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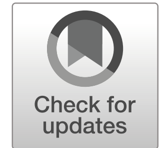
INVITED REVIEW



Transporters of glucose and other carbohydrates in bacteria

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Abstract
Glucose arguably is the most important energy carrier, carbon source for metabolites and building block for biopolymers in all kingdoms of life. The proper function of animal organs and tissues depends on the continuous supply of glucose from the bloodstream. Most animals can resorb only a small number of monosaccharides, mostly glucose, galactose and fructose, while all other sugars oligosaccharides and dietary fibers are degraded and metabolized by the microbiota of the lower intestine. Bacteria, in contrast, are omnivorous. They can import and metabolize structurally different sugars and, as a consortium of different species, utilize almost any sugar, sugar derivative and oligosaccharide occurring in nature. Bacteria have membrane transport systems for the uptake of sugars against steep concentration gradients energized by ATP, the proton motive force and the high energy glycolytic intermediate phosphoenolpyruvate (PEP). Different uptake mechanisms and the broad range of overlapping substrate specificities allow bacteria to quickly adapt to and colonize changing environments. Here, we review the structures and mechanisms of bacterial representatives of (i) ATP-dependent cassette (ABC) transporters, (ii) major facilitator (MFS) superfamily proton symporters, (iii) sodium solute symporters (SSS) and (iv) enzyme II integral membrane subunits of the bacterial PEP-dependent phosphotransferase system (PTS). We give a short overview on the distribution of transporter genes and their phylogenetic relationship in different bacterial species. Some sugar transporters are hijacked for import of bacteriophage DNA and antibacterial toxins (bacteriocins) and they facilitate the penetration of polar antibiotics. Finally, we describe how the expression and activity of certain sugar transporters are controlled in response to the availability of sugars and how the presence and uptake of sugars may affect pathogenicity and host-microbiota interactions.

Keywords ABC · Antibiotic · Bacteriocin · Bacteriophage · Chemotaxis · Glucose · Maltose · Mannose · Microbiota · Phosphotransferase system · PTS · Sugar transport · Symporter · Xylose

Introduction

Glucose (Glc) is the primary product of photosynthetic CO_2 assimilation by marine algae, cyanobacteria and terrestrial plants. An estimated $2.6 \cdot 10^{11}$ tons of CO_2 is converted annually corresponding to the production of $1.7 \cdot 10^{11}$ tons of Glc. Glc and N-acetyl-D-glucosamine (GlcNAc) are the building blocks of cellulose and of chitin, the most abundant and second most abundant biopolymers, respectively. Cellulose is the basic component of the plant cell wall. Chitin is the major component of fungal cell walls and the organic matrix of the exoskeleton of arthropods (crustaceans and insects). A variety of bacteria and fungi secrete enzymes that degrade insoluble cellulose and chitin to soluble tri- and disaccharides (cellobiose, N,N′-diacetylchitobiose) [5, 88, 105, 161]. The latter are taken up by bacteria through membrane transport proteins, intracellularly hydrolysed or phosphorolysed to monosaccharides, and converted to Glc and glycolytic intermediates for energy (ATP) production by fermentation and oxidative phosphorylation (Fig. 1). The intermediates of Glc breakdown provide the carbon scaffolds for the biosynthesis of amino acids, fatty acids and secondary metabolites.

Glucose and other carbohydrates are the most important nutrients for the majority of heterotrophic bacteria. Not surprisingly, bacteria are equipped with numerous transporters with different and often overlapping sugar specificities for mono-, di and trisaccharides [79]. They can accumulate sugars

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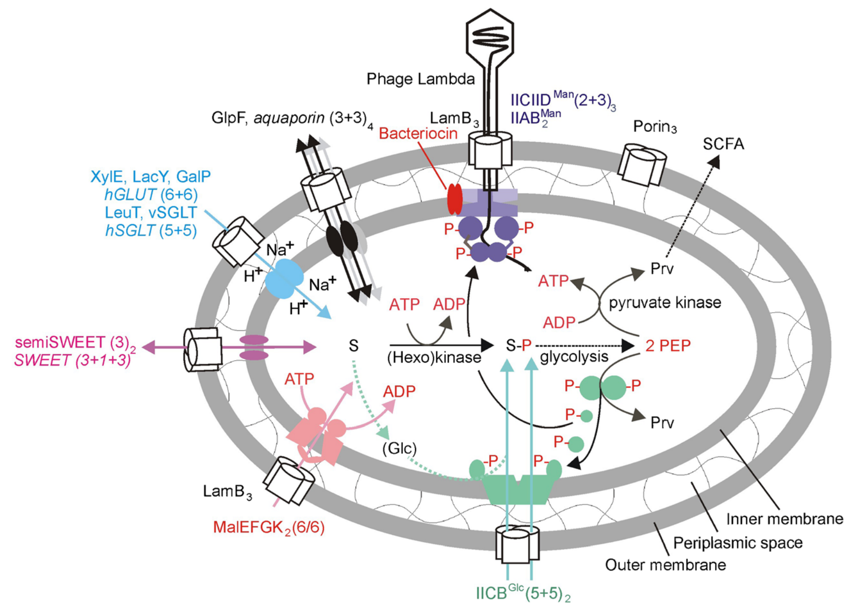

Fig. 1 Transport and metabolism of sugars in bacteria: facilitative (black and magenta), secondary active (cyan), primary active (pink), group translocation (green, and violet), outer membrane porins (white). The abbreviations refer to representative transporters of *E. coli* and eukaryotic homologs (*italics*). Indicated in parentheses are the number of transmembrane helices (TM) and their domain organization. Imported sugars (S) are first transformed to phosphorylated glycolytic intermediates (by kinases) and then metabolized to phosphoenolpyruvate (PEP), pyruvate and short chain fatty acids (SCFA). ATP and PEP serve as energy sources for the uptake of sugars. Sugar uptake by transporters of the PEP-dependent phosphotransferase system (PTS) is coupled with sugar phosphorylation (Fig. 4b). Cytoplasmic Glc can be phosphorylated by $IICB^{Glc}$(dotted green). The properties of the proteins are summarized in Table 1. $IIAB^{Man}$ is required for mannose uptake and phosphorylation but not for penetration of bacteriophage lambda DNA and bacteriocins. Porins (OmpA, OmpC, LamB) are trimeric beta-barrel proteins in the outer membrane. LamB is a porin for maltose and maltodextrins (maltoporin). LamB serves as the outer membrane receptor for bacteriophage lambda

against steep concentration gradients, utilizing ATP (by ATP binding cassette, ABC transporters), ion gradients (by major facilitator superfamily, MFS transporters) and phosphoenolpyruvate (by PEP-dependent phosphotransferase system, PTS transporters) as energy sources. *E. coli* for instance has six different Glc transporters employing all three different energy sources (MglABC (ABC2); GalP (MFS); $IICB^{Glc}$, $IICIID^{Man}$, $IICBA^{GlcNac}$ and MalX (PTS) see below) and two for xylose (XylE (MFS); XylFGH (ABC2)) [53, 54] (Table 1 and below*: Structure and mechanism of primary ATP binding cassette (ABC) transporters*). A sugar transporter usually is expressed only when the sugar substrate is available. In this case, the sugar or an early metabolite of it acts as inducer, by either activating a transcription activator or inactivating a repressor of the sugar-specific operon. These operons contain the genes encoding the transporter (subunits) and frequently also the enzymes that convert the transported sugar into a glycolytic intermediate. In nutrient-rich environments, not all available sugars are taken up simultaneously, but sequentially, the easiest metabolizable (usually Glc) first and the others only after Glc is exhausted [47, 100, 131]. The phenomenon of hierarchical use of sugars is termed carbon catabolite repression (CCR [191]).

Sugar uptake is different in bacteria and animals [152]. Bacteria are equipped with sugar transporters of great diversity with respect to structure, mechanism and substrate specificity. Animals in contrast have only a few types, but a much larger number of tissue-specific paralogs [30]. In animals, oligosaccharides (e.g. lactose), glycogen and proteoglycans are cleaved in the small intestine by hydrolases on the surface of the brush border membrane. Only monosaccharides, Glc, galactose and possibly xylose are taken up against a concentration gradient across the apical membrane of endothelial cells by the sodium Glc cotransporter 1 (SGLT-1) and released into the capillary bloodstream by diffusion across the basolateral membrane facilitated by the Glc-transporter 2 (GLUT2) [200]. Fructose is taken up by facilitated diffusion (GLUT5). Once in the bloodstream Glc enters tissue cells by facilitated diffusion (GLUT2 or GLUT4), down the concentration gradient. Blood Glc concentration is kept constant by the combined activity of several pancreatic hormones. Excess Glc is converted to glycogen in muscle and liver from where it can be mobilized when needed. Bacteria also can store energy in the form of glycogen and polyphosphate [148, 198], but the storage capacity is limited and bacteria just stop growing when nutrients are exhausted. Polysaccharides and glycopeptides not digested, and sugars not resorbed in the small intestine pass into the large intestine where they are degraded by enzymes of the gut microbiota. “Glycophagic” *Bacteroides* ferment sugars to short chain fatty acids (SCFA, e.g.

