SWEETs, transporters for intracellular and intercellular sugar translocation

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Three families of transporters have been identified as key players in intercellular transport of sugars: MSTs (monosaccharide transporters), SUTs (sucrose transporters) and SWEETs (hexose and sucrose transporters). MSTs and SUTs fall into the major facilitator superfamily; SWEETs constitute a structurally different class of transporters with only seven transmembrane spanning domains. The predicted topology of SWEETs is supported by crystal structures of bacterial homologs (SemiSWEETs). On average, angiosperm genomes contain ~20 paralogs, most of which serve distinct physiological roles. In *Arabidopsis*, AtSWEET8 and 13 feed the pollen; SWEET11 and 12 provide sucrose to the SUTs for phloem loading; AtSWEET11, 12 and 15 have distinct roles in seed filling; AtSWEET16 and 17 are vacuolar hexose transporters; and SWEET9 is essential for nectar secretion. The remaining family members await characterization, and could play roles in the gametophyte as well as other important roles in sugar transport in the plant. In rice and cassava, and possibly other systems, sucrose transporting SWEETs play central roles in pathogen resistance. Notably, the human genome also contains a glucose transporting isoform. Further analysis promises new insights into mechanism and regulation of assimilate allocation and a new potential for increasing crop yield.

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Introduction

Historically, humans relied primarily on bio-based economies. However, during the industrial revolution a shift occurred toward a fossil fuel economy, most notably in energy, as well as industrial scale production of synthetic chemicals and materials. There is an ongoing discussion regarding a return to an industrial scale bio-based economy. However, such concepts, while at first sight potential innovative drivers of the economy, with the added value of apparent sustainability, also bear major risks. Feeding a world population of 6–9 billion people is already a challenge and has major ecological impacts, thus if industry begins to compete for land and crop production, humans will need new ways to ensure efficient food production and secure biodiversity. In that sense, biofuels were a test case — probably for complex reasons, including the not yet fully developed science, only a major success in Brazil. Yet it initiated a new thinking — the production of high value products from photosynthesis to support the development of other bio-based products — that is returns on high value products could generate enough income to make biofuels competitive and to ultimately transition from the fossil fuel to a bio-based economy. Since today's agriculture is not sustainable, and since productivity is already limiting, scientists and breeders need to find creative new ways to massively increase productivity. Potential targets for crop yield engineering have been carefully explored [1••]. There is no doubt that carbon allocation in plants must be a central player. Yet this fundamental process is still poorly understood; therefore rational engineering is not yet feasible and demands further research.

Sucrose is produced in photosynthetically active tissues of the leaf and stem, is actively loaded into the phloem, from which it is withdrawn at the various tissues and cells that depend on external sugar supply. At the same time, concentration of sucrose as the dominant osmoticum in the phloem sap, is thought to create the driving force for translocation of all other solutes in the phloem. A bit more than 20 years ago, the first sucrose transporter gene responsible for phloem loading was identified [2•], a significant step toward the understanding of sugar translocation. More recently, the lessons learned from model species are starting to be reconciled and implemented in crops such as corn [3•]. Yet the story is incomplete: sucrose transporters (SUTs) function as sucrose/proton symporters, thus under

standard conditions (high negative membrane potential and acidified cell wall), SUTs primarily import sucrose from the cell wall into the cells responsible for long distance translocation. However, sucrose is synthesized from photosynthetically derived precursors in mesophyll cells. Thus at some point sucrose must be released into the cell wall, either directly from mesophyll or from bundle sheath cells, or if sucrose can move from cell to cell via the conspicuous plasmodesmata, release would be expected to occur from cells inside the phloem, such as the phloem parenchyma. Similarly, the sugar efflux transporters for nectar secretion, efflux from seed coat, tapetum, and transmitting tract, the transporters supplying symbiotic and pathogenic microorganisms and the effluxers from the root epidermis, are missing. A unique new family of sugar transporters, the SWEETs, could fill this gap at many of the expected sites. This review focuses on SWEETs from Arabidopsis since the physiological function of these transporters has been studied in most detail in this reference organism, and we highlight a few other SWEETs, for example, from rice and cassava in the context of their role in pathogen susceptibility.

