

# A guide to plasma membrane solute carrier proteins

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## Keywords

amino acids; cancer; cell surface; cellular metabolism; cellular transport; glucose; pH; physiology; plasma membrane; solute carrier transporter

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(Received 27 March 2020, revised 7 August 2020, accepted 17 August 2020)

doi:10.1111/febs.15531

This review aims to serve as an introduction to the solute carrier proteins (SLC) superfamily of transporter proteins and their roles in human cells. The SLC superfamily currently includes 458 transport proteins in 65 families that carry a wide variety of substances across cellular membranes. While members of this superfamily are found throughout cellular organelles, this review focuses on transporters expressed at the plasma membrane. At the cell surface, SLC proteins may be viewed as gatekeepers of the cellular milieu, dynamically responding to different metabolic states. With altered metabolism being one of the hallmarks of cancer, we also briefly review the roles that surface SLC proteins play in the development and progression of cancer through their influence on regulating metabolism and environmental conditions.

## Introduction

In order to survive and maintain proper function, cells must closely monitor and control their intracellular contents. By allowing specific molecules such as metabolites and ions to pass through the lipid bilayer and enter or leave the cell, transport proteins control nutrient levels, remove waste from cells, and regulate cell volume [1]. Mirroring the large range of compounds requiring transport, different types of transporter proteins have evolved that can be subdivided into four main superfamilies: (a) the ATP-binding cassette (ABC) transporters, (b) ATPases, (c) ion channels, and (d) solute carrier proteins (SLC) [2,3]. The current review aims to serve as an introduction to the SLC superfamily of transporter proteins and their roles in human cells. Members of this superfamily are found throughout the cell in the membrane of almost every organelle, as well

as the plasma membrane. In the first section, we summarize how the family is defined, highlight common structural features, and briefly introduce their roles in human health and diseases. Next, we provide an overview of the various SLC families in humans, focusing on SLC proteins that are expressed on the cell surface and may be considered the gatekeepers of cellular contents. We briefly review their roles in various pathologies and potential therapeutic implications. We decided to focus on cell surface SLC proteins because of considerable evidence to suggest that the composition of surface-expressed transporters changes in response to the environment and during cellular differentiation and thus reflect cellular and metabolic states. We refer to existing reviews to cover specific topics, organelles, or families of SLC proteins [4–9].

## Abbreviations

7TMIR, 7TM-inverted repeat; ABC, ATP-binding cassette transporters; ATP, adenosine triphosphate; HATs, heteromeric amino acid transporters; LATs, L-type amino acid transporters; LeuT, leucine transporter; MFS, major facilitator superfamily; PM, plasma membrane; SLC, solute carrier transporter; TM, transmembrane.

In this review, we also mention examples of how the transport of specific classes of molecules can affect the development and progression of disease. Hopefully, a deeper understanding of the functional integration of transporters at the interface between cells and their environment will grant a better appreciation for how SLC proteins allow cells use to thrive under physiological conditions and how this changes in disease states (in particular cancer).

## Other transport protein families

While this review aims to provide a guide to plasma membrane SLCs, it is important to place these in the context of other transport proteins that play complementary and essential roles in the uptake and secretion of metabolites and ions and are thus part of the ‘general equation’ of cellular metabolism.

There are four types of transporters that are driven by ATP hydrolysis or drive the synthesis of ATP: P, V, or F-type ATPases and ABC transporters [10]. ABC transporters serve mainly as exporters in eukaryotic cells, using energy derived from ATP hydrolysis to efficiently drive the transport of their substrates out of the cell [11]. ABC transporters generally consist of four domains: two transmembrane domains, which act as the passageway for substrates, and two nucleotide-binding domains that bind and hydrolyze ATP. While the transmembrane domains have a wide variety of structures and amino acid sequences, the nucleotide-binding domains show sequence conservation [12]. Many ABC transport proteins are implicated in resistance to cytotoxic drugs and other targeted chemotherapies [13]. For more information regarding ABC transporters, the reader is referred to Liu [14].

The ATPase family encompasses a large variety of proteins that also interact with ATP in order to perform their function. They can be further subdivided into F-, V-, or P-type ATPases. F- and V-type ATPases are both rotary ATPases, meaning they rotate about an axis as they perform their function, but are specialized in opposite functions. F-type ATPases drive the synthesis of ATP using established ion gradients, whereas the V-type ATPases use the energy derived from ATP hydrolysis to pump ions across a membrane and build up an electrochemical gradient [15]. P-type ATPases, on the other hand, drive the transport of ions and lipids across cellular membranes using extensive conformational changes driven by free energy released by ATP hydrolysis [16]. For more information regarding ATPase transporters, the reader is referred to Futai *et al.*, Palmgren *et al.* and Lippe *et al.* [16–18].

Ion channels perform passive transport, meaning substrates are transported down their electrochemical gradient. These proteins provide a pathway to specific ions and allow them to passively move down their concentration gradient [19]. This results in rapid transport, as the channels do not undergo such drastic conformational changes [19]. As their name suggests, the ion channel family transports a wide array of ions across cell membranes, maintaining the membrane potential and playing a critical role in cellular excitation and signaling [20]. For more information regarding ion channels, the reader is referred to Alexander *et al.* [21].

## SLC superfamily

The SLC superfamily currently includes 458 transport proteins in 65 families that transport a wide variety of substances across cell membranes [22]. These families are defined by the HUGO Gene Nomenclature Committee (HGNC) of the Human Genome Organization (HUGO) and organized such that member proteins within each family share at least 20–25% sequence similarity with at least one other member of the family [22,23]. The average SLC family contains seven members, with eight families containing only one member (SLC32, SLC40, SLC48, SLC50, SLC53, SLC61, SLC62, and SLC64) and the largest, SLC25, containing 53 members. More recently, newer models of classification have emerged based on clustering and phylogenetic analysis or a combination of functional and phylogenetic analysis [24–26]. For example, Höglund *et al.* analyzed the entire human genome (along with 16 other species) and identified 400 unique SLC genes [25]. They further found that several of the HUGO-defined families could be organized into four large phylogenetic clusters. The largest of these clusters was the  $\alpha$  group, containing 13 SLC families. For a comprehensive overview of the naming and classification systems used for SLC proteins, we refer the reader to Perland *et al.* [27].

Overall, SLC proteins transport a wide array of molecules, including sugars, amino acids, vitamins, nucleotides, metals, inorganic ions, organic anions, oligopeptides, and drugs [23]. General substrate class specificity tends to be consistent within most families. As detailed below and in Table 1, SLC proteins also have a range of substrate specificity, with some proteins transporting a range of biomolecules, while others are currently known to transport only one biomolecule and still others are ‘orphan’—with no known substrate. Recent reviews estimated that as many as 30% of SLC proteins remain such orphan

**Table 1.** Summary of SLC families, their general structure, and relation to the development or progression of cancer. Proteins in bold are described in more depth in the review. Proteins in italics have been annotated in other parts of the cell in addition to the plasma membrane. Protein folds have been classified as either the MFS, the LeuT or labeled with 'Other' and the prokaryotic homolog structure is in parentheses (ND, not determined). The Major substrates column is a representative but not exhaustive list of substrates transported by the proteins in the given SLC family. For more specific information regarding substrates, the reader is referred to the literature reviewed in the article. The number of transmembrane domains was obtained from Uniprot and literature cited in the respective sections. This table was assembled using information from [36] and [559]. For more specific structural information for these protein families, the reader is referred to Bai *et al.* [36]. A continuously updated resource containing similar information will be available through Meixner, Girardi *et al.* [562].

