia AtSWEET9 homologue, PhSWEET9 (PhNEC1), is found in nectaries. The expression of PhSWEET9 is inversely correlated with the starch content of the nectaries, suggesting functional similarities to AtSWEET9 (Ge *et al*., 2000; Lin *et al*., 2014). In *Arabidopsis*, FT is found to induce the expression of *AtSWEET10* during the floral transition (Andrés *et al*., 2020). Transformed plants overexpressing *AtSWEET10* flowered earlier than controls, suggesting that this transporter plays a role in providing sugars to sustain increased growth and cell division during the floral transition (Andrés *et al*., 2020). The potato *StSWEET11*, expressed in phloem, stolon and tuber parenchyma cells, mediates sucrose transport into the apoplastic space from sink tissues (Abelenda *et al*., 2019). The mode of sucrose unloading switches at the onset of tuberization from apoplastic to symplastic routes, which requires inhibition of StSWEET11 activity. The tuberization-specific flowering locus T (FT) homologue StSP6A (self-pruning 6A) physically interacts with StSWEET11 to block its activity and thus sucrose transport, favouring the symplastic sucrose transport routes (Abelenda *et al*., 2019). These reports highlight the crosstalk between SWEETs and FT that regulates the photoperiod-dependent movement of sugars for the development of different sink organs.

The clade I rice glucose transporter *OsSWEET3a*, which is expressed in vascular bundles in the basal regions of seedlings such as the scutella and mesocotyl, is known to transport GA (Morii *et al*., 2020). Functional analysis of *ossweet3a* knockout mutants suggests that OsSWEET3a mediates the loading of both glucose and GA from the endosperm to the phloem for transport to the shoot in order to promote seedling growth and development (Morii *et al*., 2020). Differential expression patterns of the sucrose transporter genes *AtSWEET11-15* are observed in stems and roots of *Arabidopsis* under different physiological conditions (Durand *et al*., 2018), suggesting their implication in carbon partitioning during different stages of plant development and under variable growth conditions. For example, *AtSWEET11* and *12* are strongly expressed in roots under osmotic stress conditions to enhance sucrose phloem unloading and increased carbon allocation to roots for improved osmotic stress tolerance (Durand *et al*., 2016, 2018).

SWEETs in source tissues

SWEETs in source tissues (photosynthesizing leaves) mediate sucrose efflux from phloem parenchyma cells to the apoplastic space, an essential step in the apoplastic sucrose phloem loading pathway (Chen *et al*., 2012). In *Arabidopsis*, clade III sucrose transporters AtSWEET11 and 12, which are localized to the plasma membrane of phloem parenchyma cells, mediate this step. The *atsweet11;12* double-knockout mutants had defective phloem loading and consequently restricted sucrose transport to sink tissues resulting in stunted growth and accumulation of starch and soluble sugars in leaves (Chen *et al*., 2012). In maize, the essential role of sucrose transport into the apoplast for phloem loading is carried out by three close paralogues ZmSWEET13a, b and c, which are highly expressed in leaves (Bezrutczyk *et al*., 2018a). The triple-knockout mutants of *zmsweet13a;b;c* exhibited severe growth retardation and carbohydrate accumulation in leaves, indicating impaired phloem loading (Bezrutczyk *et al*., 2018a). Similarly, RNAi mutants of *StSWEET11* also exhibited features of blocked phloem loading, such as reduced yield and elevated carbohydrate levels in leaves, suggesting that StSWEET11 is essential for apoplastic sucrose phloem loading in potatoes (Abelenda *et al*., 2019). Transcript and GUS expression studies have shown a high expression of *IbSWEET10* in the leaf vasculature of mature sweet potatoes, suggesting that IbSWEET10 plays a role in sucrose export from source leaves and in phloem loading (Li *et al*., 2017).

The *OsSWEET13* is the most highly expressed clade III *SWEET* gene in the rice leaf phloem, whereas *OsSWEET11* and *14* are expressed at relatively low levels in this tissue (Eom *et al*., 2019; Ma *et al*., 2017; Mathan *et al*., 2021a; Yuan *et al*., 2014). All these genes encode sucrose transporters and are thought to fulfil roles in phloem loading (Eom *et al*., 2019). Analysis of single-knockout mutants of *ossweet11*, *13* and *14* revealed no growth penalty. These mutants grew similar to the wild types (Eom *et al*., 2019; Fei *et al*., 2021; Ma *et al*., 2017). Similarly, double-knockout mutants of *ossweet11;14* and *ossweet13;14* showed no noticeable phenotypic differences compared to the wild types, suggesting that SWEET-mediated apoplastic sucrose phloem loading is not the predominant pathway used in rice for sucrose phloem transport (Eom *et al*., 2019; Fei *et al*., 2021). However, a previous report had shown that rice *sweet14* T-DNA insertional knockout mutants had a shorter plant phenotype and produced smaller seeds than the wild type (Antony *et al*., 2010), suggesting that phloem loading is impaired in these mutants.