Identification of SWEETs

SWEETs were identified by coexpression of membrane proteins with no assigned function with genetically encoded fluorescent sugar sensors in human HEK293T cells. HEK293T cells are characterized by low endogenous glucose uptake activity and do not show significant sucrose uptake [4,5[••],6]. With the help of a FRET glucose sensor we performed a screen for glucose transporters at neutral pH, expecting that this would enable us to identify potential pH-independent uniporters. In this way, we succeeded in identifying members (Clade I and II) of the SWEET family, which contain 17 members that fall into four phylogenetic clades in *Arabidopsis*

Figure 1

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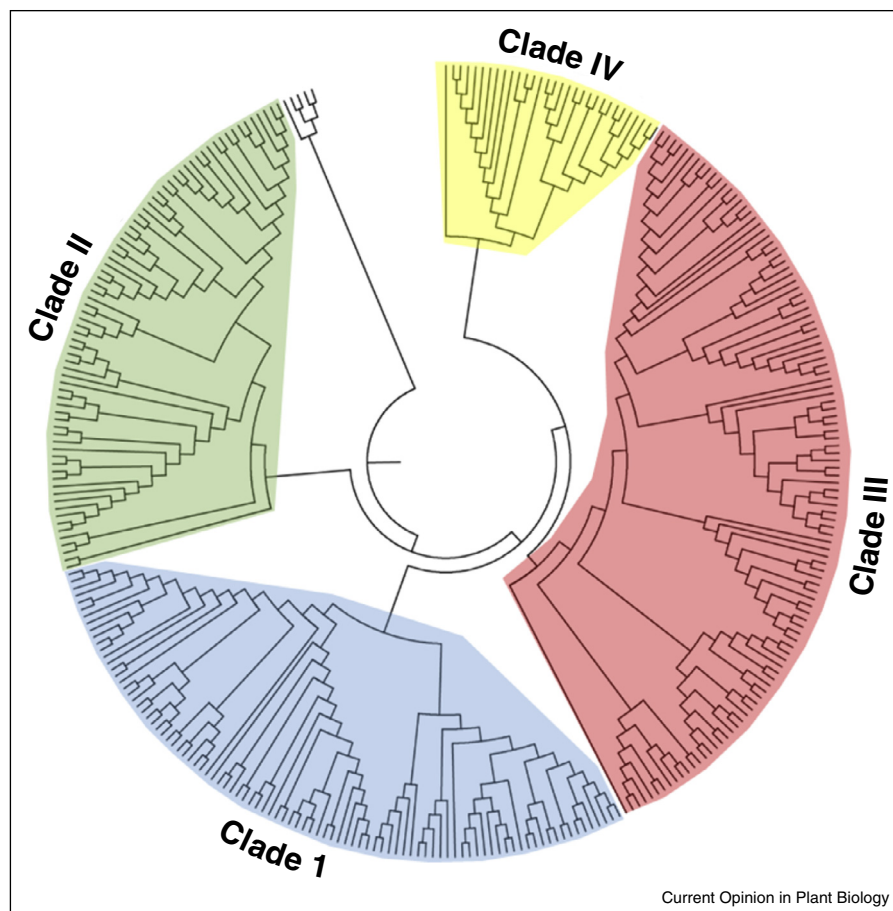
A phylogenetic tree of SWEET proteins from fifteen plant taxa focusing on the Angiosperms. Accessions were identified through BLAST on Phytozome, Ensembl Plants, NCBI, and CoGe. The SWEET lists were filtered to only include proteins containing two triple-helix-bundle repeats (MtN3 domains). An alignment was generated using default parameters on MUSCLE, and was then curated using Gblocks to exclude non-informative sites [52,53]. The maximum likelihood method PhyML was used to generate the phylogeny [54,55]. CrSWEET1 from *Chlamydomonas reinhardtii* was used as an outgroup. See the Supplementary Figure 1 and the Interactive Phylogenetic Tree online for individual protein names and bootstrap values.

(Figure 1 and Interactive Phylogenetic Tree online) [5••]. We used an analogous approach to identify novel sucrose transporters, that is, we expressed a FRET sucrose sensor in HEK293T cells and confirmed the absence of sucrose uptake in the human cells. We then performed a screen of unknown membrane proteins including SWEET homologs, and to our surprise found that clade III SWEETs (SWEET9–15) are able to transport sucrose [7••,8•]. We note that, although SWEET do not appear to show strong pH-dependencies, and although they can function in both uptake and efflux assays, formally a uniport function has not been demonstrated.