Table 1 Proteins and properties referred to in this review

Protein/complex	Length and oligomeric struct.[a]	Properties[b]	UniProt Entry[c]	PDB codes[d]	TCDB Nr.[e]	*Gene*
ATP-Binding Cassette (ABC) 3.A						
* $MalEFGK_2$	$396 + 514 + 296 + (371)_2$	Maltose TP; MalE, Mal binding protein; MalFG, transport units; MalK, ATP binding	P0AEX9, P02916, P68183 P68187	4KHZ, 3RLF	3.A.1.1.1	*malEFGK*
MalT	901	Transcription activator of *mal* operons. Inactivated by binding/sequestration to MalK	P06993	1HZ4		*malT*
LamB	$(446)_3$	Maltoporin, bacteriophage lambda outer membrane receptor	P02943	1MPO	1.B.3.1.1	*lamB*
MglABC	$332 + (336)_2 + 506$	Glucose/galactose TP	P0AEE5, P0AAG8, P23200		3.A.1.2.3	*mglBCA*
XylFGH	$320 + (393)_2 + 513$	Xylose TP	P37387, P37388, PP0AGI4		3.A.1.2.4	*xylFGH*
Major Facilitator Superfamily (MFS) 2.A.1						
* XylE	491	D-xylose:H^+ TP	P0AGF4	4QIQ, 4GBY	2.A.1.1.3	*xylE*
LacY	417	Lactose:H^+ TP	P02920	5GXB	2.A.1.5.1	*lacY*
GLUT1/SLC2A1	492	facilitative glucose TP, *Homo sapiens*	P11166	4PYP	2.A.1.1.28	*SLC2A1*
GLUT2/SLC2A2	524	facilitative glucose TP, *Homo sapiens*	P11168		2.A.1.1.29	*SLC2A2*
GLUT3/SLC2A3	496	facilitative glucose TP, *Homo sapiens*	P11169	4ZW9	2.A.1.1.91	*SLC2A3*
GLUT4/SLC2A4	509	facilitative glucose TP, *Homo sapiens*	P14672		2.A.1.1.80	*SLC2A4*
GLUT5/SLC2A5	501	facilitative fructose TP, *Bos taurus*	P58353	4YB9	2.A.1.1.133	*SLC2A5*
GalP	$(464)_3$	glucose/galactose :H^+ TP	P0AEP1		2.A.1.1.1	*galP*
Solute sodium symporter (SSS) 2.A.2						
* vSGLT	543	Galactose:Na^+ TP *Vibrio haemolyticus*	P96169	3DH4	2.A.21.3.2	*sglT*
LeuT	513	Leucine:Na^+ TP, *Aquifex aeolicus*	O67854	2A65	2.A.22.4.2	*snf*
hSGLT1/SLC5A1	664	Glucose/galactose:Na^+ TP, *Homo sapiens*	P13866		2.A.21.3.1	*SLC5A1*
Sweet family 2.A.123						
* semiSWEET	892	sugar transport by facilitated diffusion	P0DMV3	4X5M, 4X5N 4QNC 4QND	2.A.123.2.7 2.A.123.2.6 2.A.123.-3.1	*G925_ 04926*
The Major Intrinsic Protein (MIP) Family 1.A.8						
GlpF	$(281)_4$	glycerol transport by facilitated diffusion	P0AER0	1FX8	1.A.8.1.1	*glpF*
Phosphotransferase System (PTS) 4.A						
ec$IICB^{Glc}$	$(385\text{-}92)_2$	Glucose TP, phosphorylated at C421 of B-domain	P69786		4.A.1.1.1	*ptsG*
* *bc*$IICB^{Mal}$	$(456\text{-}89)_2$	*B. cereus* maltose TP, phosphorylated at C489 of B-domain	Q63GK8	6BVG, 5IWS,* C-domain	4.A.1.1.17	*malT*
bcIIC^{Chb}	$(433)_2$	*B. cereus* chitobiose TP	Q72XQ0	3QNQ	4.A.3.2.8	*celB*
MalX (*ec*$IICB^{Mal}$)		Glucose/maltose TP	P19642		4.A.1.1.3	*malX*
* *ec*IIA^{Glc}	169	PTS subunit, reversibly associated with $IICB^{Glc}$; allosteric activator of Cya and GlpK, inhibitor of $MalEFGK_2$ and LacY	P69783	1ggr, 1GLA	4.A.1.1.1	*crr*
Cya	848	Adenylate(cAMP)cyclase	P00936			*cyaA*
Crp	210	cAMP dependent global transcription activator of PTS and metabolic operons	P0ACJ8	2GZW		*crp*
GlpK	$(502)_4$	Glycerol kinase	P0A6F3	1GLA		*glpK*
EI	$(575)_2$	Enzyme I, transfers P from PEP to HPr, phosphorylated at H189	P08839	2HWG, 3eza		*ptsI*
HPr	85	Heat-stable protein, transfers P from EI to IIA^{Sugar}, phosphorylated at H15	P0AA04	3eza, 1ggr		*ptsH*

Table 1 (continued)

Protein/complex	Length and oligomeric struct.[a]	Properties[b]	UniProt Entry[c]	PDB codes[d]	TCDB Nr.[e]	*Gene*
Mlc	$(406)_2$	Transcription inhibitor of *ptsG* and *manXYZ* genes. Inactivated by binding/sequestration to *ec*IICB^{Glc}	P50456	3BP8 (Mlc::IIB), 1Z6R	4.A.1	*mlc*
SgrR	551	Glc6P dependent transcription activator of *sgrST* operon	P33595			*sgrR*
SgrT	43	Allosteric inhibitor of *ec*IICB^{Glc}	C1P5Z7			*sgrT*
SgrS		small RNA complementary to ptsG mRNA (IICBGlc)				*sgrS*
**ec*IICIID^{Man}	$(212 + 219)_3$	Mannose TP; penetration of phage DNA and bacteriocin	P69801, P69805	6K1H (cryoEM)	4.A.6.1.1	*manYZ*
*ec*IIAB^{Man}	$(155\text{-}168)_2$	PTS subunit, associated with IICIID^{Man}, phosphorylated at H10 and H175	P69797	1vsq	4.A.6.1.1	*manX*
DicB	62	in complex with MinC allosteric inhibitor of ecIICIIDMan	P09557			*dicB*
DicF		small RNA complementary to manXYZ mRNA				*dicF*
DhaKLM	$(356)_2 + 210 + (472)_2$	PEP dependent dihydroxyacetone kinase	P76015, P76014, P37349	1OI2, 2BTD, 3CR3 (LM complex; *L. lactis*)		*dhaKLM*

[*] Representative transporters characterized in text and Fig. 3

[a] Length of subunits in complex (+), of domains in multidomain protein (−). Subscripts indicate oligomeric form (2 dimer, 3 trimer)

[b] Of proteins of *E. coli* K12 (*ec*) if not otherwise indicated

[c] https://www.uniprot.org/.

[d] https://www.rcsb.org/. X-ray structures *upper case*. NMR structures of binary complexes, *lower case*

[e] http://www.tcdb.org/superfamily.php of transporters (TP)

propionate, butyrate and acetate), which are secreted and in turn serve as vital nutrients for colon epithelial cells [19, 52, 167, 201]. Peptides released from glycopeptides are metabolized by bacteria of the genus *Firmicutes.* Sugar malabsorption in the small intestine leads to an increased concentration of "unusual" sugars in the large intestine, inducing changes in the metabolism and composition of the microbiota. Such alterations of the microbiota composition cause unpleasant gastrointestinal symptoms and occur associated with disease (bowl inflammation, breach of immunetolerance) [70].

In this review, we will present facts and figures on (i) the distribution and composition of bacterial sugar transporters, (ii) ten structures of four different prototypical transporters and their mechanism of action (where known), (iii) regulation of sugar transporter activity, (iv) the role of sugar transporters in uptake of macromolecules and drugs and (v) the role of transporters in pathogenicity.

Since *Escherichia coli* was and still is the model and workhorse bacterium [123, 168], and since Glc transport is the topic of this Special Issue, *E. coli* and Glc-specific transporters will serve for illustration, where appropriate. A large number of high-resolution structures of bacterial sugar transporters have been determined in the past 17 years. They now serve as models for their eukaryotic counterparts of which with a few exceptions, no high-resolution structures are yet available—but coming soon.

Distribution, composition and general mechanism of bacterial sugar transporters

Bacteria utilize different transport mechanism for the uptake of sugars against a concentration gradient (Fig. 1): (i) ATP-dependent transporters (primary active transporters), which consist of several different subunits [103, 156]. (ii) Ion-symporters and antiporters (secondary active transporters), which utilize proton and sodium ion-gradients maintained by the respiratory chain and/or membrane (FoF1) ATPases [14]. Primary and secondary transporters are ubiquitous in bacteria, animals and plants. (iii) Existing only in many but not all bacteria and in a few archaebacteria are phosphoenolpyruvate (PEP)-dependent transporters. They transport sugars and sugar alcohols by a mechanism that couples translocation with phosphorylation of the substrate [81, 82]. Translocation coupled with chemical modification of the substrate is termed group translocation [119]. (iv) Transporters for facilitated diffusion of sugars (and water) along a concentration gradient occur in bacteria and eukaryotes. Some like the Glc transporter GLUT2

are structurally related to the secondary transporters, others like the glycerol transporter GlpF and the aquaporins, the SWEET of eukaryotes and *semi*SWEET of bacteria are structurally different [35]. (v) Porins are channel-forming β-barrel proteins occurring in the outer membrane of Gram-negative bacteria, mitochondria and chloroplasts of animals and plants. They permit passage to sugars and other solutes of molecular mass < 6000 Da [92, 209]. The Transporter Classification Database (TCDB; http://www.tcdb.org) provides a functional and phylogenetic classification of membrane transport proteins from all kingdoms of life [165]. It comprises more than 10,000 non-redundant transport systems hierarchically classified into classes, subclasses, families and subfamilies.

Bacterial genomes contain between 500 and 8000 protein encoding open reading frames. One third encodes membrane proteins such as transporters, signal receptors, cell adhesion proteins, protein secretion systems, motor proteins and membrane quality control proteases. A total of 3–20% encode transporters including solute transporters, ion channels and respiratory chain electron/proton transporters (Table 2). Milton Saier and colleagues [137, 153, 162] grouped the bacterial transport proteins on the basis of amino acid sequence similarity into 76 phylogenetic families (the number of structural families, however, may be smaller). Half of these families also occur in eukaryotes, the other half are bacteria-specific. The bacterial genomes encode between 20 and 300 different transport proteins. Of the primary transporters, the ATP binding cassette (ABC) transporters account for 25–65 % of all transport proteins and for 4 out of the 76 families. Of the secondary transporters, the major facilitator superfamily (MFS) and the amino acid-polyamine-organocation (APC) transporters also account for 20–68% of the transport proteins and for 54 out of the 76 families. The number of ABC and MFS transporters are inversely correlated. Anaerobic bacteria that depend mainly on substrate level phosphorylation for energy generation (ATP production by glycolysis) have a higher proportion of ATP-dependent ABC transporters. Conversely, aerobic bacteria that rely on a respiratory chain for energy production (membrane proton motive force) have a higher proportion of MFS secondary transporters [137].

Some of the genes encoding sugar transporters may be cryptic, that is they are expressed only after a mutation has occurred in their promoter region (e.g. inversion of the promoter region, insertion of promoter carrying transposon) [69, 155]. Most of the 300 different transport proteins are expressed only if the cognate substrate is present in the environment (induction).

Organisms with a larger genome size generally encode a greater number of transporters [152] because: (i) the number of distinct transporter *families* (ABC, MFS, ion channels) is increased and (ii) the number of *paralogous* transport proteins within one family is increased (paralogous genes are genes in one and the same genome, generated by gene duplication and encoding proteins of similar sequence but different function, e.g. substrate specificity). In bacteria, there is an approximately linear relationship between genome size, the number of transporter *families* and the average number of *paralogs*. But the increase in the number of different *families* per organism is approximately eight times larger than the increase in the number of *paralogs* per family. In animals and plants, the increase in the number of transporters is due to an enormous increase in the number of *paralogs* within a given family, while the number of different families remains more limited, independently of genome size. In multicellular organisms, the closely related paralogous transporters are expressed only in specific tissues, cell types and subcellular localizations, and only during limited periods of development and differentiation [152].

Also increasing with the genome size of bacteria is the range of substrate specificities. Parasitic bacteria with a strongly reduced genome size express few transporters predominantly for amino acids. Free living bacteria which have to adapt to a rapidly changing environment often have several transporters (ABC, MFS, SSS, PTS) for the same substrate. *E. coli* for instance has at least seven different transporters with overlapping substrate specificities including Glc [137]. Note that Gram-negative *E. coli* and Gram-positive *B. subtilis* [137, 163] the work horses of microbiologists are atypical with respect to their more than average large number and diversity of transport proteins (Table 2).

ABC and other active transporters work by an alternating access mechanism, which was proposed by Jardetzky already in 1966 [80]. Four types of alternating-access mechanisms are described according to how two domains of an integral membrane protein move relative to each other (Fig. 2) [14]. These domains are the transport domain (TD) which contains the substrate binding site, and the scaffold domain (SD) which anchors the protein in the lipid bilayer and/or forms the intersubunit contacts. The basic movements (Fig. 2) are (a) Rocker switch: a symmetrical rocking motion of TD and SD around the substrate binding site provides alternate access to the substrate from either side of the membrane. (b) Rocking bundle: the TD (bundle domain) is rocking (like a chopping knife) against the static SD. (c) Elevator type: the TD glides along a SD, carrying its cargo from one side to the other of the membrane. (d) Rotation/toppling type [182]: the TD (domain or protein subunit) rotates from outward to inside against the SD. The substrates may be either a sugar or a "sugar plus sodium/proton". The direction of transport is determined by the combined direction and strength of substrate concentration and electrical potential gradients.

