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Pollen likes sugars: Sucrose-specific transport by AtSWEET13

Alexis De Angeli^{a,1}

The biological function of transmembrane solute transporters (i.e., ion channels, pumps, antiporters, symporters) is intimately linked to the identity of the transported molecules. This makes the “selectivity issue” a hot topic in membrane biology. A variety of biological processes rely on the capacity of transmembrane transporters to specifically “choose” the molecules to transport in between the variety of chemical species they face in both intracellular and extracellular solutions. Classical examples are, in animals, electrical signaling that is dependent on the ability of specific ion channels to discriminate between Na⁺ and K⁺ (1) or in all eukaryotes, Ca²⁺ signaling that requires the transport of Ca²⁺ by specific channels and pumps (2). Notably, the cellular functions of complex molecules, such as hormones, neurotransmitters, or other peptides, are also dependent on their selective transport across membranes. In plants, the specific spatio-temporal function of hormones in regulating the development of organs depends on the selective transport of these molecules within and between cells (3–5).

Despite the crucial role of selectivity, ion transport systems have, like other enzymes, a certain degree of promiscuity regarding the processed substrate (6). Selectivity depends on the specific molecular interactions between the substrate and the proteins forming transmembrane transport systems. However, strong interactions with the substrate favor specificity, but they slow down the reaction speed and limit the net transport capacity. Thus, in their evolution, transport systems could optimize a trade-off between the selectivity and the rapidity of the catalyzed transport reactions. As a consequence, a single transport system can mediate the transport of different molecules with potentially different biological functions. In some cases, transported species share a similar structure, but they can also have different molecular architectures (7–10). In PNAS, Isoda et al. (11) dissect the biological significance of the transport of two different molecules by a single transporter in pollen development.

In the last decade in plant biology, “transport promiscuity” has been proposed to be an important property for the biological function of transport systems. It was found that several transporters were able to mediate fluxes of different molecules having different cellular functions, such as metabolites and phytohormones. For example, in the nitrate peptide transporters family (NPLF/NRT), some members catalyze the H⁺-coupled transport of molecules as diverse as NO₃[−] and auxins (12) or glucosinolates (13). Similarly, in the sugar transporter family of the SWEETs (Sugar Will Eventually Be Exported Transporters), some members were also proposed to transport both sucrose (electrically neutral) and the phytohormones, like gibberellic acid (negatively charged) (14). These findings pushed the issue of the selectivity of transporters in their biological context at the forefront of plant physiology. Indeed, the fact that a single kind of transporter is able to mediate the transport of, for example, metabolites involved in plant nutrition, such as NO₃[−] or sucrose, and also, of a

phytohormone controlling plant development has important physiological implications and opens some key issues. Indeed, the multiple transport capacity places these promiscuous transmembrane transport systems at the crossroad of metabolic and developmental pathways (14, 15). This is a potentially straightforward way of connecting different pathways and coordinating cellular responses. However, in most of the cases, direct transporter selectivity assays are performed in heterologous or artificial systems, leaving open the question of the molecules that are actually transported in vivo by a single type of transporter. Although crucial to understanding the molecular function of many transporters in vivo, this issue is only rarely resolved.

AtSWEET13 (*Arabidopsis thaliana* Sugar Will Eventually Be Exported 13) is part of the SWEETs transporter family, which mediates the export of sugars across the plasma membrane of plant and animal cells (16, 17). SWEETs are transmembrane proteins formed by six transmembrane α -helices and organized in dimers (18). They are passive transporters (uniporters) mediating fluxes of sugars across the plasma membrane along their chemical potential gradient. SWEETs are involved in most of the physiological processes requiring sugar excretion to the cell wall (16). SWEETs participate in the translocation of sugars between plant organs, a key process for growth and biomass production (17). They are involved in sugar secretion by the nectary to attract insects for pollination (16, 19), in pollen development (14, 20, 21), and in pollen tube growth (16). Interestingly, SWEETs were also found to be involved in the susceptibility to pathogen attack since pathogens hijack these transporters to acquire glucose from the host (16, 22).