Based on the available sequenced genomes annotations (14 April 2015), within Angiosperms, we observed that the number of SWEETs can vary from as low as eight in *Amborella trichopoda*, the earliest diverging Angiosperm, which is not a member of the monocots or dicots, to as high as 47 in *Eucalyptus grandis*, a dicotyledonous tree. Intriguingly, in comparison, the *Chlamydomonas reinhardtii* genome contains five SWEETs, and the *Physcomitrella patens* genome contains six SWEETs, indicating that there has been a great expansion in SWEET genes in both monocot and dicot lineages [5••]. Membership of a SWEET in a clade does not seem to predict the physiological process the protein is involved in, for example, AtSWEET5, AtSWEET8 and AtSWEET13 are vital for pollen nutrition, yet they are found in either clades II or III. Of the SWEETs that have been studied so far, placement of a SWEET in a clade appears to correlate well with the relative selectivity toward mono-saccharides versus di-saccharides (Clade I and II prefer hexoses, clade III are efficient sucrose transporters). As stated earlier, all of the clade III SWEETs in *Arabidopsis* transport sucrose. Also, both clade IV SWEETs in *Arabidopsis* (AtSWEET16–17) are located on the tonoplast membrane and likely transport fructose. We propose that SWEET genes identified in the future be named according to their phylogenetic relationships to the founding members of the family in *Arabidopsis* and rice [5••], that is, SWEETs 1–3 in clade I, SWEETs 4–8 in clade II, SWEETs 9–15 in Clade III, and SWEETs 16–17 in clade IV. If due to genome duplication there are multiple genes that are co-orthologous to the closest *Arabidopsis* or rice gene, we suggest a letter designation follow the gene name to distinguish closely related genes, for example, Eucalyptus EgSWEET15a–f, rather than each gene being numbered sequentially.

SWEET structure
SWEETs are different from all other known sugar transporters in that they are heptahelical proteins composed of a tandem repeat of three transmembrane domains (TMs), connected by a linker-inversion TM [5••]. Typically, angiosperm genomes contain ∼15–25 SWEET genes, with the exception of some angiosperm genomes which have a much larger gene copy number of ∼47 (*Eucalyptus grandis*). Eucalyptus is known to have a large proportion of

tandem gene duplications. Chlamydomonas and mosses contain fewer SWEET genes (∼5). SWEET homologs have also been found in animal and human genomes. Eukaryotic SWEETs most likely evolved from ancestral prokaryotic homologs that are only ∼100 amino acids in length and contain only three TMs (SemiSWEETs) [6,9•]. *Bradyrhizobium* BjSemiSWEET1 mediates sucrose transport, whereas LbSemiSWEET mediates glucose transport. Atomic structures for three SemiSWEETs have been obtained in outside open and occluded states [10••,11•]. Split ubiquitin yeast two-hybrid and split green fluorescent protein (GFP) assays indicated that *Arabidopsis* SWEETs can oligomerize [9•]. Transport-deficient mutants of AtSWEET1 were able to suppress the activity of coexpressed wild-type AtSWEET1, potentially indicating that SWEET oligomerization is necessary for function [9•]. The atomic structures are highly valuable for studying the transport mechanism as well as the regulation of SWEETs.

Clade III SWEET9 is essential for nectar secretion
Nectaries are responsible for producing nectar, which serves as an attractant and reward for pollinators. Although the function and composition of nectar are well characterized, the mechanisms driving nectar secretion had not been determined. Pre-dating the discovery of the function of SWEETs, one of the paralogs had been identified as a nectary-specific gene. Nec1 (as the *Petunia* homolog of SWEET9 was originally named) is expressed in nectaries and its developmental regulation correlates inversely with nectarial starch content, implying its role in sugar secretion in nectaries [12•]. Silencing of the clade III SWEET homolog Nec1 from *Petunia* triggered male sterility, but a nectar phenotype was not reported [13]. Once the SWEETs had been identified, SWEET9 paralogs were identified as nectary-specific in *Arabidopsis*, *Brassica* and *Nicotiana* [8•]. Furthermore, SWEET9 was found to function as a sucrose transporter and be essential for nectar production. These data are consistent with a model in which sucrose synthesized in the nectary parenchyma is secreted by SWEET9 into the apoplasm, where sucrose is partially hydrolyzed by cell wall invertase to produce a mixture of sucrose, glucose and fructose. Thus SWEET9 appears to be responsible for secreting sucrose from the nectarial cells (Figure 2a).