Studies based on anatomical, physiological and genetic approaches support the idea that sucrose phloem loading in rice predominantly takes the apoplastic route mediated by SUTs and

SWEETs (Braun, 2022; Li *et al*., 2022; Scofield *et al*., 2007; Wang *et al*., 2021). Chemical inhibition of SUTs in rice significantly reduced sucrose uptake, exudation and distribution to sink tissues such as stems and panicles (Li *et al*., 2022; Wang *et al*., 2021). Reducing the expression of *OsSUT1*, *OsSWEET11* and *OsSWEET14* in rice by knocking down/out *OsDOF11* (*DNA binding with one finger 11*), decreased rates of sucrose uptake and transport in leaves resulting in stunted plants with fewer tillers and smaller panicles (Wu *et al*., 2018). The OsDOF11 binds to the promoter regions of *OsSUT1*, *OsSWEET11* and *OsSWEET14* genes to activate their expression (Wu *et al*., 2018). Conversely, increased expression of *OsSUTs*, *OsSWEET11* and *OsSWEET14* contributed to enhanced sucrose phloem loading and transport of photoassimilates, resulting in increased grain filling percentage and hence grain yield in rice under low nitrogen conditions (Li *et al*., 2022). The *ossut1* knockout mutants showed reduced plant height and photosynthesis, together with lower thousand-grain weights than the wild types, indicating that *OsSUT1* is an important player in phloem loading and seed filling (Wang *et al*., 2021). However, the mild reduction in plant height and photosynthesis in *ossut1* knockout mutants differs significantly from the severe growth phenotypes observed in principal *sut/suc* gene knockout mutants responsible for sucrose phloem loading in species using apoplastic phloem loading mechanism (Braun, 2022; Gottwald *et al*., 2000; Slewinski *et al*., 2009). Functional redundancy among rice *SUTs* could be one of the reasons for mild phenotypes in *ossut1* mutants. The generation of higher-order mutants of different SUTs would help reveal the precise path of phloem loading in rice.

All the *SWEET* genes that show source preferential expression patterns and are implicated in sucrose loading and transport to sink tissues belong to the clade III of sucrose transporters (Abelenda *et al*., 2019; Bezrutczyk *et al*., 2018a; Chen *et al*., 2012; Mathan *et al*., 2021a). Interestingly, the expression of the *Arabidopsis AtSWEET11* and *12* genes and their rice orthologues *OsSWEET11* and *14* is induced by the bacterial and fungal pathogens to acquire sugars for virulence and growth (Antony *et al*., 2010; Chen *et al*., 2010, 2012; Fatima and Senthil-Kumar, 2021; Gao *et al*., 2018). Therefore, the increased expression of these SWEETs could alter the plant defence responses to pathogens as well as modulate the differential distribution of carbohydrates.

The overexpression of *OsSWEET11/OsSWEET14* in rice resulted in stunted growth and lower grain weights (Figure 3) rather than stimulating growth and yield (Gao *et al*., 2018; Kim *et al*., 2020; Yuan *et al*., 2009). Similarly, *Arabidopsis* plants overexpressing *AtSWEET11* and *12* were smaller than their respective wild types (Eom *et al*., 2015; Fatima and Senthil-Kumar, 2021). Constitutive overexpression of *OsDOF11*, which regulates the expression of *OsSUT1*, *OsSWEET11* and *OsSWEET14* in rice, resulted in stunted plants with lower thousand-grain weights (Kim *et al*., 2020; Wu *et al*., 2018). This is caused by the activation of *OsSWEET14* expression in these lines (Kim *et al*., 2020). Overexpression of *StSWEET11* in potatoes resulted in impaired growth, with the formation of aerial tubers and the outgrowth of above-ground stolon-like axillary buds, which commonly occurs in plants with blocked phloem transport (Abelenda *et al*., 2019). The phenotypes of the transgenic plants overexpressing clade III *SWEET* genes resemble those of their respective *SWEET* knockout mutants of *atsweet11;12* in *Arabidopsis* (Chen *et al*., 2012) and *ossweet14* in rice (Antony *et al*., 2010), and RNAi mutants of *stsweet11* in potatoes (Abelenda *et al*., 2019), which show impaired phloem loading and reduced sugar translocation to sink tissues. SWEETs-mediated sugar translocation is a highly regulated and directional process limited to specific cell types, such as vascular parenchyma cells in leaves (Eom *et al*., 2015). Ubiquitous and constitutive overexpression could thus result in random and directionless movement of sugar molecules from cells that normally do not function in sugar export. This can reduce sugar flux for phloem loading, negatively impacting plant growth (Eom *et al*., 2015; Feng and Frommer, 2015).