Structure and mechanism of primary ATP binding cassette transporters

ABC transporters utilize ATP to energize the uptake and export of solutes. They occur in all kingdoms of life. In eukaryotes, they function as exporters (efflux pumps), e.g. the cystic

Table 2 Distribution of transport proteins encoded in 18 bacterial genomes and in *E. coli*

	18 bacterial genomes[a]		*E. coli*[b]		
	Number	%	Number	%	Representative examples and comments
Genome size (kbp)	500–9000		4640		
Protein orfs	500–7500	100	4140		
Membrane proteins		~30		~30	
Transport proteins	22–304	3–20	304	7.3	
Transport proteins per 100 kbp genome seq.	2.5–6.6		6.6		
Transport proteins	22 – 304	100	304	100	
Phylogenetically distinct families	76		76		
with homologs occurring in eukaryotes		~50			
occurring only in prokaryotes		~50			
Primary ABC transporters (4 families)	8–67[c,d]	24–65	67	22	Maltose transporter ($MalEFGK_2$) predominant in anaerobes with substrate level phosphorylation[b]
Secondary MFS transporters (54 families)	66–0[c]	68–20	66	22	Lactose transporter (LacY), xylose transporter (XylE), galactose/glucose transporter (GalP); predominant in aerobes with respiration chain[b]
Secondary APC[e] transporters	0–22	0–10	22	7	
PTS transporters (6 families)	0 – 22	0–10	22	7	Glucose transporter ($IIA^{Glc}/IICB^{Glc}$) Mannose/glucose transporter ($IIAB^{Man}/IIC^{Man}/IID^{Man}$)
Facilitators (aquaporin)	0–7		7	2.3	Glycerol transporter (GlpF), aquaporin
Sugar specific transporters (ABC, MFS, PTS)		0–27		5.9-9.8	
Amino acid specific transporters (ABC, MFS)		2–40		7.7-9.7	
Amine, amide and peptides (ABC, MFS)		0–19		2.4-3.1	
Drug exporters (ABC, MFS)		6–19		3.7-5.3	

[a] 7 Gram-negative, 4 Gram-positive, 2 spirochetes, 1 cyanobacterium, 4 archaea [137]

[b] For a detailed comparative genome analysis of 9 different *E. coli* and *S. typhimurium* strains see [38]

[c] Numbers are anticorrelated (aerobic/anaerobic life style)

[d] Numbers refer to open reading frames. The number of ABC transporters is smaller because each consists of 3–5 different subunits (open reading frames)

[e] Amino acid-polyamine-organocation (APC) superfamily [165]

fibrosis transmembrane conductance regulator (CFTR), the MHC peptide-antigen transporters (TAP) of T-cells and drug/toxin efflux-pumps that clean the membrane bilayer of apolar compounds. Bacteria have both, systems for the uptake of nutrients, ions and vitamins and systems for the expulsion of antibiotics, toxic metabolites and metal ions [33, 62].

Oligomeric structure of the transporter unit ABC transporters share a common building plan. They consist of four protein subunits: (i) two identical, or homologous, or structurally different transmembrane domains/subunits (TMD) building the pore-forming core and (ii) two identical cytoplasmic ATP binding domains (NBD). All NBDs have a similar fold and are of monophyletic origin. The TMDs, in contrast, are of three different phylogenetic origins and have been grouped into three structurally distinct (super)families: ABC1, ABC2 and ABC3 [126, 156, 194]. ABC1 comprises eukaryotic and bacterial exporters with six transmembrane helices (TM) per

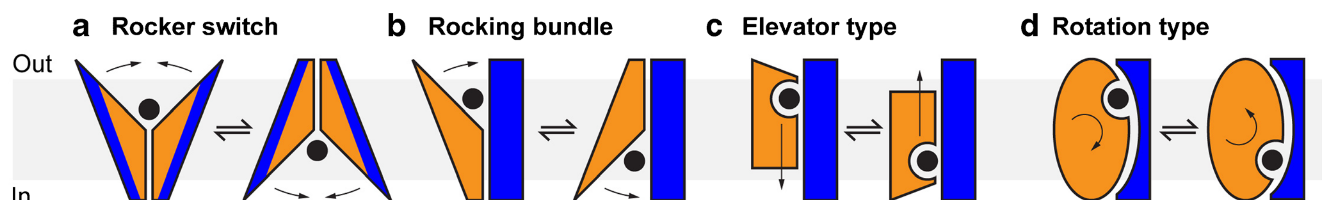

Fig. 2 Different alternating-access mechanisms of solute transport across the inner (cytoplasmic) membrane. **a** Rocker switch, **b** rocking bundle, **c** elevator, **d** rotation. Scaffold and transport domains (SD and TD) are coloured in blue and orange, respectively. Note that a functional transport unit may consist of one or several subunits (monomeric or (hetero)dimeric)

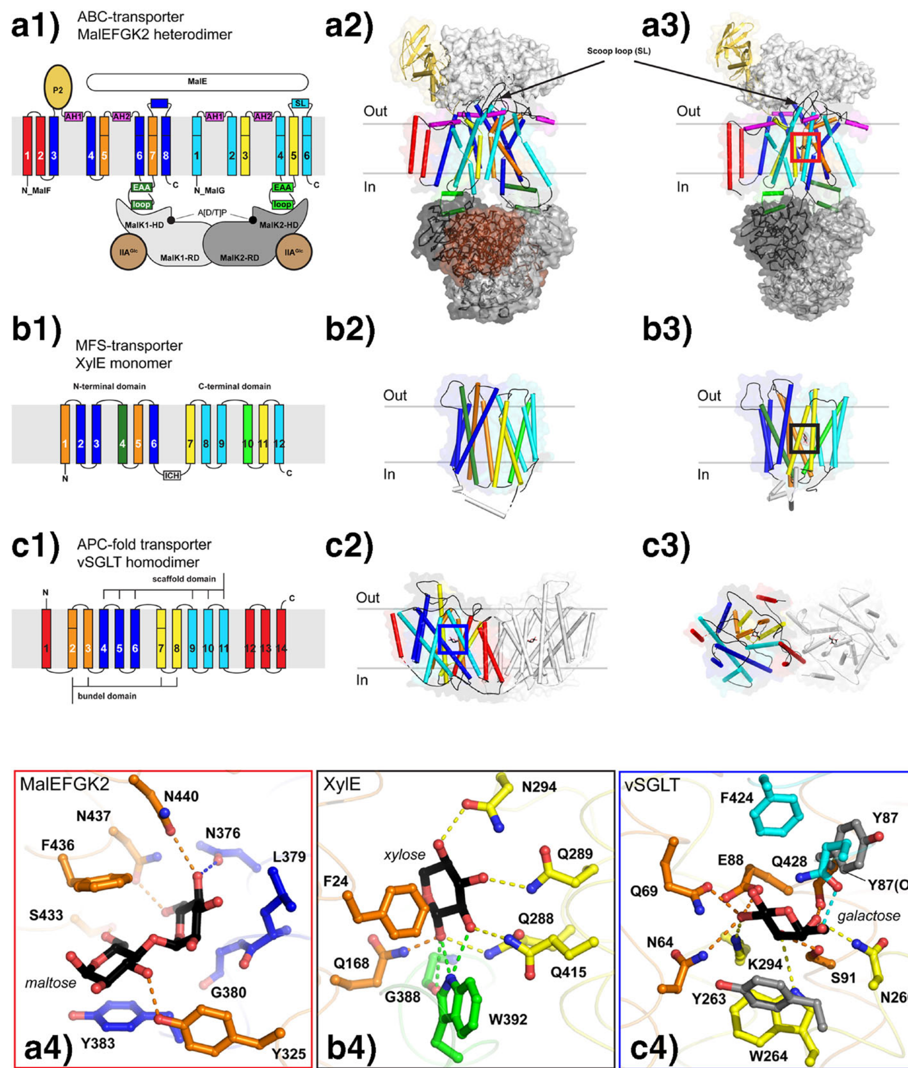

Fig. 3 Structures of six bacterial sugar transporters and their sugar binding sites. Membrane topologies (**a1**–**f1**); structural models of the inward (**a2**–**f2**) and outward (**a3**–**e3**)) oriented conformation, with cylinder representation of helices. The models are color coded to highlight helical folds, domains and subunits. Of homooligomeric transporters, only one protomer is colored, the others are shown in grey (**c**, **e**, **f**). Periplasmic and cytoplasmic subunits of the ABC transporter are shown as grey, spacefilling models (**a2**, **a3**). **a** ABC transporter, MalEFKGK$_2$ in complex with IIA^{Glc} (brown); **b** MFS transporter, XylE; **c** SSS transporter, vSGLT; **d** semiSWEET, homodimer (both subunits coloured); **e** group translocator/PTS-transporter of the GFL-family, homodimeric *bc*IIC^{Mal}; **f** group translocator/PTS-transporter of the mannose-family, trimeric IICIID^{Man}, a trimer of three IICIID heterodimers. **a4**–**f4** Substrate binding sites in the same orientation as in **a2**–**f2.** Amino acids in ≤ 3.8 Å distance to the sugar are displayed as sticks, colour coded according to the topology. **c3** and **f3** vSGLT and IICIID^{Man} viewed from the outside. **f5** Structural alignment of the transport domains (yellow, ocher) and of the scaffold domains (cyan, blue) of IIC^{Man} and IID^{Man}, respectively (same orientation as in **f2**). Note that the complexation of IIA^{Glc} (brown) to the MalEFGK$_2$ structure (**a2**) was modeled according to the MalFGK$_2$::IIA^{Glc} complex structure (PDB 4JBW). Colour code: N-terminal domains/repeats, blue/ocher; C-terminal domains/repeats, cyan/yellow. Mobile transport (substrate binding domain (TD) ocher/yellow; static scaffold domain (SD) blue/cyan. Acessory TM (variable between transporters of the same superfamily), red. Reentrant loops (**e1, f1**), yellow. Cartoons were prepared using PyMol (Version 2.3.0, Schrödinger). The structural alignment **f6** was prepared with TMalign [210]

TMD (consisting of 3 × 2 hairpin repeats). ABC2 comprises bacterial uptake systems and bacterial as well as eukaryotic exporters with six TM per TMD (2 × 3 TM bundle repeats). Bacterial ABC2 importers are further divided into type I and type II. Type I import small substrates (sugars, amino acids) have a smaller number of TM, and ATP binding and hydrolysis is driven by substrate binding. Type II import larger substrate (vitamin B12) has a larger number of TM, and substrate is bound in the nucleotide-free state [24, 51]. ABC3 are bacterial exporters with eight TM per TMD (2 × 4 TM repeats). Extra helices can be fused to the 6- and 8-TM cores, such that the total number of TM per TMD can be as high as 20. For instance, the MalF subunit (but not MalG) of the maltose transporter (MalEFGK$_2$) has two extra helices at the N-terminus (Fig. 3a). Two extra helices can be inserted between the two 4-TM repeats of ABC3 transporters. In bacteria, the