Clade III SWEETs in phloem loading
Phloem loading is a multi-step process: sucrose is produced in mesophyll cells and traffics between cells possibly through plasmodesmata toward the phloem. Since SUTs load the sieve element companion cell complex with sucrose from the cell wall space, sucrose exits the symplasm with the help of sucrose transporting SWEETs. SWEET11 and 12 were found to be expressed in leaves, and subject to diurnal/circadian regulation [7••,14]. Both proteins, as judged from analyses of GUS reporter fusions,

Figure 2
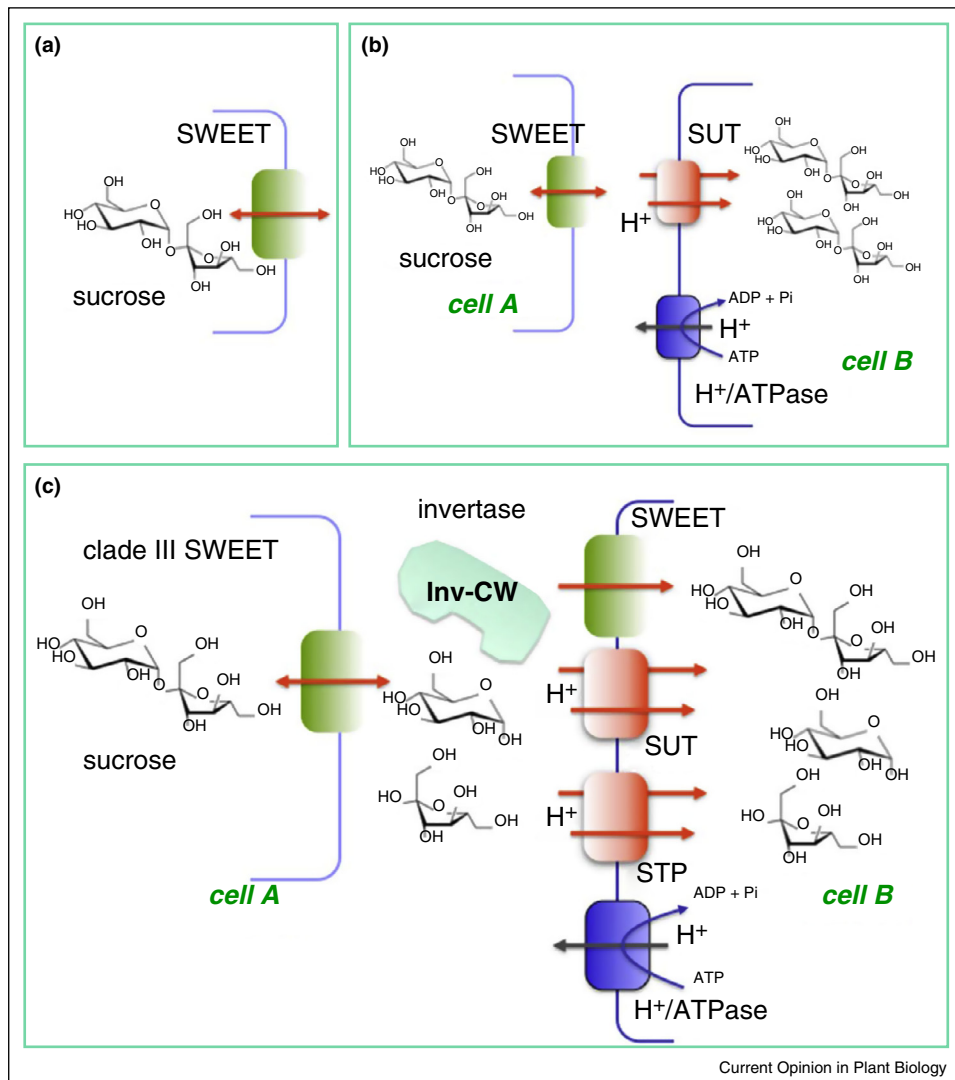
SWEETs in sugar secretion. **(a)** Sugars can be exported from cells, for example in the nectary, by SWEETs. **(b)** SWEETs for the secretion of sucrose from the phloem parenchyma for phloem loading. Cell A secretes sucrose, which is subsequently loaded (against a concentration gradient) into the sieve element companion cell complex (cell B) via a sucrose/H^+ symporter SUT. Secondary active sucrose uptake is energized by the H^+/ATPase. **(c)** SWEETs in secretion of sucrose from the seed coat to supply the developing endosperm and the embryo. Sucrose secreted from cell A is either taken up by SUTs or SWEETs into cell B, or after cleavage by a cell wall invertase (Inv-CW) taken up via clade I/II SWEETs or by monosaccharide transporters, for example of the STP family of hexose/H^+ symporters. Note that formal uniport, as indicated by the arrows has not been formally demonstrated for the SWEETs.