Family	Proteins at cell membrane	Fold type	Range of TM domains	Major substrates	Cancer related genes mentioned in this review
Sugars					
SLC2	<b>SLC2A1, SLC2A2, SLC2A3, SLC2A4, SLC2A5, SLC2A7, SLC2A9, SLC2A10, SLC2A11, SLC2A12, SLC2A13, SLC2A14</b>	MFS	12	Glucose, fructose, mannose, galactose	SLC2A1, SLC2A3
SLC5	<b>SLC5A1, SLC5A2, SLC5A3, SLC5A4, SLC5A4, SLC5A5, SLC5A6, SLC5A7, SLC5A8, SLC5A12</b>	LeuT	11–13	Glucose, fructose, mannose, galactose	SLC5A1
Amino acids and peptides*					
SLC1	SLC1A1, SLC1A2, SLC1A3, SLC1A4, <b>SLC1A5</b> , SLC1A6, SLC1A7	Other (GltPh)	8–10	Ala, Ser, Cys, Thr	SLC1A5
SLC3; SLC7	<b>SLC3A1, SLC3A2; SLC7A1, SLC7A2, SLC7A3, SLC7A4, SLC7A5, SLC7A7, SLC7A8, SLC7A9, SLC7A10, SLC7A11, SLC7A13</b>	ND (SLC3); LeuT (SLC7)	1 (SLC3); 9–14 (SLC7)	Leu, Val, Gly, Ala, Ser, Glu, Cys	LAT1 (SLC7A5 and SLC3A2), xCT (SLC7A11 and SLC3A2)
SLC6	<b>SLC6A1, SLC6A2, SLC6A3, SLC6A4, SLC6A5, SLC6A6, SLC6A7, SLC6A8, SLC6A9, SLC6A11, SLC6A12, SLC6A13, SLC6A14, SLC6A15, SLC6A18, SLC6A19, SLC6A20</b>	LeuT	12	GABA, norepinephrine, dopamine, serotonin, Gly, Leu, Iso, Val, Pro	SLC6A14
SLC38	SLC38A1, <b>SLC38A2</b> , SLC38A4, <b>SLC38A10</b>	LeuT	10–11	Ala, Glu, Ser, Gly, Met, Thr	
SLC43	<b>SLC43A1, SLC43A2</b> , SLC43A3	ND	12	Leu, Phe, Iso, Val, Met	SLC43A1
Vitamins					
SLC19	<b>SLC19A1, SLC19A2, SLC19A3</b>	MFS	12	Folates (e.g., 5-methyl tetrahydrofolate, 5-formyl)	tetrahydrofolate), thiamine
SLC19A1, SLC23	SLC19A3 <b>SLC23A1, SLC23A2</b> , SLC23A3	Other (UraA, UapA)	14	Ascorbate	SLC23A2
SLC46	<b>SLC46A1</b>	ND	12	Folates (eg. 5-methyl tetrahydrofolate, 5-formyl tetrahydrofolate)	SLC46A1
Nucleotides/nucleosides					
SLC28	<b>SLC28A1, SLC28A2, SLC28A3</b>	Other (vcCNT)	13–14	Nucleotides/nucleosides	SLC28A1
SLC29	<b>SLC29A1, SLC29A2, SLC29A3, SLC29A4</b>	MFS	10–11	Nucleotides/nucleosides	SLC29A1, SLC29A2
Bicarbonate ions and protons					
SLC4			10–14		SLC4A7

**Table 1.** (Continued).

Family	Proteins at cell membrane	Fold type	Range of TM domains	Major substrates	Cancer related genes mentioned in this review
	<b>SLC4A1, SLC4A2, SLC4A3, SLC4A4, SLC4A5, SLC4A7, SLC4A8, SLC4A9, SLC4A10, SLC4A11</b>	Other (UraA, UapA)		Bicarbonate, carbonate	
SLC9	<b>SLC9A1</b> , SLC9A2, SLC9A3, <b>SLC9A6</b> , SLC9A7, <b>SLC9B2</b>	Other (NhaA)	10–14	Protons	SLC9A1
SLC26	<b>SLC26A1, SLC26A2, SLC26A3</b> , SLC26A4, SLC26A4 SLC26A5, SLC26A6, <i>SLC26A7</i> , SLC26A9, SLC26A11	Other (UraA, UapA)	8–13	Bicarbonate, sulfate, formate	SLC26A3
Calcium ions					
SLC8	<b>SLC8A1, SLC8A2, SLC8A3</b>	CaCA	10–11	Ca <sup>2+</sup>	SLC8A1, SLC8A2, SLC8A3
SLC24	<b>SLC24A1, SLC24A2</b> , SLC24A3, <b>SLC24A4</b>	CaCA	10–11	Ca <sup>2+</sup>	SLC24A4
Inorganic ions					
SLC12	SLC12A1, <b>SLC12A2</b> , SLC12A3, <i>SLC12A4</i> , SLC12A5, <b>SLC12A6, SLC12A7</b>	LeuT	12	Cl <sup>-</sup>	SLC12A2, SLC12A6, SLC12A7
Carboxylates					
SLC13	<b>SLC13A1, SLC13A2, SLC13A3, SLC13A4, SLC13A5</b>	Other (VclINDY)	11–12	Sulfates, di- and tricarboxylates	SLC13A2, SLC13A3
SLC16	<b>SLC16A1, SLC16A2, SLC16A3</b> , SLC16A4, SLC16A5, SLC16A6, <b>SLC16A7, SLC16A8</b> , <i>SLC16A9, SLC16A10, SLC16A11, SLC16A12, SLC16A13</i>	MFS	12		Monocarboxylates
SLC16A1,	SLC16A3, SLC16A7				
Phosphate					
SLC20	<b>SLC20A1, SLC20A2</b>	ND	10–12	HPO <sub>4</sub> <sup>2-</sup> , H <sub>2</sub> PO <sub>4</sub> <sup>-</sup>	SLC20A1
SLC34	<b>SLC34A1, SLC34A2, SLC34A3</b>	ND	8	Inorganic phosphate	SLC34A2
Organic ions					
SLC14	<b>SLC14A1, SLC14A2</b>	Channel like	10	Urea	SLC14A1
SLC22	<b>SLC22A1, SLC22A2</b> , SLC22A3, <i>SLC22A4</i> , SLC22A5, <b>SLC22A6</b> , SLC22A7, <b>SLC22A8</b> , SLC22A9, <b>SLC22A11</b> , SLC22A12, <b>SLC22A13, SLC22A16, SLC22A17</b> , SLC22A24	MFS; Other (UraA)	7–12	Urate, prostaglandins, bile acids, $\alpha$ -ketoglutarate, amines	SLC22A1, SLC22A2, SLC22A11
Trace metals					
SLC11	<b>SLC11A2</b>	LeuT	12	Fe <sup>2+</sup> , Mn <sup>2+</sup> , Cu <sup>2+</sup> , Co <sup>2+</sup> , Cd <sup>2+</sup> , Ni <sup>2+</sup> , Pb <sup>2+</sup>	
SLC30	<b>SLC30A1</b> , <i>SLC30A2, SLC30A5, SLC30A10</i>	Other (Yiip)	5–16	Zn <sup>2+</sup>	
SLC31	<b>SLC31A1</b> , <i>SLC31A2</i>	ND	3	Cu <sup>2+</sup>	SLC31A1
SLC39	<b>SLC39A1</b> , SLC39A2, <i>SLC39A3, SLC39A4</i> , SLC39A5, <i>SLC39A6, SLC39A8, SLC39A10, SLC39A14</i>	MFS	6–8	Zn <sup>2+</sup>	
SLC40	<b>SLC40A1</b>	ND	10	Fe <sup>2+</sup> , Mn <sup>2+</sup>	SLC40A1
SLC41	<b>SLC41A1</b> , SLC41A2, SLC41A3	ND	10–11	Mg <sup>2+</sup> , Fe <sup>2+</sup> , Zn <sup>2+</sup> , Cu <sup>2+</sup>	SLC41A1
SLC49	<b>SLC49A1</b>	ND	13	Heme	
Other organic compounds					
SLC10	<b>SLC10A1, SLC10A2</b> , <i>SLC10A4, SLC10A5, SLC10A6, SLC10A7</i>	Other (NhaA)	8–10	Bile acids, steroid hormones	SLC10A2
SLCO	<b>SLCO1A2, SLCO1B1, SLCO1B3, SLCO1B7</b> , SLC01C1, <b>SLCO2A1, SLCO2B1, SLCO3A1, SLC04A1</b> , SLC04C1, <i>SLCO5A1</i>	ND	11–12	Wide variety of organic anions and cations	SLCO1A2, SLCO1B1, SLCO1B3, SLC2B1