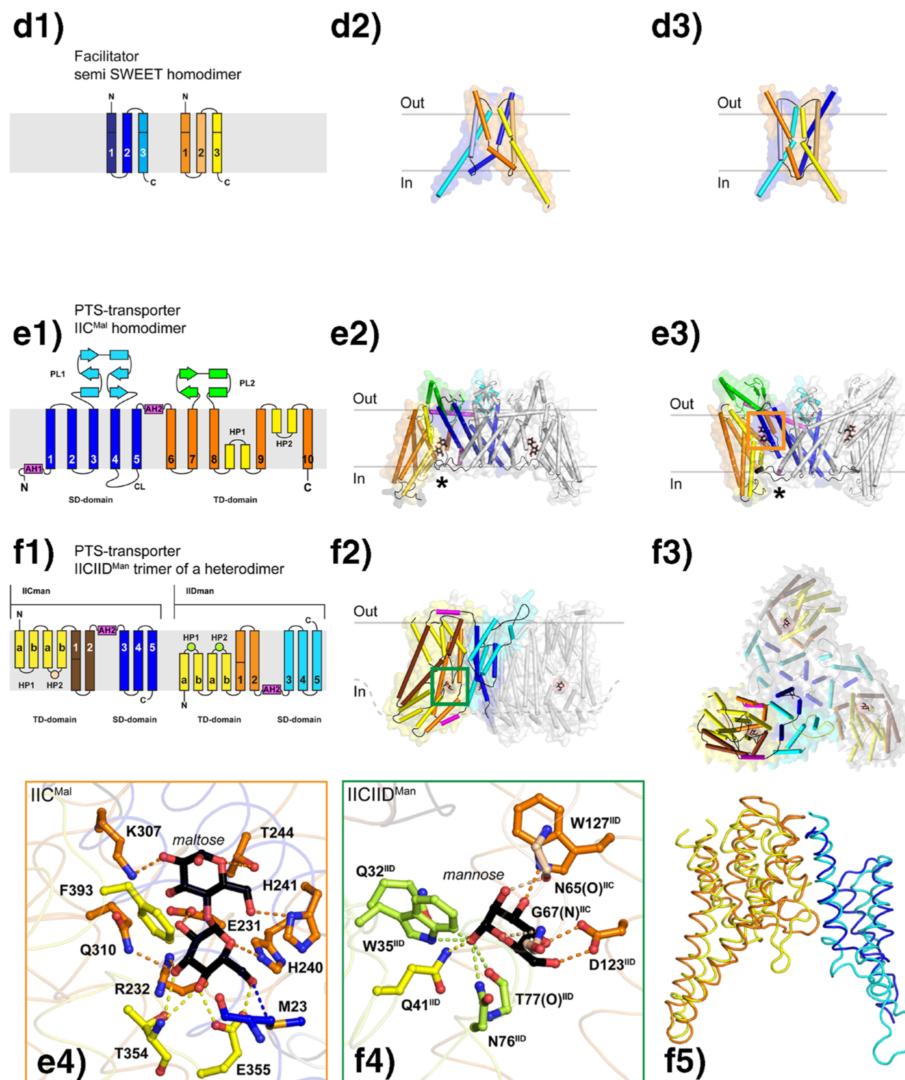

Fig. 3 continued

NBD and TMD usually occur as separate subunits, in eukaryotic transporters as fusion proteins in diverse combinations (e.g. TMD-NBD-TMD-NBD or $(NBD\text{-}TMD)_2$).

Bacterial ABC2 uptake transporters contain an extra substrate-binding subunit/domain (SBD, receptor). In Gram-negative bacteria, the SBD is a soluble subunit in the periplasmic space (substrate binding protein, SBP or periplasmic binding protein, PBP). In Gram-positive bacteria, the substrate binding domain is either fused with a TMD subunit or otherwise membrane anchored. SBD consist of two α/β domains that fold up to capture the substrate at their interface (Venus flytrap mechanism). They confer the high micromolar substrate binding affinity, whereas the TMD have much lower (mM) or no affinity. Some SBDs of Gram-negative bacteria also function as chemotactic receptors. They bind to the membrane spanning chemotaxis receptors (Tar and Trg; MCP, methyl accepting chemotaxis proteins) where they trigger a chemotactic response [104, 211]. The same two domain architecture and ligand binding mechanism also occur in other proteins throughout prokaryotes and eukaryotes, e.g. in the inducer-binding domain of the LacI transcription repressor [49].

To add diversity, there is a fourth structural/functional family of ABC bacterial uptake systems for vitamins and transition metals termed energy-coupling factor (ECF) transporters. It is a phylogenetically different subfamily of the ABC2 superfamily. Members consist of two identical or very similar NBD subunits (A,A′) and two structurally completely different TMD subunits, the T subunit (our scaffold domain, SD) and the S subunit (our transport domain, TD), but no SBD (Fig. 2d). The T subunit (SD) and the two A domains constitute the energy-coupling module, the S subunit (TD) the substrate binding unit. Different S subunits (TDs) of different substrate specificity can reversibly associate with one and

the same AA'T module. For solute translocation the S subunit (TD) rotates (Fig. 2d, orange colored) from outward oriented (with helices membrane-spanning) to inside oriented (with helices parallel to the membrane) [151, 182]

ABC sugar transporters: the prototypical maltose transporter MalEFGK$_2$

E. coli has ABC2 transporters for the uptake of arabinose, galactose/glucose, allose, xylose, maltose and as yet unidentified substrates [55, 74]. The maltose transporter (Fig. 3a) is the best characterized receiving over 500 titles in the PubMed database (for reviews [33, 111]). The most recent review by Machtel et al. [111] with 167 references and the original paper describing the oligomeric structure [129, 130] serve as the basis for the subsequent overview.

Structure The maltose transporter consists of two transmembrane protein subunits (TMDs) MalF and MalG, two identical copies of the cytoplasmic ATP binding proteins (NBD) MalK and one copy of the periplasmic maltose binding protein (SBP) MalE (Fig. 3a1–4, Table 1). The core structures of MalF (helices 3–8) and MalG (helices 1–6) are similar (23% identity, 50% similarity) each consisting of 2 transmembrane 3-helix bundles. MalF has a 180 amino acids long periplasmic domain (P2) inserted between core helix 3 and 4 and two additional transmembrane helices (1 and 2, 70 amino acids) preceeding core helix 3. The periplasmic domain assumes an immuno-globulin (Ig)-like fold. Helices 5 and 7 of MalF and 3 and 5 of MalG surround the solute translocation channel, a cavity large enough to accommodate maltoheptaose (1.15 kDa). MalK consists of an N-terminal RecA-like ATP-binding domain and a C-terminal regulatory/dimerization domain (RD). The MalK subunits are oriented head to tail, and the two ATP binding sites are located at the interface between the RecA-like domain. A helical subdomain (HD) separating Walker A and B motives forms a deep cleft, which captures the helical EAA loop of MalF and MalG, respectively. MalE, the periplasmic binding protein, binds with its two lobes to MalF and MalG, respectively. The Ig-like periplasmic domain (loop P2) of MalF grasps the MalE N-terminal domain, and a short periplasmic loop (the "scoop loop") between helices 3 and 4 of MalG inserts into the sugar binding cleft [21, 130]. Loop P2, a unique feature of MalF, is missing in other ABC2 sugar transporters.

Transport mechanism Maltose is imported by an alternating access mechanism in which the TMD alternate between an inward and outward open state (Fig. 2). Over a dozen X-ray structures of the complex in different conformational states and complementary measurements of intracomplex distances by single molecule fluorescence resonance energy transfer (smFRET) and electron paramagnetic resonance (EPR) provide a detailed picture of the sequence of conformational transitions occurring between solute uptake in the periplasm and release into the cytoplasm [11, 13, 20, 203]. To describe them all goes beyond the constraints of this review. A coarse grained model discerns the following steps. (i) Resting state: the MalF/MalG sugar binding cavity is inward open, the MalK dimer is in the nucleotide free or ADP complexed form and expanded. The periplasmic MalE without sugar may be weakly or not complexed with MalF/MalG. (iia) MalE free floating or attached to MalF/MalG captures (oligo)maltose, whereupon the two lobes close (Venus fly trap), and the interaction with MalF/MalG is stabilized. (iib) Two ADP are exchanged for two ATP at the MalK dimer interface, resulting in the closure of the dimer. The contraction of MalK effects the closing of the inward open binding cavity of MalF/MalG. (iiia) In the presence of the MalE:substrate complex, the MalF/MalG conformation change proceeds, the MalE lobes and the MalF/MalG cavity open and the substrate is transferred from MalE to the binding cavity (Fig. 3a4). (iiib) MalE binding and substrate release induce a conformation change of MalF and MalG that triggers ATP hydrolysis in MalK. (iv) Upon ATP hydrolysis, the MalK dimer expands and thereby pries the binding cavity inward open. The substrate is released.

MalE has a 1000-fold higher affinity for oligomaltose than MalF/MalG, but not all substrates that bind to MalE are also transported by MalFGK$_2$. Maltoheptaose is the largest substrate that is transported, maltooctaose binds to MalE but is no longer transported [12, 130]. Similarly, a mutant MalE can bind sucrose, but this sucrose is not transported. An excess of ligand-free MalE competitively inhibits transport of maltose but does not stimulate the ATPase activity of MalK [116] .

Control of uptake activity MalK plays an additional role in control of maltose uptake and expression of the maltose operons. (i) Dephosphorylated IIA^{Glc}, a subunit of the PTS (see below), which is abundant when glucose and other PTS sugars are transported binds to MalK and inhibits its ATPase activity (Figs. 3a2 and 4c [21]). Uptake of maltose, the inducer of *mal* operon transcription, is prevented. This process is termed inducer exclusion [34]. (ii) MalT is a transcription activator of the *mal* operon [174]. In the absence of a substrate when MalEFGK$_2$ is resting in the inward-open state, MalT is sequestered to the membrane in a complex with MalK [10, 84]. In this state, MalT cannot be activated by internal maltotriose. MalT is released when MalEFGK$_2$ turns over during the uptake of an external substrate. Free MalT binds maltose and ATP whereupon it polymerizes into a homooligomer that acts as transcription activator of the *mal* operons [157].

