Review

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# Structure and function of SemiSWEET and SWEET sugar transporters

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**SemiSWEETs and SWEETs have emerged as unique sugar transporters. First discovered in plants with the help of fluorescent biosensors, homologs exist in all kingdoms of life. Bacterial and plant homologs transport hexoses and sucrose, whereas animal SWEETs transport glucose. Prokaryotic SemiSWEETs are small and comprise a parallel homodimer of an approximately 100 amino acid-long triple helix bundle (THB). Duplicated THBs are fused to create eukaryotic SWEETs in a parallel orientation via an inversion linker helix, producing a similar configuration to that of SemiSWEET dimers. Structures of four SemiSWEETs have been resolved in three states: open outside, occluded, and open inside, indicating alternating access. As we discuss here, these atomic structures provide a basis for exploring the evolution of structure–function relations in this new class of transporters.**

## SWEETs and sugar transport

Living organisms depend on soluble sugars as the major source of carbon skeletons and energy. Organisms have found ways to facilitate the passage of sugars across cellular membranes and to control sugar influx and efflux depending on their supply and demand. Over the past 20 years, many key sugar transporters have been identified from bacteria, fungi, plants, and humans [1]. These transporters can be categorized into four superfamilies: bacterial phosphotransferase (PTS) systems, ATP-binding cassette transporters, major facilitator superfamily (MFS) transporters found across all kingdoms and the bacterial and metazoan sodium-solute symporter family (SSF) transporters. The most prominent members of the MFS family include the bacterial lac permease [2], the yeast HXTs, the human glucose transporters (GLUTs) and the plant STPs (Sugar TransPorters) and SUTs (SUcrose Transporters) [3]; the best-studied sugar transporters in the SSF family are the sodium glucose transporters (SGLTs) [4]. Recently, a novel family of sugar transporters was identified, which includes SWEETs and SemiSWEETs. Both belong to the MtN3/saliva clan (CL0141) and their homologs are found in all kingdoms of life [5–8]. The founding members of this family were identified by using fluorescent sugar sensors to screen membrane proteins from plants for which no biological function had been assigned. Screens using fluorescent glucose sensors identified the first members (e.g., *Arabidopsis* SWEET1 and 8 as hexose transporters) [5]; later, a similar screen using fluorescent sucrose sensors identified members that were able to transport sucrose [6,8]. Homologs able to transport glucose were also found in humans and the worm *Caenorhabditis elegans* [5]. Eukaryotic SWEETs all have a predicted topology comprising a repeat of three transmembrane-spanning domains (TMs) separated by a single TM [5] (Figure 1). Bioinformatic studies identified homologs in bacteria (named SemiSWEETs), which are much smaller, with only approximately 100 amino acids and predicted to contain only one of the THB repeats [9]. SemiSWEETs are widely distributed among prokaryotes, including Archaea and Eubacteria, but are sparse; that is, not all bacteria have a SemiSWEET. A SemiSWEET (LbSemiSWEET from *Leptospira biflexa* serovar Patoc [10]) has been shown to transport glucose, while two members (BjSemiSWEET from *Bradyrhizobium* [9] and EcSemiSWEET from *Escherichia coli* [11]) are able to mediate sucrose transport. Much information has been gained relating to the physiological role of the plant SWEETs, while currently little is known about animal SWEETs and nothing is known to date about the physiological role of bacterial SemiSWEETs. Here, we summarize information on the biological role of SWEETs and focus on the recent analysis of atomic resolution structures of several SemiSWEETs.

## Important physiological roles of SWEETs in plants

Plant genomes typically contain approximately 20 SWEET paralogs, which are differentially expressed, implicating them in a range of sugar translocation steps. *Arabidopsis* SWEETs fall into four subclades and share 27–80% identity. Clades I, II, and IV appear to be predominantly hexose transporters, whereas clade III SWEETs transport predominantly sucrose, although some also can transport hexoses. SWEETs can localize to different cellular compartments, in particular the plasma membrane (e.g., SWEET1, 8, 9, 11,12, and 15 [5–8,12,13]), the tonoplast (SWEET16 and 17 [14–16]), and the Golgi (SWEET9 and 15 [7,8]). As is common for transporters, which typically are polytopic membrane proteins (type IV multiple-pass α-helices), no apparent N-terminal signal sequences for targeting to a specific membrane compartment can be discerned. The existence of transporters from the same family