transporters, even as recent technological developments have afforded novel methods to study these transport proteins [27,28]. The SLC superfamily does not contain active transporters that directly use the energy released by ATP hydrolysis to drive the transport of substances against their concentration gradient. Rather, these proteins act as passive facilitative transporters or secondary active transporters [29]. Facilitative transport is a system of transport in which the SLC acts as a simple gatekeeper for a compound to passively move down its gradient [2]. Facilitative transport refers to systems in which only one molecule is transported in a thermodynamically favorable direction. In secondary active transport, transporters couple the passage of two or more substances. One substrate goes down its electrochemical gradient, which provides the free energy to drive the transport of the other substrate(s). Thus, the thermodynamically favorable transport of one substance provides the necessary free energy to transport the other in an unfavorable direction. In many of these cases, the rate of transport is proportional to the electrochemical gradient of the coupled ion [30]. Such secondary active transporters can either be symporters, which transport their substrates in the same direction, or antiporters, in which the substrates cross the membrane in opposite directions [2]. The substrate specificity of these transporters is determined not only by interactions between amino acid residues and the substrate, but also by intramolecular interactions that regulate gating and/or selectivity elements [31–34]. Most secondary active transporters are thought to use the ‘alternating access’ transport mechanism, whereby protein domains are arranged to have a ligand binding site available on only one side of the membrane at a time, changing conformations to transport their substrates by shifting to the other side of the membrane [35].

## Structure

Since SLCs are grouped together as a ‘superfamily’, SLC proteins belonging to different SLC families have a variety of different three-dimensional folds that are not all phylogenetically related [29]. Nevertheless, there are certain structural features common to most if not all the SLC transporters. When analyzing hydropathy plots, SLC proteins are predicted to contain between 1 and 16 transmembrane (TM) domains, although most (~83%) tend to contain between 7 and 12 TM domains [36,37]. An overview is provided in Table 1.

SLC proteins with known structures have so far been shown to share a distinct feature: a pseudosymmetry across the core TM domains [38]. Although, as

is detailed in Table 1, there are other structural homologues used to classify SLC structures, two of the most common structural folds among SLC proteins are the major facilitator superfamily (MFS) and the leucine transporter (LeuT)-like folds [36]. The MFS fold consists of two pseudo-repeats of six TM helices connected by a cytoplasmic loop, while the LeuT-like fold consists of two five-TM helices, each of which contains a bundle and a scaffold domain [38]. The specific mechanism that drives alternating access transport depends heavily on the physical structure of proteins [39]. Proteins of the MFS fold utilize a rocker and switch mechanism, while proteins with a LeuT fold utilize a rocking-bundle approach, and a third ‘elevator’ mechanism is also used by SLC proteins [39,40]. As mentioned previously, in the alternating access transport mechanism, the substrate-binding site is available only on one side of the membrane at a time. During the intermediate steps of these transport cycles, the substrate is occluded from access to either side of the membrane. In both the rocker-switch and the rocking-bundle model, the substrate binds to the available binding site. Next, the two transmembrane domains shift around the substrate, exposing the binding site to the other side of the membrane and releasing the substrate [40]. The rocking-bundle mechanism has a similarly centrally localized substrate-binding site between the two transmembrane domains. However, rather than moving both transmembrane domains around the substrate, only one domain shifts around the binding site and change the side the substrate is exposed to [40]. Finally, in the elevator mechanism, the two domains have distinctly different roles. There is a scaffold domain and a transport domain, which binds the substrate. The transport domain, through rigid body movement, migrates across the membrane and release the substrate [40].

One problem that persists when investigating the structure and function of SLC proteins is how difficult it is to purify and study transmembrane proteins [23]. Thus far, very few high-resolution structures for human SLC proteins have been determined, exemplified by SLC2A1, SLC2A3, SLC4A1, SLC6A4, and SLC42A3 [41–46]. The structures of SLC homologues in other species combined with computer modeling have provided insights to human SLC transporters [47]. As an example, the crystal structure of vSGLT, the sodium/glucose cotransporter from *Vibrio parahaemolyticus*, has been determined, providing insight on the mechanism of similar proteins like SLC5A1 (which has 32% sequence similarity) [48]. Similarly, the high-resolution atomic structure of a bacterial amino acid transporter has further provided structural

context for how the SLC6 family of proteins transports its substrates [49,50]. However, one of the major limitations of using bacterial transporters as a method to elucidate the structure and function of human transporters is that these crystalized bacterial proteins can lack the longer cytoplasmic tails that play a significant role in transporter activity and specificity [51]. Compounding these difficulties to predict SLC protein behavior a priori is the complex web of regulation resulting from interaction partners, selective gating, and post-translational modification. Although transporters may have similar binding residues, differences in these factors can change the specificity of a transporter.