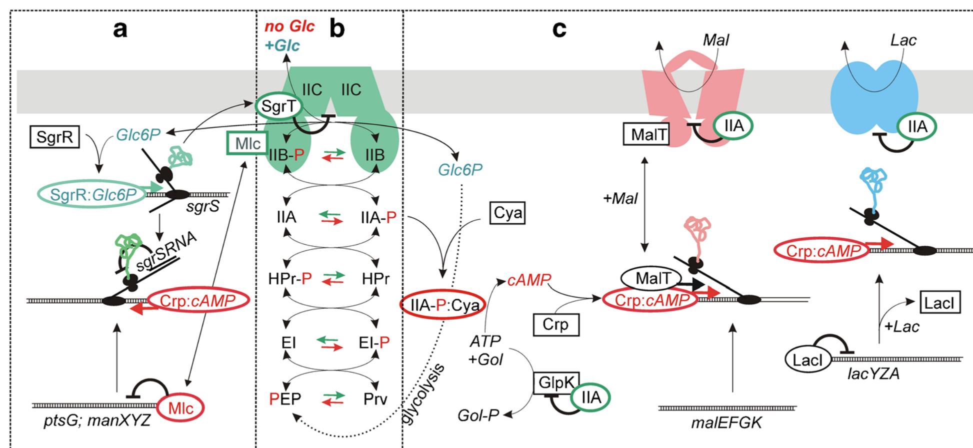

Fig. 4 Sugar uptake and control of metabolism by the PTS of *E. coli*. **b** The general phosphoryltransfer proteins EI and HPr and the glucose-specific complex of IIA^{Glc} (IIA) and IICB^{Glc} (IICB) sequentially transfer phosphorylgroups from phosphoenolpyruvate (PEP) to glucose (Glc). HPr transfers phosphorylgroups also to the IIA subunits/domains of other PTS transporters (not shown). In the presence of Glc (+*Glc*) the PTS proteins are predominantly in the dephosphorylated form (*green arrows*). In the absence of Glc (*no Glc*), they are in the phosphorylated form (*red arrows*). (**a, c**) Control of transcription and enzyme activities by components of the Glc-PTS. *Oval frames* denote the active form, *rectangular frames* the inactived form of the regulatory proteins. *Green frames* indicate regulatory proteins active in the presence of Glc (+*Glc*), *red frames* indicate proteins active in the absence of Glc (*no Glc*). **a**, **b** Transcriptional, translational and posttranslation autoregulation of IICB^{Glc} activity. *Activation of ptsG transcription*: IICB^{Glc} is partially dephosphorylated during steady-state uptake of Glc. Dephospho-IICB^{Glc} binds/sequesters the transcription repressor Mlc enabling the transcription/expression of *ptsG* encoding IICB^{Glc}. Expression is further stimulated by the global transcription activator Crp::cAMP. *Feedback inhibition of IICB^{Glc} activity*: (i) the concentration of Crp::cAMP decreases (**c**) with increasing Glc uptake, slowing down *ptsG* transcription. (ii) Accumulation of glucose-6-phosphate (phosphate stress) triggers expression of the small RNA sgrS and small protein SgrT, which downregulate translation of *ptsG* mRNA by antisense binding, and inhibit IICB^{Glc} allosterically [102, 193]. **c** Transcriptional and allosteric control of non-PTS sugar transporters and enzymes (CCR, Carbon Catabolite Repression). In the *presence of glucose* (+*Glc*) dephospho-IIA^{Glc} inhibits the maltose- and lactose transporters (inducer exclusion) and glycerol kinase (GlpK). In the *absence of glucose* (*no Glc*) P-IIA^{Glc} (IIA-P) activates adenylate cyclase (Cya), and cyclic AMP (cAMP) activates the cyclic AMP receptor protein (Crp). Crp::cAMP is a global transcription activator. Crp::cAMP activates transcription: (i) of the *lacYZA* operon under the condition that the *LacI repressor* is inactivated in the presence of lactose (inducer); (ii) of the *malEFGK* operon under the condition that the *transcription activator* MalT is released (activated) from $MalEFGK_2$ in the presence of maltose (inducer). Crp::cAMP affects transcription of an estimated 200 additional metabolic genes (not shown). The properties of the proteins shown are summarized in Table 1

Structure and mechanism of secondary (active) transporters

Secondary active sugar transporters occur in the major facilitator superfamily (MFS) and in the solute sodium symporter (SSS) family of electrochemical potential-driven transporters [14, 149].

The MFS superfamily comprises bacterial sugar transporters (described below) and the mammalian glucose/fructose transporters GLUT1, GLUT3, GLUT4 and GLUT5 (Table 1; accompanying reviews in this special issue). The sodium xylose symporter XylE of *E. coli* is the closest relative of eukaryotic GLUT sharing 28% sequence identity and 62% sequence similarity with human GLUT1. Six X-ray structures of XylE in different conformations and one of GLUT1 have been solved [179, 199]. In this review, XylE will serve as the model for the description of structure and function of the MFS sugar transporters (Fig. 3b1–4). Note that although bacterial transporters and eukaryotic GLUT transporters share the same MFS structural fold (see below), GLUTs mediate facilitated diffusion whereas bacterial transporters mediate ion-driven active solute uptake. Whether the latter can be converted from a wild-type active to a mutated facilitative form with a single amino acid mutation in the proton binding site is controversial [86, 199].

The SSS family comprises bacterial sugar and amino acid transporters and the mammalian sodium-glucose transporters SGLT (see the accompanying reviews in this special issue). The vSGLT of *Vibrio parahaemolyticus* shares 28% sequence identity and 60% sequence similarity to human SGLT1. Its structure has been solved, and it will serve as a model for the description of structure and function (Fig. 3c1–4) [48].

The MFS fold and the rocker switch transport cycle

Forty-eight X-ray structures of 12 structurally similar MFS transporters, including 20 structures of seven sugar transporters, all in distinct conformational states provide snapshots to visualize the progress of substrate translocation from the outside to the inside [14]. Biophysical (single-molecule fluorescence resonance energy transfer) and biochemical (counterflow) experiments with transporter mutants and substrate analogues and more recently molecular dynamics

calculations provide complementary and confirming evidence for the sequence of events.

The MFS core fold of the D-xylose transporter XylE consists of two 6 TM domains (Fig. 3b). Each 6 TM domain in turn consists of 2 repeat folds of three interwined transmembrane helices (TM) arranged in a 1,3,2 order. Inserted between the N terminal (TM1-6) and C terminal (TM7-12) domain on the cytoplasmic face of the membrane is a small helical domain (ICH) which serves as an inner gate (Fig. 3b1–3). The flat domain interface is formed by hydrophobic residues of the symmetrically related TM2,5 and TM8,11. TM3,6, TM9,12 are in contact with the lipid bilayer.

The substrate binding site is located in the middle of a cavity between the N- and C-terminal domain (Fig. 3b4). D-xylose is oriented parallel to the TMs (perpendicular to the plane of the membrane) liganded by hydrogen bonds between the hydroxyl groups and conserved amino acid side chains located in the symmetrically related TM1,5 and TM7,11 and TM10 [199].

MFS sugar transporters operate by the rocker switch mechanism (Fig. 2a). The inward-outward exposure of the binding site of XylE is effected by a 16° rigid body rotation of the two domains (around an axis parallel to the membrane plane). Substrate binding and release are triggered by local conformation changes in TM7 and TM10 of the C-terminal domain, the two TM helices that provide the most important hydrogen bonding with the substrate (Fig. 3b4). Coupling of proton and substrate transport depends of a salt bridge between an aspartate in TM1 (D27) and an arginine in TM4 (R133). The salt bridge stabilizes XylE in the outward conformation. The substrate can bind and the binding site close, but the outwards-inward switch cannot occur. Protonation of D27 breaks the ionic interaction, and R133 forms an alternative salt bridge with the C-domain, bringing about the outward to inward transition. Deprotonation of D27 on the cytoplasmic side triggers substrate release and allows XylE to switch back to the outward conformation. The D27N mutation abolishes proton-xylose symport but not facilitated diffusion [199].

The SSS fold and the rocking bundle transport cycle

The SSS core fold (also termed amino acid-polyamine-organocation (APC) and LeuT fold [171, 206]) consists of two 5 transmembrane helix (TM) repeats, which are related by a two-fold symmetry around an axis parallel to the plane of the membrane (Fig. 3c1) [48]. The TMs of the two repeats are interdigitated forming a single compact domain (and not apposed like the 6 TM domains of the MFS fold). Extra TMs may be located on the N- and/or C-terminus of the 5 + 5 TM core. The sodium galactose cotransporter vSGLT, for instance, has 14 TM, one before and three after the core (Fig. 3c1–3; extra TMs red). Core TM2,3 and 7,8 form the substrate transport domain (TD) better known as the "bundle domain", core TM4,5,6 and 9,10,11 the scaffold domain (SD) (Fig. 3c1). The inward-outward exposure of the galactose binding site of vSGLT is effected by a rigid-body motion of the bundle around the scaffold domain.

In vSGLT, galactose is oriented perpendicular to the TMs (parallel to plane of the membrane) liganded by hydrogen bonds between the hydroxyl groups and conserved amino acid side chains located in the symmetrically related pairs TM2,3 and TM7,8 and in TM11 (Fig. 3c4). At the cytoplasmic exit, the substrate translocation pathway is blocked by Tyr 263, which forms the inner gate (Fig. 3c4). At the periplasmic entry, Tyr 87 forms a similar outer gate. Sodium is complexed between TM2 and TM9. Sodium binding and the negative membrane potential (but not sodium binding alone!) shift the conformation equilibrium towards the outward-open conformation. Sugar binding induces a rocking-bundle conformation switch towards the inward open state (Fig. 2c), where galactose and sodium are released [138].

The SWEET and semiSWEET facilitative sugar transporters

SWEETS were initially identified as Glc and sucrose transporters in plants ([205] and accompanying review in this special issue). Homologs occur in all eukaryotic kingdoms. SWEETs consist of seven TM, two 3TM repeats in parallel orientation and a connecting TM (3 + 1 + 3). SemiSWEETs are the bacterial homologs of the plant SWEETS. They are homodimers of two 3TM subunits (Fig. 3d1–3). The sugar translocation pore is inbetween the 3TM repeats/subunits. Crystal structures of semiSWEETS in outward open and occluded state suggest a rocker-switch transport cycle (Fig. 2, [204]). Pangenome analysis indicates that 3 + 1 + 3 SWEETS also occur in bacteria and that membrane proteins containing one or several 3TM repeats (extraSWEET and superSWEET) exist [83].

Structure and mechanism of the phosphoenolpyruvate-phosphotransferase system transporters

The bacterial PEP/sugar phosphotransferase system (PTS) was discovered serendipitously during research into the metabolism of sialic acid [93, 160]. N-acetyl-mannosamine (ManNAc) is phosphorylated by an ATP-dependent liver kinase. Bacteria were expected to contain a similar kinase because they could grow on ManNAc as only carbon source. But such a kinase could not be detected in cellular extracts.

Instead, a PEP-dependent activity was found, and this activity turned out to be tightly coupled with sugar uptake [93, 160] leading to the discovery of the sugar transporters of the PTS. The PTS-transporters differ from primary and secondary active transporters in three important aspects [41, 144, 159]: (i) PTS and its transporters occur only in bacteria, in some arachaebacteria but not in animals and plants. (ii) The sugar is not taken up unchanged, but transport is coupled with sugar phosphorylation. (iii) In addition to sugar uptake and phosphorylation, PTS control the carbon and nitrogen metabolism in response to the availability of carbohydrates, in particular of Glc [139, 192]. All PTS transporters (sugar-specific enzyme II^{Sugar} complexes) consist of three functional units IIA^{Sugar}, IIB^{Sugar} and IIC^{Sugar} or $IICIID^{Sugar}$, which are either subunits or domains of multidomain proteins [82]. The integral membrane subunits IIC and IICIID contain the sugar binding site. Some PTS transporters have multiple substrates (mono- and disaccharides, sugar alcohols and ascorbic acid), and some sugars are transported by more than one transporter [7]. Phosphorylgroups are sequentially transferred from phosphoenolpyruvate (PEP) to the incoming substrate by the two "general" phosphotransferase proteins, EI and HPr, and by the IIA^{Sugar} and IIB^{Sugar} subunits/domains of the enzyme II^{Sugar} complexes (Figs. 1 and 4b, Table 1).