were detected in the phloem. AtSWEET11–GFP was found to localize to the plasma membrane of cells inside the phloem, most likely phloem parenchyma [7••], restricting sucrose flux to the interface between the phloem parenchyma and the sieve element companion cell complex deep inside the leaf. Analysis of *atsweet11;12* double mutants provided strong evidence for a key role in sucrose translocation out of the leaf; in particular the double mutants accumulated starch in leaves, and radio-tracer efflux from petioles was reduced [7••] (Figure 2b). Interestingly, AtSWEET13, the closest homolog of

SWEET11/12, was upregulated in the *atsweet11;12* mu-tant, implying regulatory systems that adjust SWEET transcript levels. Key future questions are whether SWEETs play similar roles in crop plants, how their activities are coordinated with sucrose anabolism and catabolism and SUT transport activity. The apparent restriction of apoplasmic transfer to the interface between phloem parenchyma and the sieve element companion cell complex may indicate that apoplasmic sucrose levels in other parts of the leaf are low. It may thus be necessary to reevaluate the hypothesis that sugars accumulate to

millimolar levels in the leaf apoplasm, which is mainly based on apoplasmic wash fluids, a technology that measures solute efflux into sucrose-free medium and averages across the whole leaf. Cell surface-targeted FRET sucrose sensors may be a suitable tool for monitoring sucrose, such as in the apoplasm surrounding epidermal and mesophyll cells [15].

Role of SWEETs during senescence

Hexoses, in particular galactose, fructose and glucose, accumulate in senescent leaves, and it has been speculated that SWEET members may also function in remobilization of carbohydrate during senescence [16]. The expression of the At*SWEET15* (SAG29) gene is highly induced in leaves during senescence. *Arabidopsis* plants overexpressing At*SWEET15* showed accelerated senescence and salt hypersensitivity while *atsweet15* mutants were less sensitive to high salinity. However, translational fusion with GUS under control of its own promoter indicate that AtSWEET15 protein does not accumulate to high levels during senescence [17]. This apparent difference may be attributable to overall changes in RNA turnover or to post-translational regulation. Similarly, overexpression of OsSWEET5, which can transport galactose, in rice causes growth retardation and early senescence [18]. We observed that overexpression of other SWEETs (e.g. AtSWEET11 and 12) had similar phenotypic effects of growth retardation (Chen and Frommer unpublished; Figure 3). The negative impact of SWEET ectopic expression on plant growth may not be surprising; sugar translocation is limited to a subset of cell types (e.g. phloem parenchyma in the leaf) and polarized. Ectopic expression is expected to lead to a loss in the directionality of sugar flux, and to general leakage of sucrose from cells, thereby reducing phloem loading and causing rather non-specific effects. Therefore, a potential role in reallocation of carbon under conditions of salinity may be indicated, but additional work is required to evaluate the role of SWEETs in leaves for recapturing of carbon during stress or senescence.

Clade III SWEETs in seed filling

Based on the finding that SWEETs act as cellular efflux transporters in phloem parenchyma and nectaries, we hypothesized that they may also contribute to assimilate transfer from maternal seed coat to developing embryo. GFP fusions show that AtSWEET11, 12 and 15 are expressed in seed coat and endosperm. Analysis of the triple knockout mutant showed a severe delay in embryo development and a wrinkled seed phenotype at maturity due to lower starch and lipid content and a smaller embryo [17] (Figure 2c). These findings are exciting because the identification of SWEETs involved in seed coat efflux opens up the possibility of identifying the mechanisms that coordinate the delivery of sucrose from leaves with the needs of the developing seed. Extensive studies of the regulation of post-phloem unloading into seeds by osmotic gradients and sucrose provide guidance for further analysis [19••]. A generalized model of phloem unloading is presented in Figure 4.

SWEETs in pollen nutrition

Large-scale gene expression analyses indicate that at least four AtSWEETs may play roles in nurturing the gametophyte [20]. At*SWEET5* (*VEX1*) is expressed in mature, hydrated and germinating pollen and was found specifically in the vegetative cell of pollen grains, which may supply the generative cell with sugars [21]. Mutation of the hexose transporting clade II AtSWEET8 (RPG1) caused male sterility [5••,22]. More recent work showed