We recently simultaneously co-expressed *OsSUT1*, *OsSWEET11* and *OsSWEET14* in rice under the control of their native promoters. The aim was to maintain tissue specificity and enhance sucrose translocation from leaves to sink tissues (Singh *et al*., 2021). However, the transgenic lines showed multiple phenotypes, such as stunting, reduced tiller numbers and decreased grain yields. These phenotypes were similar to those observed in transgenic rice plants that individually overexpress either *OsSWEET11* or *OsSWEET14* (Gao *et al*., 2018; Kim *et al*., 2020; Yuan *et al*., 2009). This finding suggests that the phenotypes result from increased *OsSWEET11* and *OsSWEET14* expression, not *OsSUT1* overexpression. Rather, *OsSUT1* overexpression has been shown to stimulate growth and yield in rice (Feng *et al*., 2018). Further analysis of the lines that co-express *OsSUT1*, *OsSWEET11* and *OsSWEET14* revealed that these plants accumulated starch in their leaves at the end of the dark period and had reduced sucrose transport to sink tissues, indicative of impaired phloem loading (Singh *et al*., 2021). Moreover, the photosynthesis and sucrose synthesis rates were significantly reduced in transgenic plants compared to the wild type, leading to lower leaf-soluble sugar contents (Singh *et al*., 2021).

It is predicted that the overexpression of clade III *SWEETs* would enhance sucrose availability in the apoplast leading to increased pathogen susceptibility. Surprisingly, the transgenic rice plants overexpressing *OsSWEET11* and *OsSWEET14* showed improved resistance to pathogens such as *Xoo* and *R. solani* that are known to induce the expression of these genes for virulence (Kim *et al*., 2020; Singh *et al*., 2021; Yuan *et al*., 2009). Similarly, constitutive overexpression of *AtSWEET12* in *Arabidopsis* resulted in enhanced resistance to bacterial pathogens (Fatima and Senthil-Kumar, 2021). Also, enhanced expression of *BjSWEET11* in *Brassica juncea* has been shown to attenuate the growth and multiplication of aphids feeding on transgenic plants compared to controls (Zauva *et al*., 2020). Up-regulation of *SWEETs* could trigger defence responses via the translocation of sugars to the sites of infection, which may include enhanced expression of sugar transporter proteins (STPs) (Bezrutczyk *et al*., 2018b). STPs are proton–hexose symporters that retrieve hexoses from apoplastic space to the cytoplasm in response to the perception of pathogens to reduce the sugar levels in the apoplastic space in order to restrict pathogen growth, supporting the 'pathogen starvation hypothesis' (Figure 4) (Bezrutczyk *et al*., 2018b; Lemonnier *et al*., 2014). It is also plausible that increases in SWEETs activities transiently elevate apoplastic sugar levels to activate defence reactions via 'sugar signalling' pathways that confer pathogen resistance (Bezrutczyk *et al*., 2018b). Overexpression of *BjSWEET11* in *Brassica juncea* is accompanied by transcriptional activation of many defence-related genes such as ABC transporter G family member 36 (ABCG36), pathogenesis-related protein 1 (PR1) and WRKY transcription factor 70 (WRKY70), which are known to regulate plant defence responses (Zauva *et al*., 2020).