Clade III of the SWEET family, to which AtSWEET13 belongs, was proposed to be formed by promiscuous transporters. AtSWEET13 mediates the transport of sucrose and gibberellic acid when expressed in heterologous systems (14). Further, AtSWEET13 is, together with AtSWEET8 and AtSWEET14, essential for male fertility in *Arabidopsis*, and double-knockout *sweet13 sweet14* plants display marked reduced seed production (14, 23). AtSWEET13 and AtSWEET14 are expressed in the anthers, the organs where pollen grains are produced, at the level of the tapetum cell layer and in meiotic cells (20). Accordingly, *sweet13 sweet14* plants display a delayed pollen dispersal

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(dehiscence) of the anther, explaining the reduced fertility. At a molecular level, this loss of fertility in *sweet13 sweet14* double-mutant plants was proposed to be linked to a defect in gibberellic acid transport, rather than sugar, in mutants of AtSWEET13 or AtSWEET14 (14). Nonetheless, given the tight correlation between sugars and gibberellic acid in plant cells, it is not straightforward to distinguish between the relative importance of the transport of these two species.

In PNAS, Isoda et al. (11) dissect in vivo the physiological relevance of the sucrose and gibberellic acid transport mediated by the AtSWEET13 transporter. They asked a simple but fundamental question. Is the AtSWEET13-mediated transport of both sucrose and gibberellic acid important in plant cells, or is only one of them the relevant one? To answer this question, the authors used an elegant strategy aiming at the separation of sucrose transport from gibberellic acid transport by AtSWEET13. To reach this objective, they took advantage of the available high-resolution structure of AtSWEET13 (18) and used it to explore the molecular interactions between sucrose and AtSWEET13 and between gibberellic acid and AtSWEET13. Molecular dynamic simulations predicted the key residues specifically interacting with sucrose or with gibberellic acid. Notably, the gibberellic acid interaction with AtSWEET13 appeared to be more rigid than the one with sucrose, and this analysis allowed them to identify potential target residues for site-directed mutagenesis in order to modify the selectivity of the transporter. The analysis of the transport capacity of the selected mutated versions of AtSWEET13 allowed them to identify two mutants, N76Q and S142N, that have an alternatively modified sucrose to gibberellic acid selectivity. Indeed, AtSWEET13^{N76Q} became specific to gibberellic acid, while AtSWEET13^{S142N} became sucrose selective.

The identification of these two point mutant versions of AtSWEET13 allowed the authors to understand if the defects in pollen viability of SWEETs mutant depend on the transport of sucrose, gibberellic acid, or both substrates.

Expression of both AtSWEET13 versions in *sweet13 sweet14* double-mutant plants demonstrated that pollen grain viability was only rescued by the “sucrose-only” selective AtSWEET13^{S142N}. These findings answer the initial question of the authors and show that in this process, the transport of sucrose is the relevant function of AtSWEET13 in vivo. Interestingly, the same conclusion was recently drawn by other authors using a slightly less direct approach (23). The analysis of the expression of AtSWEET13 in the anthers shows that it is expressed in the endothecium at floral developmental stages when cellular sucrose concentrations rapidly fluctuate in response to the third wave of amylolysis. AtSWEET13 is, therefore, essential to mediate the sucrose fluxes necessary for pollen grain development, providing an important step further in our understanding of this important biological process.

The present findings are an important example of the possibility of dissecting the relative importance of different substrates transported by the same membrane protein in vivo. Some other examples illustrate that, even if in vitro or artificial assays demonstrate the possibility that a single transporter mediates fluxes of different molecules, this might not be the case within the physiological context (24) or vice versa. Understanding the action mechanisms of transmembrane solute transport and its integration within metabolic pathways of plant cells will impact our capacities to develop strategies to adapt crops to changing environmental conditions. Indeed, transmembrane transport is fundamental in a wide variety of processes, such as resource allocation between leaves and roots, leaf transpiration, pathogen resistance, drought tolerance, nutrition, and reproduction.

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