Solute carrier proteins are regulated by different post-translational modifications on the intracellular loops between TM domains and the N and/or C termini. These modifications include phosphorylation, acetylation, and ubiquitination, while the extracellular loops and termini can be heavily glycosylated (reviewed by Czuba *et al.* [7]). Such modifications have been shown to affect both the rate of transport, affinity for their substrates, and SLC protein activity [52,53]. As an example of such complex regulatory networks, the activity of every well-characterized SLC12 transporter is regulated through the phosphorylation and dephosphorylation of serine/threonine residues [54]. The location of these regulatory sites and the effect of modification differs between the different subfamilies of SLC12 [54,55]. Furthermore and of particular relevance for this review, ubiquitination often regulates the translocation of SLC proteins from vacuoles and/or other intracellular organelles to the plasma membrane and vice versa [56]. As an example, the insulin-dependent translocation of SLC2A4 to the PM is regulated by ubiquitination and clathrin-mediated vesicular trafficking [57,58]. Of note, the activity of SLC proteins is also not only affected by the modification of the transporters themselves, but changes to their intermolecular interactions with other proteins and intramolecular interactions between domains [31–34]. For example, the substrate specificity of FurE, a fungal transport protein, is regulated by interactions between its terminal cytoplasmic domains that create a gating system for this transporter. As another example, the substrate specificity of the fungal protein UapA is regulated by residues that are not part of the substrate-binding site [59]. Intermolecular interactions between proteins like PCBP2 and SLC11A2 regulate the proper transport of iron to intracellular sites [60]. SLC16A1, 16A3, and 16A7 also all have their transport function increased in part through their interactions with carbonic anhydrases (CA) (CAII for

SLC16A1 and 16A3; CAIV for SLC16A7) [61,62]. This increase in efficiency is due to a direct supply of protons from the anhydrases to the transporters [63,64].

For a more comprehensive review on inter- and intramolecular interactions and how they impact transporter activity, readers are referred to Mikros *et al.* [51].

## Roles in health and disease

Owing to their role as one of the main regulators of what enters or leaves cells, the transport function of SLC proteins is linked to a wide range of cellular and physiological processes. Some SLC proteins have been found to be tissue specific, performing roles unique to certain cell types, best exemplified by specific transporters of the SLC6 and SLC18 family, which regulate the concentration of neurotransmitters in synapses [65]. Many different SLC families are also involved in transporting nutrients across selective barriers between tissues (like the blood–brain barrier or the gut epithelium) to provide them with the necessary nutrients [66]. Some SLC proteins are now also understood to act as ‘transceptors’, acting as both a transporter and receptor for the cell, allowing transport to also serve as a signaling system within the cell (further reviewed in Hundal *et al.* [67]). In this vein, some believe that SLC proteins are involved in ‘remote sensing and signaling’, a hypothesis that suggests SLCs and other transporters regulate cell and even tissue function by their altered expression/activity [68]. According to this hypothesis, transporters could play a role in signaling between organs [69]. For example, SLC30A8, a zinc transporter that has been closely linked to diabetes, is highly expressed at the membrane of pancreatic cells [70–72]. There, the transporter imports zinc from the cytoplasm into insulin secretory granules [71]. The subsequent cosecretion of insulin and zinc will impact not only neighboring endocrine cells, but the zinc serves as a signaling molecule that inhibits downstream hepatic insulin clearance, allowing the delivery of insulin throughout the body [71]. In another transport-independent role, SLC proteins from several different families contain a virus-binding site, thus facilitating viral entry into cells, including SLC1A5, SLC3A2, SLC7A1, and SLC52A1 [73–77].

As a consequence of their importance in physiology, mutations of SLC proteins have been linked to various diseases by contributing to an imbalance in the uptake, disposal, or absorption of metabolites and ions across different tissues resulting in disease states [78,79]. According to the Online Mendelian Inheritance in

Man (OMIM) database, about 190 different SLC genes have been linked to an inherited disease, resulting in phenotypes ranging from deafness (SLC17A8), anemia (SLC25A38), thyroid dysphormogenesis (SLC5A5), and choreoacanthocytosis (SLC4A1) [28,80–84]. Furthermore, genomewide association studies (GWAS) have linked polymorphisms of SLC genes to complex diseases. For example, variants of SLC16A11 have been associated with type 2 diabetes in a GWAS in Mexico, although the exact role that SLC16A11 plays in the development of type 2 diabetes remains unclear [85,86]. Other examples, such as SLC2A9 (gout), SLC22A4 (inflammatory bowel disease), and SLCOB1 (jaundice), are further reviewed in Lin *et al.* [78].

Solute carrier proteins are not only transporters of endogenous metabolites and ions, but are also the system by which many drugs are thought to cross the lipid bilayer and gain access to biological systems. Thus, SLC proteins indirectly affect disease outcome by affecting drug pharmacokinetics. In recent drug development guidelines, the FDA emphasizes the importance of screening SLC proteins for potential drug–drug interactions [87]. This further underscores the central role that SLC proteins play in the absorption of drugs in the intestine and across other interfaces [88]. A recent analysis of transport proteins (371 SLC and 46 ABC transporter genes) and their potential as drug interactors linked a total of 493 pharmacological compounds to 107 transporters [89]. The effect can be either via direct transport or indirect, for example, by importing a cofactor needed by an enzyme to convert a prodrug. As an example, SLC proteins play a critical role in the transport of antimetabolites such as 5-fluorouracil (SLC29A1) and methotrexate (SLC19A1) [90]. Although a wide variety of SLC proteins are known to participate in drug transport, the SLC22 and SLCO families are among the best understood in terms of pharmacokinetics [28]. These findings have led to the hypothesis, which we support, that most drug uptake occurs through transporters rather than simple diffusion through the plasma membrane [91]. Hence, we postulate that more drug transporters will be identified in the future, leading to a better understanding of solute carriers, and particularly those expressed on the cell surface. Unraveling such drug transporters may enable the development of treatments that take advantage of transport discrepancies in disease versus healthy states.

A few SLC proteins are the direct target of approved drugs, most of which are members of the SLC5, SLC6, SLC12, or SLC22 families [92]. The potential afforded by modulating SLC protein

activities continues to expand as their significance in pathophysiology continues to unravel, along with structures and transport mechanisms (see review by Rives *et al.* and Wang *et al.* [5,8]). Such potential is best exemplified by the SLC6 family, different members of which are associated with 42 drugs currently approved by the US Food and Drug Administration, mainly for the treatment of psychiatric disorders [92].