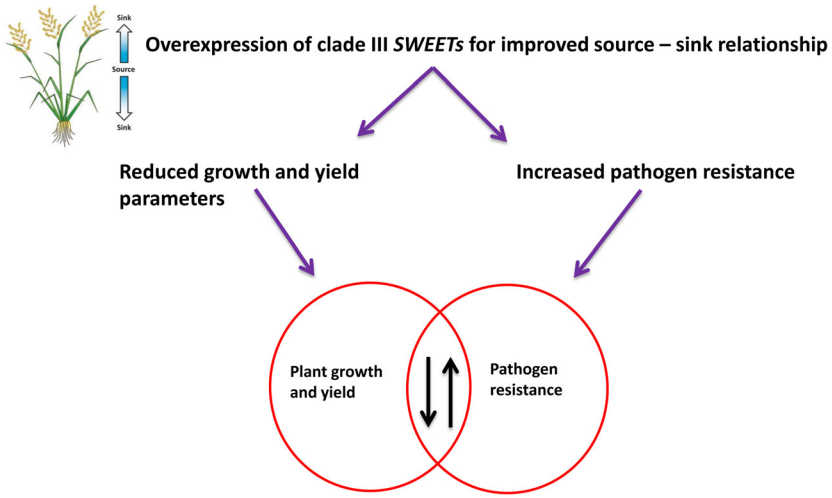

Figure 3 Trade-off between plant growth and immunity induced by *SWEETs*. Transgenic rice plants overexpressing clade III sucrose exporting *SWEETs*, *OsSWEET11* and *14*, have been shown to exhibit reduced growth parameters. However, these transgenics showed increased resistance to pathogens (Kim *et al*., 2020; Singh *et al*., 2021; Yuan *et al*., 2009). Similarly, overexpression of clade III *ASWEET11* and *12* in *Arabidopsis* resulted in growth retardation, and increased tolerance to pathogens in plants overexpressing *AtSWEET12* (Eom *et al*., 2015; Fatima and Senthil-Kumar, 2021). These reports indicate that overexpression of *SWEETs* induced a trade-off between plant growth and defence.

We found that co-expression of *OsSWEET11* and *OsSWEET14* in rice reduced sucrose synthesis and transport (Singh *et al*., 2021). This indicates that the up-regulation of *OsSWEET11* and *OsSWEET14* in rice mimics the attack of *Xoo*. The 'pathogen starvation hypothesis' response strategy serves to prevent *Xoo* growth and proliferation by inhibiting sucrose synthesis via decreased expression of the genes encoding the enzymes of the sucrose synthesis pathway, as well as restricting sucrose transport (Figure 4) (Bezrutczyk *et al*., 2018b; Singh *et al*., 2021). Supporting evidence for this concept has come from another very recent study in which the overexpression of *AtSWEET12* in transgenic *Arabidopsis* plants conferred resistance to bacterial pathogens. The transgenic lines had 50% less sucrose in the apoplast than the wild types (Fatima and Senthil-Kumar, 2021). Similarly, overexpression of the *IbSWEET10* gene in sweet potatoes reduced leaf sugar levels, which led to enhanced resistance to *Fusarium oxysporum*. Increased resistance to pathogens, however, came at a cost in the transgenic rice and *Arabidopsis* plants overexpressing *OsSWEET11/14* and *AtSWEET12* respectively. Reduced sucrose levels in the leaves of transgenic plants resulted in poor plant growth and yield (Fatima and Senthil-Kumar, 2021; Singh *et al*., 2021). These results indicate that there is a trade-off between plant growth and defence that is modulated by the SWEETs (Figure 3).

Exploiting SWEETs for improved plant growth and defence

The above discussion has highlighted the tight linkage between plant growth and pathogen defence and demonstrated that these traits are inversely related in plants overexpressing clade III *SWEETs* that serve a dual function in sucrose export from source tissues and in pathogenesis. Any changes in the expression levels of clade III *SWEETs* disturb the balance between sugar transport and pathogen susceptibility. Novel and innovative approaches that uncouple pathogenesis and sugar translocation are required to improve source–sink relationships and yield sustainability.

Sugar signalling is a central component of plant defence responses activated during plant–microbe interactions. The sucrose non-fermenting-1-related protein kinase 1 (SnRK1) and the target of rapamycin (TOR) kinase are key regulatory nodes in the sugar-sensing cascade. These kinases regulate the growth–immunity trade-off via multiple transcriptional and post-translational mechanisms, hormonal crosstalk and carbohydrate partitioning (Margalha *et al*., 2019). The SnRK1 positively regulates immunity while inhibiting growth. In contrast, TOR promotes growth and limits immune responses to pathogens (Choudhary *et al*., 2022). Transgenic rice plants overexpressing *OsSnRK1* showed reduced growth and yield but exhibited broad-spectrum resistance to bacterial and fungal pathogens such as *Xoo* and *R. solani* (Filipe *et al*., 2018). Similar phenotypes of impaired growth and enhanced resistance to *Xoo* and *R. solani* were also observed in transgenic rice plants overexpressing *OsSWEET11* and *14* (Kim *et al*., 2020; Singh *et al*., 2021; Yuan *et al*., 2009). These findings hint towards the involvement of SnRK1 in regulating the growth–immunity trade-off in *SWEET* transgenics. SnRK1 is, therefore, an attractive candidate for targeted modulation of plant growth and defence responses in transgenics overexpressing *SWEETs*.