Figure 3

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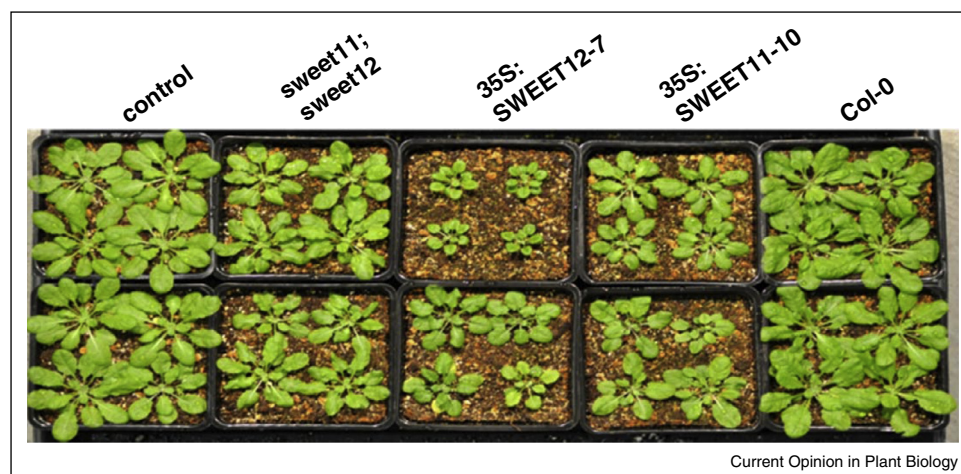
Negative impact of mutation of ectopic expression of clade III SWEETs. Both the *sweet11;12* double mutant [7••] and overexpressor lines for *SWEET11* and *SWEET12* driven by the CaMV 35S promoter (Chen and Frommer, unpublished) show reduced growth.

Figure 4
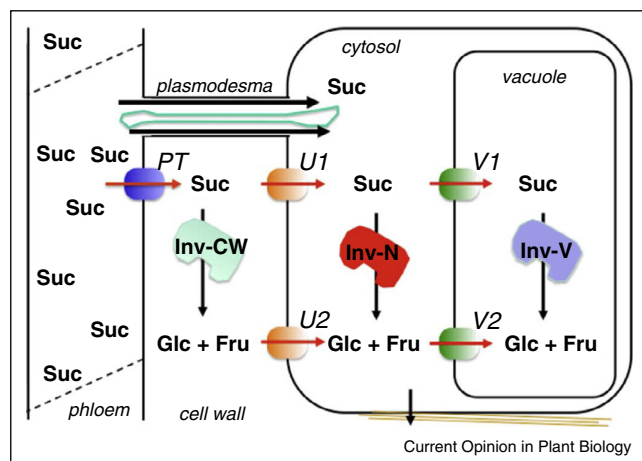
Generic model for principal transport steps and pathways for phloem unloading in various tissues. Sucrose arriving at the phloem endings is either moving symplasmically via plasmodesmata or unloaded (from phloem or after moving symplasmically from post-phloem cells) via a transporter (PT); it can be taken up by sink cells using either a sucrose importer (U1), or by a hexose importer (U2) after cleavage by an extracellular invertase (Inv-CW). Imported sucrose can be catabolized to hexoses by a cytosolic invertase (Inv-N) or sucrose synthetase. Subsequently sucrose or hexoses can be transferred to the vacuole by sucrose or hexose transporters on the tonoplast (V1, V2). The model represents a simplification of the phloem and postphloem unloading pathways.

that AtSWEET13 (RPG2) also plays a role in pollen nutrition [23]. In rice, OsSWEET5 is also expressed in anthers.

SWEET recruitment by pathogens

Apparently, sucrose efflux by SWEETs for phloem loading is restricted to an interface of a few microns deep inside the leaf. One would therefore assume that the apoplasmic space (e.g. between epidermal or mesophyll cells) contains only low sugar levels. Consequentially, the large majority of the apoplasmic space in a leaf may not serve as a good environment for rapid growth of pathogens. Thus pathogens may have to find ways to increase apoplasmic sugar levels in their vicinity. One such example is the direct induction of rice SWEETs by TAL effectors (transcriptional activator-like proteins) from *Xanthomonas oryzae*. Five out of the 21 SWEET genes in the rice genome have been shown to support pathogen growth [24••]. This group of SWEETs all belong to clade III (OsSWEET11–15), and almost all were tested and function as sucrose transporters ([7••,25] and Qu, Sosso, Chen & Frommer, unpublished). Interestingly, two of the SWEETs had been identified as recessive blight resistance loci, named *xa13* and *xa25*; *xa13* corresponds to OsSWEET11 [26••] and *xa25* to its close homolog OsSWEET13 [27]. Furthermore, OsSWEET14 is targeted by various *X. oryzae* pv. *oryzae* (Xoo) strains [28]. Interestingly, OsSWEET12 and 15 have not been found to be targets

