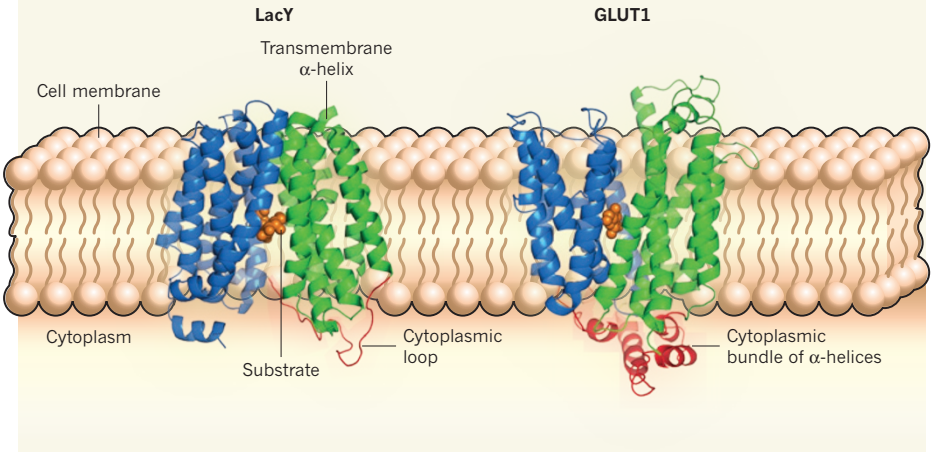


Figure 1 | Relatives but not twins. Proteins belonging to the major facilitator superfamily (MFS) transport vital nutrients such as sugars across cell membranes, and it is thought that their mechanism of action involves alternating inward-facing and outward-facing conformations. MFS proteins typically consist of 12 transmembrane α-helices, organized into two similar bundles (blue and green), as well as cytoplasmic loops. One such protein, LacY, is shown here bound to an analogue of its substrate (the sugar lactose) and in an inward-facing conformation. Sun *et al.*[2] solved the outward-facing structure of another MFS member, the bacterial protein XylE, and used it to construct plausible models of similar human proteins, the glucose transporters GLUT1 to GLUT4. The authors show that, in contrast to other MFS proteins, XylE and GLUTs have a cytoplasmic bundle of four α-helices that might participate in the transport mechanism. (LacY and GLUT1 images courtesy of N. Yan, Tsinghua University, Beijing, China.)

with amino-acid residues in the carboxy-terminal bundle. These residues are largely the same in GLUT1 to GLUT4, which suggests a common mode of sugar binding (Fig. 1).

Surprisingly, the reported structures and models cannot explain a profound difference that exists between XylE and GLUT1–GLUT4: sugar intake is coupled to proton (H^+) translocation in XylE but not in its human counterparts. Proton transport into the bacterial cell drives xylose uptake against its concentration gradient because it is an energetically favourable process (there is a lower concentration of protons inside the cell than outside). By contrast, GLUT1 to GLUT4 facilitate diffusion of glucose only down its concentration gradient. However, comparison of the XylE structure with the GLUT models did not reveal any obvious candidates for proton-binding residues that could account for this functional difference.

Transport of molecules across the membrane is generally thought to occur through a mechanism in which changes in the protein's conformation make the substrate binding site alternately accessible from one or other side of the membrane[5,6]. However, Sun *et al.* report that XylE and the GLUT models have a bundle of four α-helices on the cytoplasmic side of the membrane that are not present in the structures of other MFS proteins (Fig. 1), implying possible mechanistic differences. These additional α-helices participate in an intricate network of hydrogen bonds with residues located near the cytoplasmic ends of some of the transmembrane helices. Interestingly, such residues are found in signature-sequence motifs that are evolutionarily conserved in other members of the sugar-porter family, and the authors observed that mutations affecting these residues had drastic effects on transport.

The precise role of the hydrogen-bond network in substrate translocation remains to be determined. However, it has been shown for GLUT1 that truncation of the carboxy-terminal end of the protein (which would remove some of those interactions) 'locks' the transporter in an inward-facing conformation in which it is able to bind to the sugar but not to transport it[7]. By contrast, the cytoplasmic domain in non-sugar-porter MSF transporters seems to have only a minor role in the proteins' function, as previously shown[8] by mutation of the TM6–TM7 loop in the *E. coli* lactose transporter LacY. Therefore, despite a common evolutionary origin, the precise mechanism of transport might vary in different MFS subfamilies.

The XylE structure and the GLUT models open the way to a greater understanding of the physiological functions, mechanisms and regulation of these proteins. For example, it could be possible to design selective small-molecule inhibitors of these proteins to address the question of why mammals need 14 different GLUT proteins[9]. Similarly, Sun and colleagues' results should help to clarify the molecular basis for the different substrate selectivities displayed by GLUTs; for example, GLUT9 transports urate (a compound resulting from the metabolic breakdown of nucleotides) in addition to sugars[9].

But the significance of the XylE structure extends beyond mammalian metabolism,

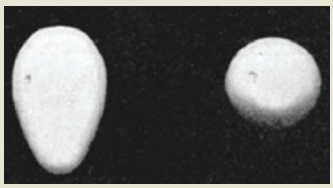
50 Years Ago

The distance travelled by grazing sheep and the energy cost of locomotion have been measured … This leaves the energy cost of grazing *per se* and of the animal's reactions to its environment to be accounted for; the first measurements of the former can now be reported. Two sheep were allowed to graze normally for a week. A patch of turf 1.0 × 1.5 m was then dug up and relaid on the floor of a respiration chamber. The sheep, which had both been trained for such work, were then, one at a time, placed in the respiration chamber … The energy expenditure of the sheep always increased during grazing and fell again during the subsequent rest period, but there was no significant change when pre-cut grass was given to the sheep. The grazing increment did not vary significantly from sward to sward, and had a mean value of 0.62 ± 0.04 kcal/h/kg body-weight for a 29-kg Merino ewe and of 0.84 ± 0.12 for a 53-kg Merino wether.

From *Nature* 20 October 1962

100 Years Ago

The accompanying photograph shows a pearl … alleged to have been found in *Nautilus pompilus*, from the Sulu archipelago.



The pearl … weighs 18 carats (72 grains), and is composed of the porcellanous (not the nacreous) constituent of the shell. It is somewhat translucent, white, with a slight creamy tinge, rather suggesting fine Beleek china

From *Nature* 17 October 1912