The IIA, IIB, IIC and IICIID subunits/domains are of polyphyletic origin. The IIC and IICIID transporters have been grouped in four *superfamilies*: (1) glucose/fructose/lactose (GFL), (2) glucitol, (3) ascorbate/galactitol and (4) mannose/sorbose/fructose [4, 164]. A fifth superfamily contains the PEP-dependent dihydroxyacetonekinases, which are supplied with phosphorylgroups by EI and HPr but do not comprise integral membrane proteins [41, 45]. *Escherichia coli* contains representatives from all five superfamilies [187]. Otherwise, the number of IIC and IICIID complexes varies broadly between bacterial species. Genome analyses of 136 species revealed that 34% have from two to thirty different enzyme II^{Sugar} complexes (IIA, IIB, IIC, IICIID), 21% have only one complete PTS (EI, HPr, IIA, IIB, IIC), 21% an incomplete PTS (EI, HPr, IIA but no IIB and IIC) and 22% do not contain any PTS genes at all. For instance, *Listeria monocytogenes* has 30 different systems with IIA, IIB, IIC, IICIID subunits encoded by 91 genes accounting for 3.2% of all genes [4]. Multiple PTS systems occur in bacteria growing in the rumen, the oxygen-free and carbohydrate-rich section of the stomach of ruminant animals, and multiple IICIID systems in bacteria from the intestinal microbiota [216]. Where only one or two systems are present, they always are Glc and/or fructose specific. Incomplete PTS may have regulatory functions.

The general phosphotransferase proteins EI, HPr and the transporter subunits/domains are transiently phosphorylated at histidines, the IIB subunits/domains at cysteines [128, 136], with the exception of the IIB of the mannose (Man) superfamily which are phosphorylated at a histidine [44]. The structures of the general phosphotransferase proteins EI and HPr, of representative IIA and IIB cytosolic subunits and domains, and of some binary complexes have been determined by NMR and X-ray diffraction [25, 41]. High-resolution X-ray structures of six *Bacillus cereus* and *E. coli* IICs belonging to the GFL and AG superfamilies [18, 107, 108, 114, 154] and a cryo-electron microscopic structure of the *E. coli* $IICIID^{Man}$ complex are known [101]. Still unknown is the structure of a poorly characterized glucitol transporter [150].

The main PTS transporters for Glc of *E. coli* are IIA^{Glc}/$IICB^{Glc}$ and $IIAB^{Man}$/$IICIID^{Man}$. The former is specific for the uptake of Glc. The latter has a broad substrate specificity for glucopyranoses with modifications at the C-2 position (Glc, Man, GlcNAc). It is believed to be a scavenger of carbohydrates released during cell wall remodeling [140].

bcIIC^{Mal}—a glucose transporter of the GFL superfamily

E. coli ec$IICB^{Glc}$ has been functionally characterized but the structures are not known. The structurally characterized *Bacillus cereus bc*$IICB^{Mal}$ and *bc*IIC^{Chb} share 32% and 18% sequence identity with *ec*$IICB^{Glc}$. *ec*$IICB^{Glc}$ and *bc*$IICB^{Mal}$ can be characterized as follows.

ec$IICB^{Glc}$ is a dimer of subunits consisting of two domains, the N-terminal transport domain IIC and the cytoplasmic phosphorylation domain IIB. IIC and IIB are connected by a conserved linker sequence [16, 95]. "Relaxed" $IICB^{Glc}$ mutants exist that can transport without phosphorylation (in the absence of a phosphoryldonor), phosphorylate without transport or have an extended substrate specificity [40]. Interallelic complementation indicates that the IIB domain of one subunit can donate phosphoryl groups to Glc translocated by the same and by the opposite subunit [95]. Negative dominance, that is inactivation of the active subunit by an inactive one, has not been observed. It is still controversial, whether the two subunits of the dimer function independently, or whether their transport cycles are allosterically coupled. $IICB^{Glc}$ can phosphorylate intracellular Glc in a kinase-like reaction (Fig. 1; [15]). Low and high affinity binding sites have been characterized, but it is not clear whether they correspond to inward- and outward-oriented transporter subunits, or to the same sites of subunits in different conformational states [59, 60]

Structure The IIC domain of *bc*$IICB^{Mal}$ is composed of 10 transmembrane helices (TM1-10) two reentrant loops (HP1 and HP2) between TM8/9 and TM9/10, respectively, two amphipathic helices (AH1 and AH2) preceding TM1 and TM6, two periplasmic loops (PL1 and PL2) between TM3/4 and TM7/8 and one cytoplasmic loop (CL) between TM4/5 (Fig. 3e1) (Ren 2017; McCoy 2016). Two domains can be discerned: the scaffold domain (SD) comprising TM1-5 and the transport domain (TD) comprising TM6-10. The SD

contains the dimer interface, the TD contains the sugar binding site and translocation pathway. Maltose is coordinated by the reentrant loops HP1 and HP2 and the loop connecting TM6 and TM7 (Fig. 3e4). The periplasmic loops (PL1 and PL2, Fig. 3e1, cyan, green) are of variable length (20–200 residues) in the different IIC of the GFL superfamily and their function is not known. The cytoplasmic loop (CL) reaches from the SD of one subunit to the TD of the other (Fig. 3e2, 3, asteriks), and may possibly play a role in allosteric coupling of the two subunits. It assumes a rigid, partially α-helical structure in the outward open conformation, but is unstructured in the inward-open conformation leaving the access open for phosphate transfer from phospho-IIB^{Mal} to the sugar (Fig. 3e2, 3) [114, 154]

Substrate binding site The substrate binding cavity of *bc*IIC^{Mal} is located in the TD near the TD/SD interface. The sugar is hydrogen-bonded by residues of the TD. All H-bonding interactions are preserved during translocation from the outward to the inward facing conformation (Fig. 3e4). TM1 walls off the binding cavity on the SD side, but the SD does not directionally interact with the sugar. The C6-OH of the non-reducing hexose is oriented towards the cytoplasmic exit where it can be phosphorylated by the IIB subunit.

Transport mechanism The structural snapshots of *bc*IIC^{Mal} and *bc*IIC^{Chb} in different conformations indicate that sugars are translocated by an alternating-access elevator mechanism (Fig. 2c), a translational rigid-body motion of the TD against the immobile SD. Substrate translocation is accomplished by a 9 Å vertical translation and a 44° rotation of the TD relative to the SD. The complete transport cycle may be more complex than what can be inferred from the structural snapshots as described in [82].

*ec*IICIID ^{Man}—a glucose/mannose transporter of the mannose superfamily

The mannose transporter (*ec*$IICIID^{Man}$) has the broadest substrate specificity of all *E. coli* PTS transporters. It tolerates substantial modifications at C-2 of the glucopyranose ring. *S. typhimurium* $IICIID^{Man}$, for instance, transports zwitterionic glucoselysine and fructoselysine which can be utilized as combined carbon and nitrogen source [118]. The mannose superfamily has been phylogenetically grouped in seven families of which the putative metabolic function and substrate specificity was inferred from their respective genome-context [216].

The *ec*$IICIID^{Man}$ complex consists of a cytoplasmic phosphotransferring two-domain protein $IIAB^{Man}$ and the integral membrane subunits IIC^{Man} and IID^{Man} [43]. $IIAB^{Man}$ forms a dimer, with subunits interwined due to a β-strand swap between the IIA domains [67, 127, 169, 175]. IIC^{Man} and IID^{Man} form a tight complex which cannot be dissociated. Attempts to experimentally and in silico predict the membrane topology of IIC and IID, produced inconsistent results or failed altogether [120]. The difficulties with oligomeric structure and membrane topology were finally resolved by cryo-electron microscopy revealing a structure unseen before [101].

Structure The *ec*IICIID ^{Man} complex is a trimer of three IICIID ^{Man} protomers [101]. The IIC and IID subunits of the protomer are related to each other by a twofold pseudosymmetry axis parallel to the plane of the membrane (Fig. 3f5). Both are composed of two reentrant loops (HP1 and HP2 and 5 TM helices (Fig. 3f5). Reentrant loops HP1, HP2 and TM1 and TM2 of the IIC and IID subunits together form the substrate-binding transport domain (TD), transmembrane helices TM3, TM4 and TM5 the scaffold domain (SD). The HP1 and HP2 can be compared to an upper and lower jaw, the TM1 and TM2 of IIC and IID form the jawjoints. The loops connecting HP1a with HP1b and HP2a with HP2b of IIC and IID form top and bottom, respectively, of the sugar binding cavity, TM1 and TM2 the sidewalls (Fig. 3f1–3). The scaffold domain (SD) consists of two three-helix bundles (TM3-5), with TM3 of each subunit swapped ([$3_D4_C5_C$] and [$3_C4_D5_D$]). This helix swap may explain the tight IICIID intersubunit contact, and why these subunits could not be separated without unfolding/inactivation *in vitro*, nor independently be expressed *in vivo* [46]. The interprotomer contact consists of a six-helix bundle ([4_C5_C]$_3$) composed of TM4 and TM5 of IIC (Fig. 3f3).

Substrate binding site and mechanism of transport Mannose is coordinated by the reentrant loops HP1 and HP2 of IIC and IID (Fig. 3f1, 4). In the resting state depicted by the cryo-EM structure, the cavity is open towards the cytoplasmic side (inward-facing conformation). Structural snapshots of alternative conformations are not yet available, and the transport mechanism outlined hereinafter is hypothetical: the ellipsoidic TD of IICIID (HP1, HP2, TM1, TM2) rotates (topples) as a rigid body from in- to outward against a static hyperboloidic SD (TM3-5) (Fig. 2d), possibly similar to the energy-coupling factor (ECF) transporters of the ABC2 superfamily [182].

Control of carbohydrate uptake and metabolism by the glucose PTS of *E. coli*

Sugars are taken up by bacteria one after the other in a predetermined order [47, 100, 188]. Glucose is the most preferred, probably because it can directly enter glycolysis, while other sugars first must be enzymatically transformed. The PTS controls the uptake of non-PTS sugars (carbon catabolite repression, CCR), intermediate metabolism (carbon, nitrogen balance, glycogen synthesis), gene expression, chemotaxis and virulence (comprehensively reviewed in [36, 57, 172]. EI, HPr, IIA and

IIB control target enzymes allosterically and by reversible transphosphorylation [196]. In *E. coli* for instance: (i) EI and IIA control chemotaxis towards PTS sugars [1, 109, 110, 125, 172]; (ii) HPr controls mannitol uptake and metabolism [22]; (iii) IIA^{Glc} controls maltose uptake by MalEFGK$_2$ (Figs. 3a2 and 4c) [21, 34], and lactose uptake by LacY [173] (Fig. 4c); (iv) IICB^{Glc} controls the activity of Mlc, the transcription repressor of the *ptsG* gene (encoding IICB^{Glc}) and of the *manXYZ* operon (encoding IIAB^{Man}IICIID^{Man}) (Fig. 4a) [97, 141, 142]. Translation of *ptsG* mRNA (IICB^{Glc}) is feed-back inhibited by antisense RNA SgrS in response to the accumulation of Glc-6-phosphate [102, 178, 193]. Which PTS component controls which target varies between bacterial species. In Gram-positive bacteria, for instance, HPr and the HPr kinase/phosphorylase (HprK/P) are the major regulators and not IIA [36, 50].

The glucose PTS is induced in the presence of Glc, and alternative carbon sources are not taken up, not even when available (inducer exclusion). When Glc and other PTS sugars are exhausted, and/or whenever the PEP/Prv ratio is high for other reasons (gluconeogenesis, unbalanced glycolysis), the ratio of P-IIA^{Glc}/IIA^{Glc} increases (Fig. 4b, *red arrows*). P-IIA^{Glc} activates adenylate cyclase (Cya) catalysing the conversion of ATP into the second messenger cyclic AMP (cAMP) [135]. cAMP is the coactivator of the general transcription factor Crp (cyclic AMP receptor protein, catabolite repression protein, also Cap for catabolite gene activator protein). Genes that are activated by cAMP-Crp are termed "catabolite repressed", because they are repressed (not active) in the presence of the catabolite Glc (absence of cAMP). Crp-cAMP activates the transcription of *ptsG* and *ptsHI*, the genes for IICB^{Glc}, EI and HPr (Fig. 4a).