## An overview of plasma membrane solute carrier proteins

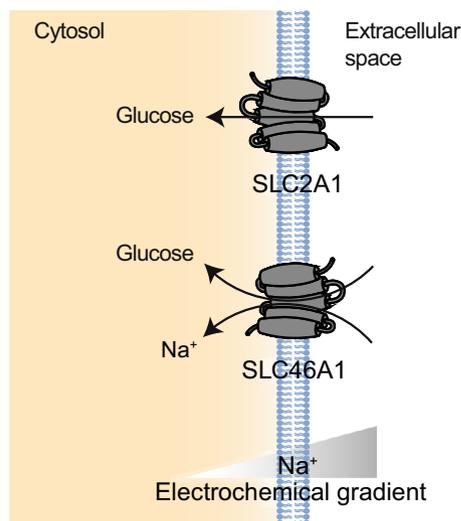
While solute carrier functions cover a broad range of transport between different cellular organelles, about 60% of SLC proteins with known localizations have been annotated at the cell surface on the plasma membrane (PM) [37]. These regulate the transport between the extracellular and intracellular milieus and hence directly control the uptake and efflux of nutrients, drugs, and other biomolecules from/to the environment. However, the expression of surface SLCs is likely to be tuned to the environment as well as the cellular programs of gene/protein expression of growth and differentiation. In this ‘guide to SLC proteins’, we focus on SLC families in which some members are known to be expressed on the PM. Owing to the fact that we do not currently have a complete understanding of the cellular localization for each SLC, this review cannot be a comprehensive list of solute carriers on the PM. We have grouped transporters by broad classes of metabolites and ions that are transported, with the aim to provide the reader with a useful survey of how metabolites and ions are transported in and out of cells. With altered metabolism being one of the hallmarks of cancer, we also briefly review the roles that surface SLC proteins play in the development and progression of cancer through their influence on regulating metabolism and environmental conditions. An overview of the SLC families described in this review is provided in Table 1.

## Transporters of sugars

A large source of energy production in cells comes from the breakdown of carbohydrates and in particular glucose. Thus, the uptake of sugars is critical to cell survival. The two major families that drive such transport are SLC2 and SLC5 (Fig. 1).

## SLC2

The SLC2 family transports a wide variety of carbon compounds, including monosaccharides and polyols.



**Fig. 1.** Examples of SLC proteins transporting sugars (SLC2 and SLC5). SLC2A1 is shown as an example of the SLC2 GLUT transporters, while SLC5A1 is shown as an example of the Na<sup>+</sup>-dependent SLC5 family of sugar transporters.

These proteins are expressed throughout the body in almost every cell type, underscoring their ubiquitous importance [93]. The subcellular localization of SLC2 proteins can be affected by cellular state and thus allows for very close regulation of monosaccharide concentrations within the cell [6]. Structurally, all SLC2 proteins contain an MFS structural fold and most possess 12 TM domain segments with a cytoplasmic linker domain. These proteins also all have cytoplasmic N and C termini [94]. This family consists of three different subfamilies of transporters based on their sequence similarity. Class 1 consists of SLC2A1, 2A2, 2A3, 2A4, and 2A14 (GLUT1-4 and 14, respectively) and contains the most closely studied members of the family. Class 2 consists of SLC2A5, 2A7, 2A9, and 2A11 (GLUT5, 7, 9, and 11, respectively) while class 3 contains SLC2A6, 2A8, 2A10, 2A12, and 2A13 (GLUT6, 8, 10, 12, and HMIT, respectively). Members of this family have been implicated in Mendelian disorders like hyperuricemia (SLC2A9), Fanconi-Bickel syndrome (SLC2A2), and GLUT1 deficiency syndrome (SLC2A1) [95–97].

The main SLC2 proteins expressed on the PM are SLC2A1–SLC2A5. One of the most well-understood SLC proteins is SLC2A1 (reviewed by Carruthers *et al.* and Zambrano *et al.*) [98,99]. SLC2A1 has been long investigated for its roles in tumor progression [100]. It is expressed at the PM throughout the human body, and functions primarily as a glucose transporter, although it can also transport mannose, galactose, and

glucosamine [98]. SLC2A2 is most highly expressed at the PM in hepatocytes [101]. This transporter has a high affinity for glucosamine and can also transport glucose, galactose, mannose, and fructose. Among other regulatory roles, SLC2A2 functions in the regulation of glucose-sensitive genes and insulin-related pathways [101,102]. One of the primary glucose transporters in brain tissue is SLC2A3, where its higher affinity and maximum turnover number help overcome the lower concentration of glucose in cerebral blood [103]. The cellular distribution of SLC2A3 varies between tissue types and cell states. In neurons, SLC2A3 is found mainly on the cell membrane, but also in vesicles and mitochondria, while in human white blood cells SLC2A3 exists mainly as a cytoplasmic vesicular protein which is then translocated to the cell membrane upon activation of the cells [103,104]. SLC2A4 is similarly stored in cytoplasmic vesicles, which can then be redistributed to the cell membrane upon activation by insulin signaling [105]. This protein is expressed mainly in skeletal muscle, adipocytes, and cardiomyocytes, where it acts as a glucose transporter after its insulin-triggered translocation to the cell membrane [106]. SLC2A5 functions mainly to transport fructose across the apical membrane of the small intestine [107]. Interestingly, SLC2A5 is also expressed across a wide array of human tissues, although fructose concentrations are minimal in the blood and thus SLC2A5's role in more peripheral tissues is uncertain [108].

## SLC5

The SLC5 family contains 12 members that perform the concentrative transport of glucose up its own concentration gradient by harnessing the electrochemical Na<sup>+</sup> gradient across the cell membrane [109]. Other substrates of SLC5 family include different sugars (mainly galactose, mannose, and fructose), anions, vitamins, and short-chain fatty acids [110]. One member of this family, SLC5A4, has been found to act not as a transporter, but rather as a glucose sensor in the plasma membrane of tissues [111]. All SLC5 proteins with the exception of SLC5A5 and SLC5A8 are composed of 14 TM helices, with the N terminus located on the extracellular side of the membrane [110].

SLC5A1 (SGLT1) is the most well-understood protein in the SLC5 family. This protein transports one molecule of glucose or galactose with two sodium ions across the brush border of the small intestine and kidney [110,112,113]. Due to the extreme sodium gradient across the cell membrane and the stoichiometric ratio of transport, SLC5A1 acts as a concentrative

transporter and is the most highly expressed transporter in the small intestine's brush-border membrane [114]. SLC5A2 (SGLT2) cotransports one sodium ion with one molecule of glucose and is most highly expressed in the kidney cortex, where it localizes to the brush-border membrane of the proximal tubule [110]. SLC5A2 plays a critical role in glucose reabsorption, absorbing ~90% of the filtered glucose [115]. Both SLC5A1 and SLC5A2 have been closely associated with diabetes and thus are significant targets of approved drugs [116–118].

SLC5A3 and SLC5A5 do not transport sugars across membranes, despite their sequence similarity to other SLC5 members. SLC5A3 (SMIT1) cotransports  $\text{Na}^+$  and myoinositol, a critical osmotic regulator for cells, across membranes, thereby playing a role in volume regulation [119]. In hypotonic environments, both the expression and the plasma membrane localization of SLC5A3 are increased, resulting in increased uptake of myoinositol [120]. SLC5A5 (NIS) is a symporter, coupling the import of an anion (primarily  $\text{I}^-$  but other substrates include  $\text{ClO}_3^-$ ,  $\text{SeCN}^-$ , and  $\text{SCN}^-$ ) with  $\text{Na}^+$  [121]. This protein is expressed primarily in the thyroid gland, but is also found in the salivary gland, stomach, small intestine, and mammary glands [122]. As the main  $\text{I}^-$ -importer in the thyroid, SLC5A5 plays a critical role in thyroid hormone biosynthesis [123].