The CRISPR-Cas-mediated tissue-specific expression of *OsDOF11* increased grain yields, as well as resistance to sheath blight, via activation of *OsSWEET14* (Kim *et al*., 2020). The regulated expression of SWEETs in a tissue-specific manner could, therefore, have positive effects on both yield and disease resistance. The indirect regulation of *SWEET* gene expression could also be beneficial. For example, the *FT* genes in *Arabidopsis* and potatoes regulate the expression of clade III *SWEET* genes that encode sucrose transporters (Abelenda *et al*., 2019; Andrés *et al*., 2020). The *FT* gene in *Arabidopsis* regulates flowering by enhancing the expression of *AtSWEET10*. Similarly, the FT homologue StSP6A inhibits StSWEET11 activity to promote tuberization (Abelenda *et al*., 2019; Andrés *et al*., 2020). Thus, the expression of *FT* genes could be tailored to modulate the expression of SWEETs and hence influence yield-related traits such as early flowering and tuber formation.

Increased oligomeric status of SWEETs enhances their sugar transport activity by forming a functional pore (Anjali *et al*., 2020; Xuan *et al*., 2013). The phosphorylation of AtSWEET11 and 12 enhanced oligomerization and, consequently, the sucrose transport activity of these SWEETs. This resulted in increased sucrose content in the roots leading to improved growth under drought stress (Chen *et al*., 2022a). Therefore, increasing the activity of SWEETs in source tissues through post-translational modifications such as protein phosphorylation could be an attractive strategy for enhanced photoassimilate transport to sink tissues. The *in*