IICB^{Glc} and IIA^{Glc} are dephosphorylated when Glc is taken up and phosphorylated. And this has two effects: (i) dephosphorylated IICB^{Glc} binds (sequesters) Mlc, the transcription repressor of *ptsG* (encoding IICB^{Glc}). Consequently, *ptsG* repression by Mlc is relieved, and IICB^{Glc} expression is stimulated. (ii) Dephosphorylated IIA^{Glc} does not stimulate adenylate cyclase activity, cAMP concentration is low, and consequently the cAMP-Crp-dependent activation of PTS genes is reduced (Fig. 4a). Depending on the timing of the two opposing effects (Mlc sequestration and cAMP depletion), Glc could first increase the rate of *pts* gene expression (by sequestration of Mlc to dephosphorylated IICB^{Glc}) and then limit it (prevent an overshoot) via the reduction of cAMP. The cAMP-*crp* regulon comprises over 200 metabolic operons including a few encoding small RNAs [77, 98, 176, 189, 212]. About 70–80% are activated by cAMP-Crp, the remaining are inhibited, depending on where the Crp-binding nucleotide sequence is located relative to the promoter-sequence [64, 68, 122, 124]. In most cases, cAMP-Crp acts not alone but in concert with one or several more specific transcription factors (for additional references see Erni, 2013).

Bacterial sugar transporters: targets and open doors for macromolecules and drugs

Certain bacterial sugar transporters are hijacked by bacteria and bacteriophages to channel in bacteriocins, nucleic acids, and antibiotics.

Bacteriocins Bacteriocins are antimicrobial peptides produced by lactic acid bacteria. They are of interest as food preservatives against food born pathogens (for a review, see [158]). Bacteriocins inhibit peptidoglycan synthesis, protein synthesis or form pores in the inner membrane causing membrane depolarization. Both uptake and pore formation require outer and inner membrane proteins as scaffolds. The bacteriocin-scaffold interactions are specific, and dependency on a cognate inner membrane protein restricts the bacteriocidal spectrum of each bacteriocin to a narrow range of target bacteria, often to species closely related to the producer [90, 190]. A phylogenetic subgroup of IICIID of the mannose superfamily [32, 70, 147, 181] and certain IICB of the GFL superfamily [58] serve as inner membrane scaffolds. The *E. coli* IICIID^{Man} complex, for instance, serves as a gate for the bacteriocin MccE492 [8, 9]. MccE492 compromised the uptake of Man and caused loss of proton motive force in a wild-type but not in a *manXYZ* mutant, indicating that a functional IICIID^{Man} complex is essential for MccE492 toxicity. In the MccE492 producer bacterium, the bacteriocin and the (self)immunity protein MceB (which protects against killing of the producer) form a ternary complex with IICIID^{Man} [9]. Similarly, the bacteriocin lactococcin A and its cognate immunity protein LciA copurify with the IICIID complex of the *Lactococcus* producer strain [37]. Notice that (i) the majority of bacteriocin uptake systems belong to ABC (not PTS) transporters specific for oligopeptides [6], one exception being the maltose ABC transporter of *Lactococcus* [56]. (ii) Bacteria utilize specific ABC transporters for bacteriocin export [6].

Bacteriophage DNA injection Phage infection of bacteria is a complex process that requires interactions between bacteriophage and bacterial host proteins. Bacteriophages utilize host membrane proteins as receptors and for DNA injection [61]. Elliott and Arber [39] characterized *E. coli* mutants, which were resistant against bacteriophage lambda and also unable to grow on mannose. The genetic linkage between phage sensitivity and ability to grow on Man suggested that phage lambda hijacks a Man transporter for DNA transfer across the inner membrane [134]. IIC^{Man} turned out to be the major specificity determinant for lambda infection, but not sufficient, most likely because IIC is stably expressed only in a complex with IID [42, 43, 46, 197]. But *E. coli* also has a counter-defence against IICIID^{Man} mediated infection [146]. The *E. coli* K12 strain, for instance, harbors between one and several cryptic prophages Qin which encode a small RNA (DicF) and a small

protein (DicB) that inhibit cell division. DicB in complex with the cell division protein MinC in addition inhibits growth on Man as sole carbon source, and in parallel it specifically inhibits phage lambda DNA injection through IICIID^{Man}. DicB does not inhibit growth on sugars taken up by PTS transporters other than IICIID^{Man}, and it does not inhibit other lambdoid phages. The small RNA DicF base pairs with and represses translation *manXYZ* mRNAs, encoding IICIID^{Man}. This is strikingly similar to the regulation of the glucose PTS (*ptsG*, IICB^{Glc}) by the small RNA SgrS and the small protein SgrT (see above and Fig. 4a).

IICB^{Glc}, belonging to the GFL family of PTS sugar transporters, is utilized by phage HK97 for DNA injection [28]. Injection depends on the interaction between IICB^{Glc} and a short C-terminal sequence/domain of the HK 97 tape measure protein (TMP, which i.a. determines the length of the phage tail). Also dependent on IICB^{Glc} is the superinfection exclusion protein gp15, which inhibits second infection of bacteria already harboring the HK97 phage. The small gp15 protein targets the same sequence of the TMP that interacts with IICB^{Glc}, and gp15, TMP and IICB^{Glc} may form a ternary complex.

Antibiotics Most currently used antibiotics are hydrophobic enough to partition into and diffuse across the bacterial inner membrane. Only a few, low molecular weight polar antibiotics utilize solute importers to enter the bacterial cell. Streptozotocin, a N-acetyl glucosamine (GlcNAc) analog produced by *Streptomyces*, is taken up by the IICBA^{GlcNAc} (a member of the GFL family) and the IICIID^{Man} transporters of the PTS [23, 78]. Streptozotocin has been earmarked as a lead candidate for anti-virulence drugs against staphylococcal infections [207]. It is currently in use for the treatment of metastatic pancreatic islet cancer [75]. Streptozotocin is also used to induce autoimmune diabetes in mice and rats. It is taken up by the facilitative transporter GLUT2, and damages beta-cells by its cytotoxic action [75]. Fosfomycin, an analog of phosphoenolpyruvate and inhibitor of peptidoglycan synthesis is a last resort option to combat multiresistant pathogens. To reach its target, it depends on import by the MFS secondary active phosphate/organophosphate antiporters for glucose-6-phosphate (UhpT) and glycerol-3-phosphate (GlpT) [27, 94, 183]. Fosmidomycin, an inhibitor of the mevalonate-independent isoprenoid biosynthesis, also enters bacteria through GlpT [166].

Inhibitors Inhibitors of animal Glc transporters play in important role in diabetes research and therapy (see the accompanying reviews in this special issue). To starve bacterial cells with similar inhibitors in order to combat resistant strains is unlikely to succeed, because more often than not bacteria have redundant transport systems for a particular sugar, and have the choice between chemically different nutrients (amino acids, carbohydrates, fatty acids). Glc analogs inhibiting bacterial Glc transporters were utilized to characterize binding sites and transport kinetics, notably glucose-6-aldehyde is a remarkably potent inhibitor of glucose phosphorylation by IICB^{Glc} [59, 60].

The role of sugar transporters in pathogenicity

Glucose is the preferred carbon source for bacteria and crucial for intracellular survival of pathogens. Not surprisingly, Glc affects not only the uptake and metabolism of alternative sugars but also the expression of virulence factors, biofilm formation [76] and of other cellular activities [91, 96, 98, 139, 143]. EI of the PTS, the unique (non redundant) component at the top of the divergent protein phosphorylation cascade, and IIA, the central regulator of carbohydrate metabolism in Gram-negative bacteria, were repeatedly found associated with virulence (for reviews see [41, 98, 195]. PtsP, an EI-paralog, and EI were identified as virulence genes in *Pseudomonas aeruginosa*, *Legionella pneumophila*, *S. typhimurium*, *E. coli*, *Vibrio cholerae* and *Group A Streptococcus* [63, 72, 73, 91, 98, 184, 195, 202]. EI has been considered as a therapeutic target [121], and *Salmonella* EI mutants as live-vaccine and as delivery vectors for heterologous antigens [213]. In the following, however, we restrict ourselves to the possible role of sugar transporters in pathogenesis.

Different approaches were used to earmark potential and identify real (sugar) transporters required for pathogenesis: (i) comparative genomics of pathogenic and non-pathogenic (commensal) strains; (ii) comparative transcriptomics of pathogens grown in an animal model versus in a laboratory medium; (iii) *IVET* (in vivo expression technology) selections and screens to identify *pathogen* genes induced during host infection; (iv) competitive growth of a sugar transport mutant and wild-type in an animal model. Whether the knockout/inhibition of a particular transporter compromises infectivity generally depends on the bacterial species and the animal virulence model [38]. So several sugar transporters could be identified as virulence factors—virulence model dependent—but they are not always the same.

Milton Saier and colleagues compared the total transport protein content in the genomes of closely related *E. coli* (probiotic/commensal, extracellular and intracellular pathogenic, laboratory strain K12), *Treponema* (pathogenic, termite symbionts, free living) and *Bacteroides* (probiotic, pathogenic) [17, 38, 185, 208]. Substrate specificity was assigned based on sequence similarity with well characterized orthologous transporters, and from the association of a transporter gene with metabolic genes of known function [185]. Over all, the probiotic (health-promoting) strains contain fewer transport systems than pathogenic (disease causing) strains. The latter for instance have extra drug efflux pumps, toxin exporters and

iron uptake systems. However, this trend does not apply for sugar transporters (ABC, MFS, SSS, PTS). Probiotic and extracellular pathogenic *E. coli* have more transporters for sugars and other nutrients available in the extracellular environment. As a "compensation" intracellular pathogens have more transport systems specific for intracellular host metabolites, such as sugar-phosphates, amino acids, or glycolytic and Krebs cycle intermediates. Of 22 putative MFS transporters detected in seven pathogenic *E. coli* and in the K12 laboratory strain, each strain contained between 13 and 17 transporters, 11 transporters occurred in all strains, 4 only once (strain specific). Of 51 ABC transporter subunits (corresponding to 12-16 multisubunit ABC transporters), 29 occurred in all strains, 3 only once, and of 61 PTS transporter subunits, 18 occurred in all strains, 6 only once.

Free living and termite symbiontic *Treponema* species [17] have between 10 and 50 ABC transporters, whereas the intracellular pathogens have only two to four. The number of MFS transporters for all seven species was between 0 and 4, and complete PTS systems are absent. *Bacteroides* [208] are the most abundant species in the microbiota of the large intestine. They have MFS and ABC transporters but no PTS. They degrade and ferment carbohydrates from plant fibers and mucins (glycoconjugates secreted by intestinal epithel cells) and in return secrete SCFAs and vitamins for the host and hydrogen for the methanogenic gut bacteria [52, 167, 201].