## Sugar transporters and cancer

Cancerous cells are known to often have altered metabolic states, relying more on glycolysis as their source of ATP [124,125]. This change requires cells to increase their uptake of glucose to fuel these more metabolically active cells [126]. Thus, targeting glucose transporters discussed above would provide a targeted strategy through which to disrupt the energetic supply of cancerous cells. The expression of both SLC2 and SLC5 proteins changes during the development of cancer, although the proteins thought to be the most significant contributors to these changes are SLC2A1, SLC2A3, and SLC5A1 [127–129]. Both SLC2A1 and SLC2A3 are expressed at significantly higher levels in most cancers, with higher expression of proteins found in more aggressive and proliferative cancers and lower protein expression being linked to higher survival rates of patients [130,131]. Higher expression of SLC2 proteins has also been linked to the development of chemotherapy resistance [128,132,133]. SLC5 proteins have been found expressed at higher levels in colon, lung, head, neck, and pancreatic cancers [127]. SLC5A1, as the main sodium-glucose transporter in

the body, is often overexpressed in cancerous tissues, allowing these higher rates of aerobic glycolysis [129]. These alterations in SLC5A1 expression at the cell membrane may be due to the EGFR increasing expression of the protein while also decreasing its degradation [129,134]. Imaging studies using a small molecule that is transported specifically by SLC5A2 have shown that also SLC5A2 is expressed at higher levels in certain cancers [135,136].

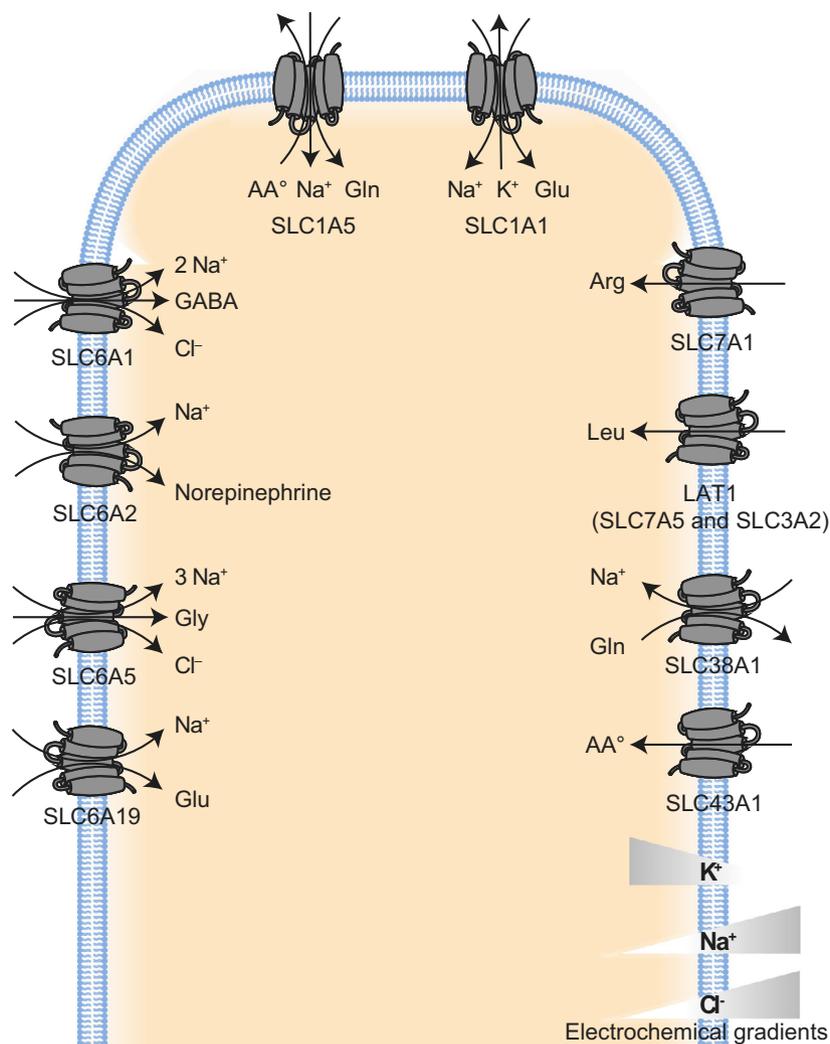
## Transporters of amino acids and peptides

Amino acids are utilized as the building blocks for proteins and also serve a multitude of different signaling and energetic roles within cells. In this section, we review SLC families 1, 3, 7, 6, 38, and 43 which together drive the majority of transport of these compounds (Fig. 2). SLCs in these families have been in the past annotated also by their transport substrates and mechanism (Table 2). However, these classifications are becoming increasingly difficult to define, as proteins like SLC38A7 possess properties of both systems of transport [137].

### SLC1

The SLC1 family contains seven different glutamate and neutral amino acid transporters expressed throughout the body, although they play a particularly important role in the central nervous system (CNS) [138]. Five of the transporters, SLC1A1 (EAAC1), SLC1A2 (GLT1), SLC1A3 (GLAST), SLC1A6 (EAAT4), and SLC1A7 (EAAT5), are high-affinity glutamate transporters, while SLC1A4 (ASCT1) and SLC1A5 (ASCT2) are referred to as neutral amino acids transporters (alanine, serine, cysteine, and threonine), although transport is not restricted to these compounds (e.g., SLC1A5's preferred substrate is glutamine and at lower pHs also readily transports glutamate) [138–140]. The high-affinity glutamate transporters cotransport glutamate with 3  $\text{Na}^+$  ions against the counter-transport of 1  $\text{K}^+$  ion [138]. This subset of SLC1 transporters functions to maintain a sufficiently low extracellular concentration of glutamate, the major excitatory neurotransmitter in the CNS that is cytotoxic at higher concentrations [141]. These transporters localize to the plasma membrane of astrocytes and neurons [142]. In addition, these high-affinity glutamate transporters also play a role in the regulation of cellular metabolism because their substrate is involved in the synthesis of glutamine [140]. The two neutral amino acid transporters are expressed throughout the body [138]. SLC1A5 is expressed at cell

**Fig. 2.** Examples of SLC proteins transporting amino acids and peptides (SLC1, SLC3, SLC6, SLC7, SLC38, and SLC43). SLC1A1 represents the SLC1 subfamily of high-affinity glutamate transporters, while SLC1A5 represents the subfamily of neutral amino acid transporters. SLC7A1 represents the subfamily of L-type amino acid transporters (LATs), while LAT1 represents the group of heterodimeric transporters called heteromeric amino acid transporters (HATs). SLC6A1 represents the SLC6 subfamily of GABA transporters. SLC6A2 represents the subfamily of monoamine transporters. SLC6A5 represents the subfamily of Na<sup>+</sup>- and Cl<sup>-</sup>-dependent amino acid transporters while SLC6A19 represents the nutrient amino acid transporters. SLC38A1 is shown as an example of SLC38 amino acid transporter, while SLC43A1 is shown as an example of the SLC43 family of system L amino acid transporters.



membranes, where its main function is to import glutamine in exchange for neutral amino acids (e.g., serine, asparagine, or threonine) in a Na<sup>+</sup>-dependent manner [77].