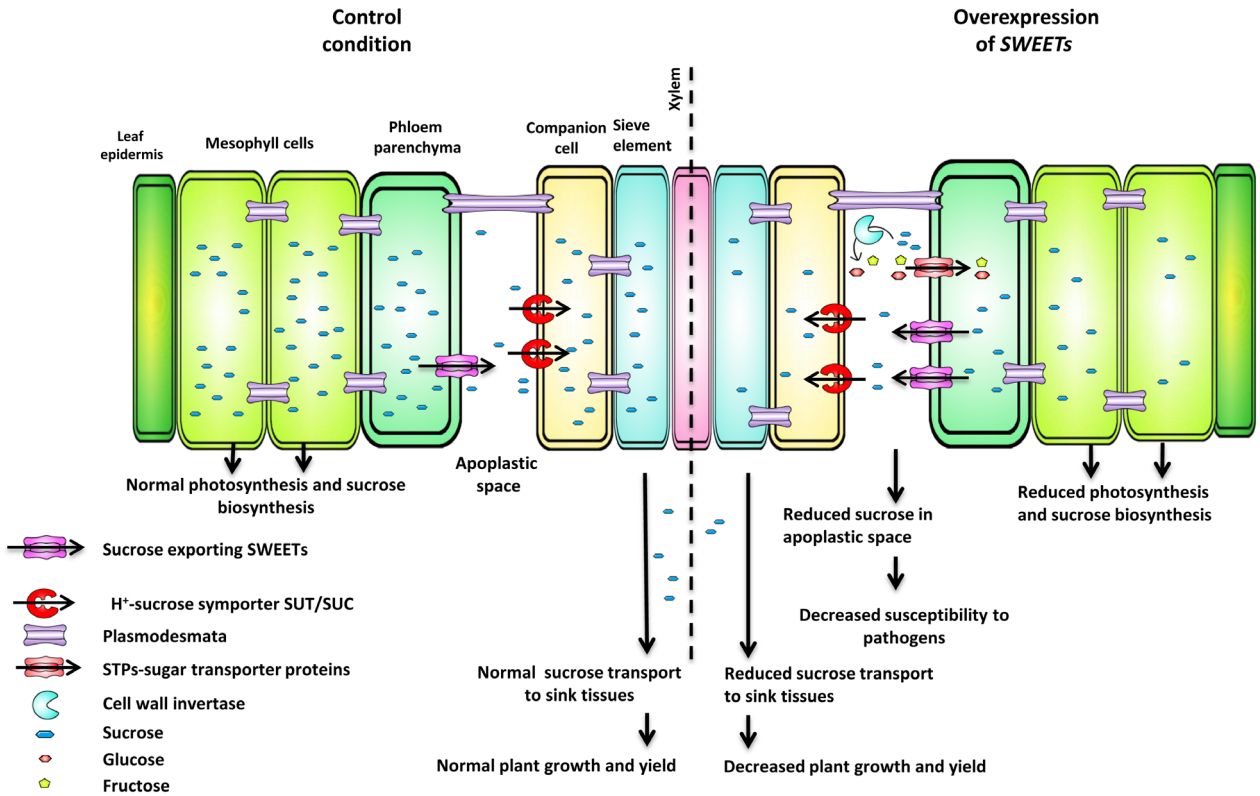

Figure 4 A possible model to explain the compromised growth and increased resistance to pathogens in plants overexpressing clade III *SWEET* genes. Overexpression of *SWEETs* that are induced by pathogens for virulence such as *AtSWEET11* and *12* in *Arabidopsis* and *OsSWEET11* and *14* in rice is perceived as pathogen attack in plants. This activates plant defence machinery for 'pathogen starvation' resulting in down-regulation of biosynthetic processes such as photosynthesis and sucrose synthesis. This reduces sugar concentrations in the leaves and apoplastic space which limits pathogen growth and also impacts plant growth negatively (Singh *et al.*, 2021). Overexpression of *SWEETs* could also increase secretion of sucrose into the apoplast. Sucrose in the apoplast is partially cleaved by cell wall invertases into glucose and fructose. Increased sugar levels in the apoplast serve as pathogen elicitors to activate STPs (proton–hexose symporters) for retrieval of hexoses from the apoplastic space. This reduces the concentration of sugars in the apoplast, thereby inhibiting pathogen growth and reducing sucrose flux to sink tissues affecting plant growth (Bezrutczyk *et al.*, 2018b; Lemonnier *et al.*, 2014).

silico analysis of SWEET proteins from various species revealed many putative phosphorylation sites in the C-terminal cytosolic region. The functions of each of these phosphorylation sites can be tested experimentally to determine whether they play a role in the regulation of SWEET activity (Anjali *et al.*, 2020).

Enhancement in photosynthesis could translate to increased biomass and yield (Foyer *et al.*, 2017). Some members of the SWEET family have been shown to regulate photosynthesis rates. Overexpression of the putative glucose transporter *ZjSWEET2.2* in *Ziziphus jujuba* increased photosynthetic carbon assimilation in the leaves, presumably through improved phloem loading (Geng *et al.*, 2020). Enhanced phloem loading is expected to decrease the carbohydrate levels in leaf mesophyll cells, which will enhance photosynthetic gene expression (Geng *et al.*, 2020). The maize *CST1* (*CLOSED STOMATA 1*) gene, which is a homologue of *AtSWEET1*, regulates stomatal movements and photosynthesis (Wang *et al.*, 2019a). *CST1* is a glucose transporter localized on the plasma membrane of subsidiary cells. *CST1* regulates stomatal movements by regulating the sugar contents of the subsidiary cells (Wang *et al.*, 2019a). Loss of *CST1* functions resulted in decreased stomatal opening and lower photosynthesis rates, leading to lower grain yields (Wang *et al.*, 2019a). Therefore, the regulated expression of *CST1* might be exploited to optimize leaf CO_2 concentrations under different environmental conditions to optimize photosynthesis (Wang *et al.*, 2019a).

Genome-wide association mapping and transcriptional analysis in species such as rice, maize, soybean and watermelon revealed candidate *SWEET* genes that were selected during the process of crop domestication for yield-related traits such as bigger grains and fruits, and seeds with higher oil content (Mathan *et al.*, 2021a; Miao *et al.*, 2020; Ren *et al.*, 2021; Sosso *et al.*, 2015; Wang *et al.*, 2020). Genome-wide association studies (GWAS) in other crop species could help identify novel sugar transporters, which can be targeted to develop new crop varieties with improved yields through genetic engineering and breeding approaches. Multi-locus genome-wide association mapping in bread wheat identified a novel candidate *SWEET* transporter that could influence spike-related traits and hence the grain yield component (Malik *et al.*, 2021). Similarly, GWAS and QTL mapping approaches can help identify *SWEET* alleles for disease resistance. Meta-QTL analysis on QTLs obtained from 58 different studies involving 62 different mapping populations for multiple disease resistance in wheat identified 194 differentially expressed candidate genes, including a *SWEET* sugar transporter (Saini *et al.*, 2022).

Role of SWEETs in C4 photosynthesis

C4 plants such as maize, *Setaria viridis* and *Sorghum bicolor* possess high rates of photosynthesis and have high expression of sugar transporters to facilitate phloem loading of photosynthates.