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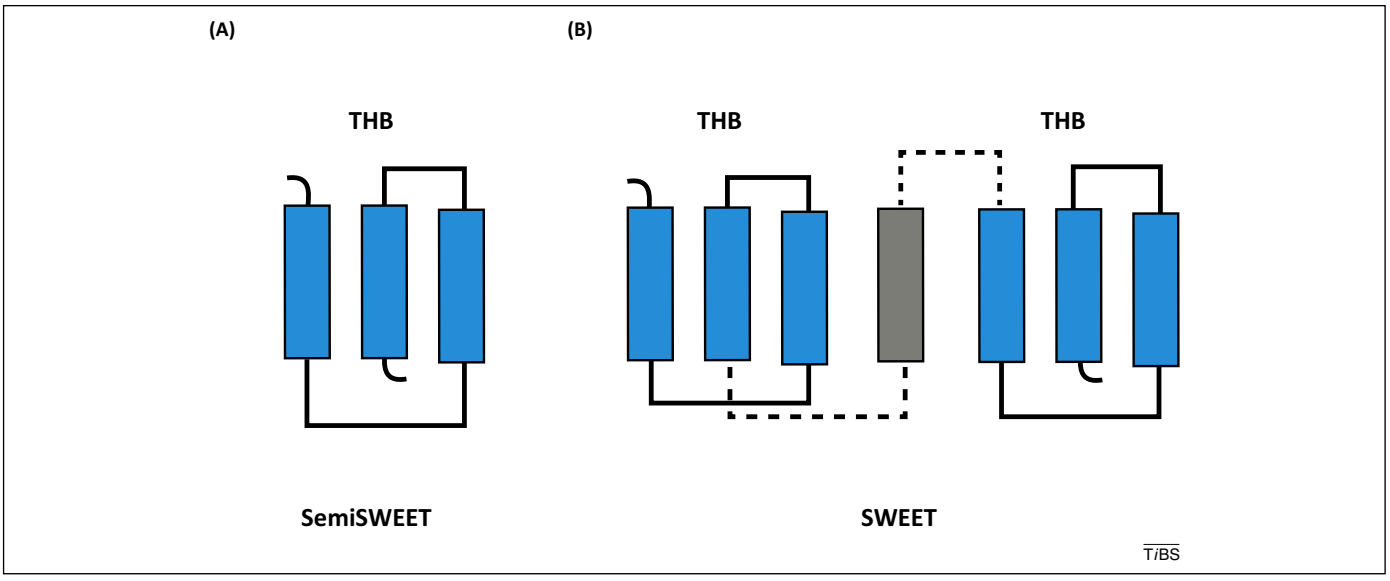


**Figure 1**. SemiSWEET and SWEET topology. **(A)** SemiSWEET comprises a simple 1-3-2 triple helix bundle (THB). **(B)** SWEET contains two THBs that are connected by an inversion linker helix.

being targeted to different compartments has been found also for other transporters, such as peptide transporters [17] and aquaporins [18].

A combination of expression analyses, localization studies, and analyses of mutants in *Arabidopsis* has enabled researchers to assign specific roles to individual SWEETs in specific steps in the sugar translocation pathways of plants, particularly sugar efflux in nectar secretion, and from phloem parenchyma cells for phloem loading, seed filling, and pollen nutrition (Table 1). A rather unexpected discovery was that SWEETs have a role in pathogen susceptibility [5]. A prominent example is the rice locus Xa13 (*SWEET11*/*Os8N3*), which is responsible for recessive rice blight resistance [30–32]. Any of the sucrose-transporting SWEETs in the rice genome could serve as a susceptibility factor [19] when recruited by a TAL effector in *Xanthomonas oryzae oryzae*, the causative agent of blight disease. However, when the respective SWEETs become unavailable due to mutations in the *SWEET* promoter or through RNAi [30,31], the sugar supply becomes limiting and the pathogen cannot multiply efficiently. Given that the pathogens must infect plants to be able to reproduce and because they also require nutrients for efficient reproduction, this may be a general mechanism. This hypothesis is supported by the observation that SWEETs are also important for susceptibility to cassava blight [20].

## Physiological role of SWEETs in animals and humans

To date, and despite the apparent potential for affecting sugar homeostasis in animals and humans, little is known about the physiological role of SWEETs in animals. Although animal genomes, including that of humans, typically contain only a single SWEET gene, a major exception is *Caenorhabditis elegans*, which contains seven SWEET paralogs. Both the human and one of the *C. elegans* SWEETs mediate glucose transport. Their broad expression patterns implicate them as fundamental sugar transporters in animal and human physiology. The first identified member of this family in animals was the *Drosophila* gene *saliva* (*slv*), now recognized as *DmSWEET1* from sequence similarity. Overexpression of *slv* affected axonal growth and guidance [21]. It remains unclear whether this is a specific effect, or whether it is due to interference with polarized sugar translocation. In plants, ectopic expression of SWEETs negatively impacts growth, indicating that uncontrolled overexpression leads to toxicity, possibly by creating leaks from cells that normally do not efflux sugars [3]. Mutations in the sea squirt SWEET gene (*CiRGA*) caused defects early in development, underlining the importance of SWEETs in Metazoa [33]. Given the importance of sugar homeostasis in humans, it will be crucial to systematically study the physiological role of SWEETs and their regulation in different states, including metabolic diseases.

## SemiSWEET structures

Recent breakthroughs in the structural determination of four SemiSWEET homologs revealed the architecture of SemiSWEET, captured three conformational states, and provided rich structural insights into the transport mechanism of these transporters [10,11,22].

This burst of structures started in 2014, when VsSemiSWEET (from *Vibrio* sp. N418) and LbSemiSWEET were determined at 1.7-Å and 2.4-Å resolution, respectively [10]. VsSemiSWEET was found to be in an outward open state, while LbSemiSWEET was in an occluded state. Then, the structure of TySemiSWEET (from *Thermodesulfovibrio yellowstonii* DSM 11347) was found to be in an occluded state [22], and structures of EcSemiSWEET were reported in both inward open and outward open states [11]. All these structures were determined using crystals grown in a lipid cubic phase (LCP), which was necessary to obtain high-quality crystals of SemiSWEETs.

These structures unambiguously revealed the architecture of SemiSWEET (Table 2). The basic structural unit of