### SLC3/7

Two SLC families, SLC3 and SLC7, are closely linked in their function. A protein from each of these families can be linked by disulfide bridges in order to form a protein complex known as the heteromeric amino acid transporters (HATs) [143]. These SLC3/SLC7 dimers facilitate a wide range of transport, described in detail below. SLC3 proteins are also known as the heavy subunit of HATs, while SLC7 proteins are also known as the light subunit. Although most SLC7 proteins form these heterodimers to transport amino acids, some members remain functional as monomers.

The SLC7 family of amino acid transporters contains 13 members, which can in turn be further divided into two subfamilies: the cationic amino acid transporters (CATs), which include SLC7A1-4 and SLC7A14, and the L-type amino acid transporters (LATs), which include SLC7A5-13 and the pseudogene SLC7A15P [143]. These two subgroups differ slightly in terms of structure, consisting of 14 and 12 TM segments, respectively. SLC7 proteins can also serve as amino acid sensors and are necessary to initiate the activation of the mTORC1 pathway [144].

SLC7A1-4 is monomeric transport proteins called CATs. These proteins function as system y<sup>+</sup> transporters (Table 2) [145,146].

LATs act as the light or catalytic subunit of the HATs and determine the transport system (Table 2) and substrate specificity of the heterodimer [143]. There are five transport systems used by the HATs:

**Table 2.** Different transport systems of amino acids.

Transport system [182,560,561]	Meaning	Transporters from SLC families
System A	Proteins cotransport Na <sup>+</sup> with small, polar amino acids	SLC38
System N	Proteins cotransport Na <sup>+</sup> with His, Gln, or Asn and the simultaneous antiport of protons	SLC38
System L	Proteins that have Na <sup>+</sup> independent transport of large hydrophobic neutral amino acids	SLC3/7, SLC43
System ASC	Proteins cotransport Na <sup>+</sup> with Ala, Ser, or Cys	SLC1
System asc	Proteins transport small neutral amino acids	SLC3/7
System x <sub>c</sub> <sup>-</sup>	Proteins exchange Cys for Glu	SLC3/7
System x <sub>AG</sub> <sup>-</sup>	Proteins cotransport Na <sup>+</sup> with Asp or Glu and antiport K <sup>+</sup>	SLC1
System y <sup>+L</sup>	Proteins cotransport Na <sup>+</sup> with cationic and neutral amino acids	SLC3/7
System y <sup>+</sup>	Proteins transport cationic amino acids	SLC7
System b <sup>0,+</sup>	Proteins transport cationic amino acids as well as neutral amino acids	SLC3/7
System B <sup>0</sup>	Proteins cotransport Na <sup>+</sup> with neutral amino acids	SLC6

system L, which is driven by SLC7A5 (LAT1) and SLC7A8 (LAT2); system asc, which is driven by SLC7A10 (Asc-1) and SLC7A12 (Asc-2); system x<sub>c</sub><sup>-</sup>, which is driven by SLC7A11 (xCT); system y<sup>+L</sup>, driven by SLC7A7 (y<sup>+LAT1</sup>) and SLC7A6 (y<sup>+LAT1</sup>), and finally system b<sup>0,+</sup>, driven by SLC7A9 (b<sup>0,+AT</sup>) [143,146,147]. The functional heterodimeric transporter is often simply referred to by the name of its light subunit. The heavy subunit is one of the two members of the SLC3 family: SLC3A1 (rBAT) and SLC3A2 (4F2hc) [148]. These proteins have a single TM domain with an extracellular C terminus and are essential to the proper routing of the light subunits of HATs to the plasma membrane, where the heterodimer drives the sodium-independent transport of amino acids [143,149].

Perhaps, the most well-understood heterodimer is LAT1, which consists of SLC3A2 and SLC7A5 and transports branched-chain and aromatic amino acids [150,151]. LAT1 is critical to cell growth due to its role as the main transporter of eight of the nine essential amino acids (leucine, isoleucine, valine, phenylalanine, tyrosine, tryptophan, methionine, and histidine) [152,153]. LAT2 on the other hand, formed by the

dimerization of SLC7A8 and SLC3A2, transports a wider range of amino acids at a lower affinity [151]. Both transport dimers are widely expressed throughout the body at varying levels [146,152].

SLC7A10 forms a heterodimer with SLC3A2 and localizes to the cell membrane of central nervous system tissue to transport small neutral amino acids like glycine, alanine, serine, threonine, and cysteine [154].

SLC7A7 and SLC7A6 both form complexes with SLC3A2, forming similar transporters called y<sup>+LAT1</sup> and y<sup>+LAT2</sup>, respectively, driving the exchange of cationic amino acids for Na<sup>+</sup> and a neutral amino acid [143,155,156].

SLC7A11 also forms a complex with SLC3A2 to form xCT, a sodium-independent exchanger of intracellular glutamate and cystine [157]. This transporter has been shown to play a critical role in maintaining the metabolic and redox balance of cells [158].

SLC7A9 forms a heterodimer with SLC3A1 to form a transporter called rBAT/b<sup>0,+AT</sup>. This transporter drives the uptake of cystine and dibasic amino acids and is highly expressed at the apical membrane of the renal proximal tubule, where it performs the majority of cystine reabsorption [147,159]. More recently, SLC3A1 has also been found to interact with SLC7A13 (AGT1) in the sections of the renal proximal tubules where SLC7A9 is not as highly expressed [160]. This newly discovered heterodimer is thought to act as a second cystine transporter on the plasma membrane of the kidney.

## SLC6

Transporters of the SLC6 family use the sodium gradient to carry out the secondary active transport of small amino acids or amino acid-like substrates [30,161]. Members of this family tend to have very specific localization in cells, owing to their specialized roles [161]. These proteins have 12 TMs with both C and N termini in the cytoplasm. These termini have been shown to play regulatory roles in protein trafficking and the stoichiometry of transport [162]. They are also implicated in the proper function of these proteins, serving as scaffolds upon which some of these proteins form dimers and higher oligomers [163,164]. Many members of this family are well-known targets of inhibitory drugs, treating epilepsy and movement disorders like Parkinson for example [162,165–168]. This family can be divided into four subfamilies based on their transport substrates: (a) the gamma-aminobutyric acid (GABA) transporters, (b) the monoamine transporters, (c) the neurotransmitter amino acid transporters, and (d) the nutrient amino acid

transporters [30]. There is also one remaining orphan transporter (SLC6A16) [161].