The loading of photoassimilates into the phloem of C4 leaves via sugar transporters is required because there are fewer plasmodesmata between the bundle sheath cells and vascular parenchyma than between the bundle sheath and mesophyll cells (Emms *et al*., 2016). The multiple paralogues of *SWEET13*, which are highly expressed in the bundle sheath cells of mature leaves in maize (three paralogues), *Setaria viridis* (two paralogues) and *Sorghum bicolor* (three paralogues), arose during the evolution of C4 plants that encompasses independent and parallel duplication events. This has led to multiple copies of this gene in C4 plants compared to the single copy in rice, i.e. orthologue *OsSWEET13* (Emms *et al*., 2016). The maize SWEET13a, b and c paralogues are highly expressed in leaves and have been shown to transport sucrose from the bundle sheath cells to the apoplast (Bezrutczyk *et al*., 2018a). Similarly, based on transcript abundance and immunolocalization studies, SWEET13 paralogues in *Setaria viridis* and *Sorghum bicolor* have been suggested to facilitate apoplastic phloem loading of photoassimilates (Chen *et al*., 2022b). The SvSWEET13a and 13b transporters have high glucose and sucrose transport capacity. They are localized in the bundle sheath and phloem parenchyma cells around both minor and major veins, where they are suggested to load photosynthates into the phloem (Chen *et al*., 2022b). The duplication of SWEET13 paralogues, therefore, played an important role in the evolution of C4 photosynthesis.

SWEETs and abiotic stress response in plants

The intracellular and intercellular levels of sugars and sugar alcohols are regulated by the SWEETs expressed in the vacuolar and plasma membranes (Breia *et al*., 2020, 2021). These transporters can contribute to acclimation to stress conditions. High levels of soluble sugars such as sucrose, glucose, trehalose and sugar alcohols mitigate abiotic stress by acting as osmoprotectants and antioxidants that stabilize membrane structures by interacting with the lipid bilayer (Ahmad *et al*., 2020; Singh and Thakur, 2018). The functional characterization of the plasma membrane-localized *AtSWEET4*, *AtSWEET11* and *AtSWEET12* genes and the *Arabidopsis* tonoplast-localized *AtSWEET16* and *AtSWEET17* genes revealed a role in freezing tolerance (Chardon *et al*., 2013; Guo *et al*., 2014; Klemens *et al*., 2013; Le Hir *et al*., 2015; Liu *et al*., 2016). Transgenic *Arabidopsis* plants overexpressing *AtSWEET4* and *AtSWEET16* showed a higher freezing tolerance than the controls linked to the higher accumulation of glucose and sucrose, both of which have anti-freezing properties. The transgenics also showed a reduced leakage of electrolytes following exposure to cold stress, a finding which indicates that membrane integrity is maintained (Klemens *et al*., 2013; Liu *et al*., 2016). Similarly, the heterologous expression of the *Camellia sinensis CsSWEET1a* and *CsSWEET17* genes, which are expressed upon exposure to cold stress, improved freezing tolerance in transgenic *Arabidopsis* plants (Yao *et al*., 2020). The study also reported a role of the alternative splicing in these genes in cold stress responses in *C. sinensis*. An alternative splice form of *CsSWEET17*, which is found to be localized in the cytosol, is strongly expressed during winter (Yao *et al*., 2020).

The *AtSWEET17* fructose transporter is highly expressed in the tonoplast of roots to regulate the levels of fructose in roots in response to cold and drought stress (Guo *et al*., 2014; Valifard *et al*., 2021). The AtSWEET17 is essential for the fructose-induced modulation of root growth and architecture, which is critical for drought stress tolerance (Valifard *et al*., 2021). The expression of *AtSWEET10* was significantly enhanced during waterlogging, which induces ethylene production (Phukan *et al*., 2018). The waterlogging-responsive ethylene response factor MaRAP2-4 from *Mentha arvensis* was shown to regulate the expression of *AtSWEET10* and hence the sugar contents of transgenic *Arabidopsis* plants by binding to the stress-responsive elements on the promoter region of *AtSWEET10* (Phukan *et al*., 2018). The *OsSWEET13* and *OsSWEET15* genes were strongly expressed in response to drought, salt and abscisic acid (ABA) treatment (Mathan *et al*., 2021b). These sucrose transporters were linked to increased levels of soluble sugars in the leaves, roots and phloem sap of plants exposed to drought or salinity stress. The ABA-responsive OsbZIP72 transcription factor binds to the promoters of the *OsSWEET13* and *OsSWEET15* genes, activating their expression (Mathan *et al*., 2021b). Understanding the gene regulatory networks that control the stress-induced expression of *SWEETs* could help improve abiotic stress tolerance in crop plants.