of Xoo pathovars so far, indicating that the survey of strains is not broad enough to identify pathovars that hijack these transporter genes, that the pathogens have difficulties targeting these genes, or that induction of these proteins has negative side effects. One possible explanation why only sucrose transporting SWEETs can support pathogen growth may be that, in contrast to sucrose pools, hexose pools in the cytosol are limiting, therefore activation of a hexose transporting SWEET may be insufficient to sustain growth of the pathogen population. The understanding of these mechanisms will help engineering broad-spectrum resistance by genomic editing of the binding sites of the bacterial TAL effectors using either CRISPR/CAs9 or TALEN technologies in rice [29••,30•].

Recessive resistance in rice involving SWEETs had originally been seen as unique; however, recently SWEETs have been shown to be induced by TAL effectors from the Cassava blight pathogen *X. axonopodis* pv. *manihotis* [31•] — interestingly, two clade III SWEETs were also induced (MeSWEET10 and 15). Mutation of the TAL effector responsible for induction of SWEET10 led to resistance. It is noteworthy that in Cassava blight, invertases are also upregulated, enabling the pathogen to acquire hexoses.

The expression of AtSWEETs from clades other than clade III are induced by *Pseudomonas syringae* pv. *tomato* strain DC3000, *Golovinomyces cichoracearum* and/or *Botrytis cinerea* [5••]. Glucose transporter VvSWEET4 from *Vitis vinifera* is involved in the interaction with *B. cinerea*, and the mutants of the orthologous AtSWEET4 are less susceptible to *B. cinerea* [32], indicating a role in facilitating glucose efflux into cell wall space to enhance fungal growth. Expression of CsSWEET1 from citrus is stimulated in a TAL effector dependent manner upon the infection of *X. citri* [33]. Notably, the founding member of the SWEET family, MtN3, was identified as a nodulation-induced gene in *Medicago truncatula* [34]. Further work will be required to determine whether SWEETs play a role in feeding the symbiotic *Rhizobium* [35]. SWEETs have been found to be induced in many systems: for example the infection of wheat by *Puccinia* [36]. It is thus tempting to speculate that SWEETs serve as host susceptibility factors for a wide variety of pathogens including oomycetes and fungi as well as different types of symbionts including mycorrhiza and the microbiota in the rhizosphere.

SWEETs and copper transport

OsSWEET11 was found to interact with two copper transporters homologs of the COPT family [37]. Data from Wang's lab indicated that OsSWEETs are involved in copper transport. Specifically, they observed that the rice copper transporters COPT1 and COPT5 interacted with OsSWEET11, and that coexpression of all three

proteins was necessary to restore copper uptake deficiency of a copper transport–deficient yeast mutant (MPY17 [ctr1Δctr3Δ]). However, copper uptake was not directly measured. The growth phenotype mutant is conditional and is not observed in the presence of glucose. An alternative interpretation of the results may be that COPT1 and 5 mediate low level copper uptake while OsSWEET11 mediates uptake of contaminant sugars from the medium (i.e. the agar), thus partially relieving the dependency of mutant growth on copper. At higher copper levels (20 μM), COPT1 and 5 complement MPY17 [38], potentially supporting the proposed mechanism. Alternatively, OsSWEET11 might affect plasma membrane targeting efficacy, thereby increasing copper transport activity. It will be important to further characterize this phenomenon *in planta*.
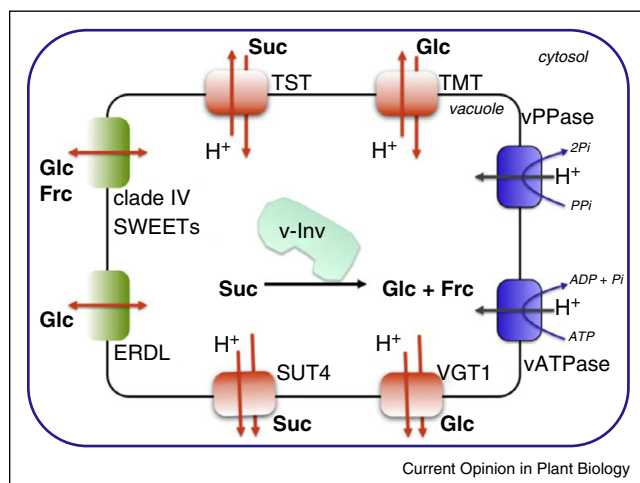
Vacuolar SWEETs