Lyme borreliosis, a common tick-transmitted disease, is caused by the spirochete *Borrelia burgdorferi*. A transposon library consisting of 434 signature-tagged *Borrelia* mutants was tested for genes required for wild-type pathogenesis in mice [99]. Seven genes for ABC, 12 for MFS and 6 for PTS transporters were found to be required for full infectivity in mice. Eight of these candidate virulence genes encoded sugar transporters: the PTS transporters for Glc, maltose, chitobiose and fructose (genes *ptsG*, *malX1*, *malX2*, *chbB*, *fruA1*, *fruA2*), the MFS transporter for lactose (*lctP*) and the ABC transporter for methylgalactoside (*mglA*). Not present among the 434 conditional mutants were EI and IICIID mutants, which accidentally might have escaped transposon insertion. All 12 PTS transporter component mutants found in the *Borrelia* genome were then analysed in greater detail. They were inactivated, one at a time and tested for virulence in mice [89]. Only one mutant with a defective $IICB^{Glc}$ (*ptsG*) was unable to infect mice, but was still viable in ticks and grew at the same rate in a complex medium with and without Glc. Transcriptome analysis of the *ptsG* mutant revealed that several genes associated with lipoprotein synthesis and virulence were 5–20-fold upregulated and a few were down regulated.

Streptococcus pneumoniae has 30 sugar transport systems which together can take up 26 out of a set of 32 different metabolizable carbohydrates [7]. Group A *Streptococcus pyogenes* (GAS) has fourteen predicted PTS sugar transporters (9 GFL, 2 AG, 3 mannose family). They were inactivated one at a time in order to characterize how they contribute to the early expression of streptolysin secretion (SLS, haemolytic activity), increased lesion size and decreased survival in a murine soft tissue infection model [180]. Six IIC and IICIID mutants displayed early onset haemolytic activity, that is a derepression/activation of virulence genes. A similar phenotype was also observed after inactivation of the two-component histidine-kinase CovS [186]. The sugar-specific uptake activity is only marginally affected by any of the 13 mutations, probably because of overlapping substrate specificities between the 13 transporters, and the uptake of Glc is not affected at all, suggesting strong redundancy for Glc uptake between PTS- and/or non-PTS transporters. A non-virulent *Streptococcus iniae* vaccine strain was compared with the virulent fish-pathogenic parent by subtractive hybridization [145]. A fructose PTS ($IIABC^{Fru}$) was found in the virulent but not in the vaccine strains. The correlation between fructose PTS and fish pathogenicity was confirmed with five virulent and five avirulent field isolates of *S. iniae*.

A *Yersinia pestis* strain carrying an in-frame deletion of *ptsG* encoding the Glc transporter of the PTS did not affect mouse infectivity [133]. However, $IICB^{Glc}$ conferred a growth advantage in the competition between wild-type and mutant in the mouse model, in serum-like medium, and in a rich culture medium containing Glc, but not in the absence of Glc.

In conclusion, it is not clear whether the loss of infectivity of sugar transport mutants is caused directly by the reduced transport capacity for an essential nutrient or indirectly by the up/down regulation of other genes and/or their products. Considering the frequent substrate specificity overlap between different transporters and the availability of different macronutrients in the host environment, transport capacity is unlikely to be limiting. At least in the case of PTS transporters, the effect may be indirect, and a compromised induction/repression of *bona fide* virulence genes may be the main cause of attenuated/augmented infectivity. Moreover some transporters may serve as sensors of host-specific compounds informing the bacterium that it has entered the host [132]. For instance, periplasmic binding proteins of ABC transporters act as chemotactic sensors in conjunction with the cognate membrane spanning chemotaxis receptors [71, 87]. It is likely that the number of lead compounds is much smaller in the host tissue/cell than the number of available carbon and nitrogen macronutrients. Inactivation of a transporter for an indicator/lead compound thus compromises signaling rather than metabolic energy-salvage.

The role of sugar transporters in the microbiota of the gut

Complex carbohydrates and polysaccharides are degraded and fermented by the gut microbiota in the large intestine, simple sugars by the microbiota in the small intestine [215].

The products of bacterial fermentation, short chain fatty acids (SCFA) are metabolized by the colon epithelium, in the liver and in muscle of the host [19, 167]. Carbohydrates are key carbon sources for the majority of resident microbiota and as such impose (i) strong competition between well adapted residents and potentially pathogenic invaders and (ii) selective pressure on cooperation between species of the bacterial consortium, for instance cross-feeding [117]. The carbohydrate metabolic network of the gut encompasses pathways of the host and of up to thousand bacterial species [29, 115]. Nutrient transporters are at the interface between host and microbial metabolism at the periphery of the bacterial network. In this position sugar transporters and in particular PTS transporters are expected to react prominently to changes of diet (fat/high sugar Western vs. plant polysaccharide-rich) and to the immune/disease state of the host (diabetes, obesity, inflammatory bowel disease) [66]. Numerous comparative omics studies revealed conditions under which microbial community (16S rRNA) and/or gene expression (transcriptomics) is altered and in consequence the abundance of carbohydrate metabolic/sugar transport pathways. But more often than not such an alteration of transport activity may be the incidental consequence of a network adaptation. A causal relation between activity and well-being of the host and its bacterial community could be detected in studies with transporter mutants in defined bacterial communities of gnotobiotic mice.

Bacteroides thetaiotaomicron, Eubacterium rectale and gut epithelial cells constitute a carbohydrate recycling system as follows [112]: *B. theta.* stimulates the host to produce mucins and secretes numerous glycoside hydrolases to degrade these mucosal glycans. *Eubacterium rectale* adapts to *B. theta.* by downregulating its own production of glycan-degrading enzymes. It increases instead the expression of sugar transporters, glycolytic enzymes and secretes SCFAs which are utilized by the gut epithelial cells. Among the most strongly up-regulated genes are three for sugar transporters of cellobiose, galactoside, and arabinose/lactose.

A hypervirulent *Clostridium difficile* strain (ribotype) was found to overexpress a trehalose PTS transporter (belonging to the GFL family), due to the acquisition of the gene *ptsT* by horizontal gene transfer [26]. *PtsT* conferred a fitness advantage against its isogenic *ptsT* deletion mutant in a human faecal minibioreactor, as well as in the mouse intestine in the presence of a complex microbiota. The 500-fold increased trehalose sensitivity of this strain confers a growth advantage, but the mechanism responsible for increased virulence is not known. Historically, the appearance of this hypervirulent strain coincides with the use of trehalose as food additive, e.g. in prepared frozen food.

The non-caloric artificial sweetener saccharin induces alterations in the composition of the intestinal microbiota (dysbiosis) and glucose intolerance in mice [177]. The glucose intolerance is transferable from saccharin consuming mice to germ-free mice by fecal transplantation, indicating that intolerance is mediated by the dysbiotic microbiota. Glycan degradation pathways leading to SCFAs, starch, sucrose, fructose and mannose metabolic pathways were enriched in the metagenome of microbiota, PTS sugar transport pathways were underrepresented. Enrichment of the former pathways was associated with obesity in mice and humans, with the SCFA possibly serving as precursors for *de novo* glucose and lipid synthesis by the host.

Mutant libraries of four human gut *Bacteroides* strains together with eleven wild-type species representing other major lineages of the gut microbiota were introduced in germ free mice and fed with either high fat/high sugar or low fat/high plant polysaccharide (arabinoxylan) diet [201]. 80–90% of the *Bacteroides* genes could be tagged (were not essential *in vitro*). Of 2238 genes conserved in all four strains, 82 had a fitness effect in the mouse microbiota independent of diet. Seven carbohydrate metabolic pathways (arabinose, fructose, xylose, fucose, rhamnose, fructose, glucose/galactose and hexuronate) had a significant effect on fitness in all four species, among them the three transporters for glucose/galactose (GlcT), arabinose (AraP) and fructose (FruP). These transporters were also significantly higher expressed in the microbiota than in a rich culture medium. GlcT and FruP were significant fitness determinants only in high fat/high sugar but not in arabinoxylan fed mice. The results suggest that sugar transporters can become metabolic bottlenecks under certain conditions.

Conclusion and outlook

This review on bacterial sugar transporters accompanies an outshining collection dedicated to eukaryotic and in particular human glucose transporters (this special issue). It is tempting to ask: what is the difference? One answer is “What is true for *E. coli* is true for the elephant” (Jacques Monod)—but not *vice versa*. The transporters of *Escherichia coli* were the training devices to sharpen the tools for the structural, biochemical, and biophysical characterization of integral membrane proteins. Genomic data, powerful sequence similarity search algorithms and homology threading methods provided evidence, that bacterial and eukaryotic transporters share sequence similarity and assume similar folds. Eukaryotic transporters were predicted to have the same number of transmembrane helices and a similar core structure. Residues essential for the function of bacterial transporters were found to be conserved between the bacterial and eukaryotic homologs [85]. The overall size of the eukaryotic homologs, however, is about twice that of prokaryotic permeases. They have longer N and C termini, often with extra helices, and the loops between the TMs of the core are longer. Some of the extracellular loops are glycosylated, and intracellular loops may

contain sites for activity control, for instance by phosphorylation or ubiquitination [31]. Isoforms of eukaryotic transporters are tissue-specifically produced by alternative promoter use and exon-skipping (pre-mRNA-splicing) [2, 170].

A comparison of the transporter repertoire of 141 bacteria, plants, protists and animals [152] indicate that organisms with larger genome sizes generally possess a greater number of transport systems. In bacteria, the increase in transporter content is correlated with a greater diversity of transporter types (superfamilies MFS, ABC, PTS). In multicellular eukaryotes, the increase is due to the large number of paralogs. Multicellular eukaryotes exhibit fewer transporter families than prokaryotic species but have generated a large number of paralogs by duplicating genes out of particular families of ABC and MFS transporters (see above). Paralogous proteins in multicellular organisms assume specific functions in terms of substrate preference, kinetics and regulation. In contrast, the single-celled prokaryotes and eukaryotes, with less paralogs but more (super)family diversity, are capable to utilize a much greater variety of carbohydrate nutrients. ABC transporter types account for 30–50% of all transporters in bacteria but for only 10–20% in animals. ABC transporters are particularly abundant in bacteria that lack respiration chains and depend on substrate level phosphorylation and photosynthesis for ATP generation. MFS secondary transporter families account for 40–60% in bacteria and animals. Ion-channels (which are not included in this review) account for 10–40% in animals but only 0–8% bacteria. Prokaryotic obligate intracellular pathogens and endosymbionts possess the most limited repertoire of membrane transporters. Multicellular organisms possess more energy-independent facilitators and channel proteins. The (blood)glucose concentration is constant within a narrow margin and glucose equilibrates by facilitated diffusion between the extra- and intracellular compartment.

A century of biochemical and biophysical research has provided a detailed picture of bacterial sugar transport proteins, of their structure and the molecular mechanism of their action. In the recent years, research priorities have shifted from the characterization of the molecular parts to a better understanding of cellular, physiological and biotechnological aspects. Attempts to improve the fermentative production of natural compounds have placed sugar transport in the spotlight of metabolic engineering and systems biology [41, 65, 106, 113]. For instance, the replacement of the PTS transporters with PEP-independent ABC and MFS transporters, and the inactivation of PTS components involved in catabolite repression have significantly improved the industrial production of aromatic metabolites, biofuels and organic acids [3, 214]. The antibiotic crisis increases the interest in bacteriocins and bacteriophages as potential antiinfectives and substitutes for low molecular weight antibiotics. Bacterial sugar transporters are gateways for bactriophage DNA penetration and receptor for pore forming bacteriocins. These functions are no yet understood, and their study opens a vast field of exciting research, and eventually therapeutical applications.

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