Enhanced expression of *AtSWEET11* and *12* under water-deficit conditions increased carbohydrate export from leaves to roots to counter drought stress (Durand *et al*., 2016). A recent study revealed the mechanistic basis of increased AtSWEET11 and 12 activities on exposure to drought stress (Chen *et al*., 2022a). Drought-induced ABA signalling in *Arabidopsis* leads to the activation of SnRK2s, which phosphorylate two highly conserved serine residues, Ser237 and Ser248, in the cytosolic carboxy-terminal regions of the key phloem sucrose transporters AtSWEET11 and 12 (Chen *et al*., 2022a). Phosphorylation at these sites enhances AtSWEET11 and 12 protein oligomerization, a process that results in increased sucrose transport activity to roots and a concomitant enhancement in root:shoot ratio of biomass and drought tolerance (Chen *et al*., 2022a). Crucially, the transgenic plants expressing phospho-mimic mutants (Ser-to-Asp/Glu mutations) of AtSWEET11 or 12 showed the development of a deeper, broader and improved root system that provided growth advantages under both normal and drought stress conditions (Chen *et al*., 2022a). Thus, enhanced source strength and transport can be an effective strategy for combating the adverse effects of stress without negative effects on plant growth.

Conclusions

Since the discovery of SWEETs nearly a decade ago, an overwhelming body of data has demonstrated that SWEETs regulate diverse physiological processes in plants, particularly plant–pathogen and source–sink interactions (Breia *et al*., 2021; Chen *et al*., 2010, 2012; Cox *et al*., 2017; Hu *et al*., 2014; Ren *et al*., 2021; Wang *et al*., 2020). Thus, the genetic manipulation of *SWEETs* is considered an effective strategy for developing disease-resistant crops and increasing source and sink strength, which can boost crop productivity. With a few exceptions, pathogens activate the expression of *SWEET* genes to acquire nutrition to support growth. Remarkable success has been achieved in generating broad-spectrum BB-resistant rice varieties that have a higher yield potential under biotic stress conditions, specifically by the gene editing of *OsSWEET11*, *13* and *14*, which *Xoo* induces to cause BB (Eom *et al*., 2019; Li *et al*., 2012; Oliva *et al*., 2019; Xu *et al*., 2019). Similarly, the *SWEET* genes in other crops are attractive potential targets for improved disease resistance.

In contrast, the significance of SWEETs in improving carbohydrate export from leaves to seeds and thus enhancing

photosynthesis and crop yield remains unclear. The overexpression of many *SWEET* genes such as *OsSWEET11* and *14* in rice, *AtSWEET11* and *12* in *Arabidopsis* and *StSWEET11* in potatoes resulted in stunted growth and reduced yields, parameters indicative of impaired phloem loading (Abelenda *et al*., 2019; Eom *et al*., 2015; Gao *et al*., 2018; Kim *et al*., 2020; Singh *et al*., 2021; Yuan *et al*., 2009). Alternate strategies such as tissue-specific controlled overexpression via CRISPR/Cas and enhancement in the activity by increasing the oligomeric state through phosphorylation of SWEET transporters could be employed to augment the rate of sugar transport to sink tissues. Such approaches may potentially reduce the risks of unintended consequences of uncontrolled overexpression.

The SWEET family is the most recently discovered class of sugar transporters and is, therefore, understudied. Thus, the physiological roles of the many *SWEET* genes present in different plant species must be studied in detail to identify suitable candidates for yield enhancements in crops through improved carbon partitioning. GWAS and QTL mapping are powerful tools that can be used to reveal candidate *SWEET* genes controlling traits for carbohydrate partitioning in source and sink tissues.

Based on the reports implicating SWEETs in plant responses to environmental stress (Chen *et al*., 2022a; Klemens *et al*., 2013; Le Hir *et al*., 2015), it is possible to suggest that the expression of *SWEETs* can be tweaked to enhance plant resistance to different abiotic stress conditions. Hence, the modulation of SWEETs may have a significant role in enhancing plant resilience and the sustainability of yield in the face of climate change and accompanying temperature variations.

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Conflict of interest

The authors declare no conflict of interest.

Authors' contributions

Conceptualization, J.S. and J.K.T. Manuscript preparation, J.S., J.K.T., C.H.F., A.R., K.J.G. and S.D. Funding acquisition, J.K.T. All authors have read and agreed to the published version of the manuscript.

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