The world's sugar supply comes from the vacuoles of sugarcane stems and sugar beet taproots. It is thus of critical importance to understand the interplay of metabolism and transport across the tonoplast. While 10 years ago little was known, now a large number of different sugar transporters on the tonoplast have been identified: proton cotransporters, likely for export of sugars (VGT1 and SUT4), and proton antiporters (TMT) and potential uniporters of the ERD-like family [39–41] (Figure 5). Most recently, homologs of the TMTs were identified as responsible for sucrose accumulation in sugarbeet [42••]. Interestingly, clade IV SWEETs have been shown to also function as vacuolar hexose transporters [43,44,45••]. Both AtSWEET 16 and 17 localize to the tonoplast,

Figure 5

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Transporters for vacuolar uptake and efflux of hexoses and sucrose. Three types of sugar transporters have been identified on the tonoplast: proton symporters (SUT4 for sucrose and VGT1 for hexoses), proton antiporters (TMT for monosaccharides and TST for sucrose) and potential uniporters (ERD-like transporters and SWEETs) for hexoses.

and AtSWEET17 is a key determinant of leaf fructose content. Despite this massive gain in knowledge, it remains a mystery how this complex suite of transporters is coordinated and how it supports transient accumulation of sugars, and what the key differences are between vacuoles that store low and high levels of sugars. An overview over activities and function of the various SWEETs has been published recently [46].

Regulation of SWEETs

If SWEETs function as uniporters, which has not yet been formally demonstrated, one might speculate that it would be important to tightly regulate their activity to prevent uncontrolled leakage. One could even envisage that their activity is feedback-regulated by their substrates, coordinated with the activity of their partners, the SUTs in the adjacent cells or regulated by turgor pressure [19••]. Post-translational regulatory mechanisms are indicated based on the finding that serine residues in the C-terminus of AtSWEET11 were phosphorylated in response to sucrose addition to seedlings grown in liquid culture [47•]. However, because the ectopic transcriptional induction by pathogens leads to sugar secretion, and AtSWEET9 overexpression led to an increase in nectar volume, post-transcriptional control systems may not be essential for SWEET activity. The typically very long cytosolic C-terminus of the SWEETs may serve as a docking platform for protein interactions, however different from the AMTs, for which the C-terminus is highly conserved and serves as an allosteric trans-activation domain [48•]. SWEET C-termini show much less conservation and are characterized by extensive length variability.

SWEETs in the animal kingdom

Excitingly, SWEETs have also been identified in humans, and we showed that both a *Caenorhabditis elegans* and the human homolog mediate glucose transport [5••]. In *C. elegans*, one of the seven SWEETs, Swt-1, was identified in a screen for mutants that accumulate lipids using Nile red staining, which could be a secondary effect of glucose accumulation [49]. Mutation of the sea squirt homolog CiSWEET1/Ci-RGA led to early developmental defects, underlining the importance of SWEETs in metazoa [50]. In *Drosophila*, SWEETs had been identified as genes expressed in embryonic salivary glands [51]. The human SWEET1 shows ubiquitous expression with highest expression in oviduct, epididymis and intestine as well as in β-cell lines. HsSWEET1 mainly localized to the Golgi of HEK293T cells [5••]. Based on the localization and weak glucose efflux activity, we hypothesize that HsSWEET1 may play a role in the vesicular glucose efflux from β-cells, the intestine and liver cells [5••].

Summary and outlook

The identification of the large SWEET family as sugar transporters has led to the discovery of many elusive

transport steps, including nectar secretion, phloem loading and post-phloem unloading as well as novel vacuolar transporters. Moreover, the human homologs likely play important roles in human physiology. The discovery of SWEETs also enabled the identification of bacterial SemiSWEETs. Atomic resolution structures of the Semi-SWEETs have provided insights into the transport mechanism and will enable detailed structure–function analyses. Importantly, SWEETs play key roles in pathogen susceptibility and promise new ways to engineer robust broad-spectrum pathogen resistance. Future studies will be directed toward understanding the regulatory networks that integrate SWEET activity with metabolism and other transporters. Genetically encoded fluorescent sugar sensors targeted to various cellular compartments promise to provide insights into the distribution and the fluxes of sugars which in combination with the analysis of sugar transporter will help us better understand the important fundamentals of phloem loading and unloading in model and crop species. Understanding and fine tuning the fluxes between cells in leaves and seeds will likely be key for engineering crop yield potential.

Acknowledgements

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.pbi.2015.04.005.

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