The GABA transporter subfamily includes SLC6A1 (GAT1), 6A6 (TauT), 6A8 (CT1), 6A11 (GAT3), 6A12 (BGT1), and 6A13 (GAT2) [30,161,169]. Although referred to widely as the GABA transporter subfamily, members also transport a variety of other substrates, including taurine (SLC6A6), creatine (SLC6A8), and betaine (SLC6A12) [161]. SLC6A1 is the main neuronal GABA transporter and one of the best understood members of this family [169]. SLC6A1 is found primarily in the synapse of presynaptic neurons, while SLC6A11 localizes to the cell membrane of astrocytes in close proximity to the synapses of GABAergic neurons [166,170]. The transport function of GABA transporters is driven by sodium and chloride cotransport, although the exact stoichiometry of this transport varies [170,171]. SLC6A13 is not only expressed in the brain but also in peripheral tissues like the liver and kidney [161]. SLC6A13 localizes to the sinusoidal membrane of periportal hepatocytes and to the basolateral membrane of proximal tubules [172]. SLC6A6 and SLC6A12 are also expressed in the brain, as well as the kidney and other tissues [161].

The SLC6 subfamily of monoamine transporters contains SLC6A2 (NET), 6A3 (DAT), and 6A4 (SERT) [30,168]. These transporters are all primarily expressed in the CNS and localize to the cell membrane of neurons at the presynaptic cleft [168]. There, these proteins perform the reuptake of norepinephrine (SLC6A2), dopamine (SLC6A3), or serotonin (SLC6A4), which is driven by the cotransport of a sodium ion [168].

The subfamily of amino acid transporters includes SLC6A5 (GlyT2), SLC6A7 (PROT), SLC6A9 (GlyT1), and SLC6A14 (ATB<sup>0,+</sup>) [30]. These transporters are all dependent on both sodium and chloride [162,173]. Both SLC6A5 and SLC6A9 transport glycine and 1 Cl<sup>-</sup> along with 3 Na<sup>+</sup> or 2 Na<sup>+</sup>, respectively [162]. The reuptake of glycine functions to prevent the over activity of glycine receptors in synapses [174]. SLC6A5 functions to maintain the concentration gradient between the extracellular space (where glycine is found at submicromolar levels) and the cytosol (millimolar levels) [174]. SLC6A9 has been shown to also reverse its direction of transport in response to dopamine stimulation of neurons, possibly as a way to rapidly transduce dopamine signaling into glycine release [175]. SLC6A7 is expressed primarily in a subset of glutamatergic neurons and functions as a high-affinity proline transporter [176]. SLC6A14 differs from the other transporters in this subfamily,

driving the transporting all essential amino acids as well as glutamine and arginine [173]. Although it is expressed at lower levels in normal tissues, it has been found to be upregulated in different kinds of cancers [177,178].

The fourth subfamily contains the nutrient amino acid transporters. This subfamily encompasses SLC6A15 (B<sup>0</sup>AT2), 6A16 (NTT5), 6A17 (NTT4), 6A18 (B<sup>0</sup>AT3), 6A19 (B<sup>0</sup>AT1), and 6A20 (SIT1) [30]. SLC6A15 and SLC6A17 both are expressed mainly at the cell membrane of neurons, although also at lower levels in kidney, pituitary, lung, and brain cells [30,161]. Mouse homologues of SLC6A15 transports leucine, isoleucine, valine, proline, and methionine, while SLC6A17 transports proline, glycine, leucine, and alanine [179,180]. SLC6A18 (B<sup>0</sup>AT3) is highly expressed at the luminal membrane of the proximal tubules in the kidney, where it acts as a sodium and chloride-dependent neutral amino acid transporter [181]. SLC6A19 (B<sup>0</sup>AT1) and SLC6A20 are brush boarder transport proteins, expressed primarily at the apical membrane of small intestine and kidney cells [182–184].

## SLC38

The SLC38 family contains 11 proteins that transport amino acids, with specificity varying greatly between the different members [137]. SLC38 proteins transport small amino acids like alanine, glutamine, serine, glycine, methionine, and threonine [185]. These transporters are expressed throughout the body [137,186]. The SLC38 family is considered to possess similar structural features throughout the family, consisting of 11 TM segments with an extracellular C terminus and intracellular N terminus [187].

Members of the SLC38 family are thought to perform either system A transport or system N (Table 2) [186]. Of the characterized proteins, SLC38A1 (SNAT1), SLC38A2 (SNAT2), SLC38A4 (SNAT4) are all thought to be System A transporters, while SLC38A3 (SNAT3), SLC38A5 (SNAT5), and SLC38A7 (SNAT7) are thought to be system N [186]. SLC38A2, among other members of the SLC38 family, is also suggested to behave as a ‘transceptor’, whereby amino acid binding or transport could trigger signaling network within the cell, resulting in both transport of a substrate and activity as a receptor [185,188,189]. SLC38A10 has been suggested to provide the bidirectional transport of glutamine, alanine, glutamate, and aspartate and the efflux of serine [190]. This protein is expressed at the plasma membrane of both neuronal cells and astrocytes [190].

## SLC43

The SLC43 family of proteins is rather small, consisting of only three members: SLC43A1 (LAT3), SLC43A2 (LAT4), and the orphan transporter SLC43A3 (EEG1) [191]. Both characterized proteins are highly similar plasma membrane system L amino acid transporters (Table 2), sharing ~ 57% amino acid similarity and consist of 12 TM domains [191]. Typical of other system L transporters, both SLC43A1 and SLC43A2 provide sodium-independent transport [192,193]. Unlike the SLC7 LATs, the SLC43 family does not require a binding partner to form a heterodimeric transport unit [193]. They act as low affinity facilitated diffusers of neutral amino acids, preferentially transporting leucine, phenylalanine, isoleucine, valine, and methionine [192–194]. Through their transport of leucine, both SLC43A1 and SLC43A2 play a role in the mTOR signaling pathway [194].

SLC43A1 is most highly expressed at the plasma membrane of liver, skeletal muscle, and pancreatic tissues, although it is also expressed at lower levels in other tissues of the body [193]. Expression of this protein is upregulated in response to starvation states, suggesting that it plays a critical role in interorgan amino acid balance [195]. SLC43A2 has a broader expression profile than SLC43A1, being expressed in the placenta, kidney, leukocytes, and at lower levels in many other tissue types [192]. The localization of this protein to the plasma membrane follows feeding patterns in mice, with increased plasma membrane expression of SLC43A2 occurring cyclically in anticipation of food intake, attesting to a role for SLC43A2 in amino acid absorption [196]. This protein is also required for proper mouse development, with knockout models exhibiting significant growth retardation and low amniotic fluid amino acid levels [197].

## Amino acid transporters and cancer

In cancer cells, the dysregulation of amino acid transporters alters amino acid levels, helping drive carcinogenesis [198]. Not only do cancer cells have a higher dependency on amino acids to drive the synthesis of proteins as they proliferate, but altered amino acid levels also contribute to the modulation of mTOR, a key protein kinase in cellular metabolism [198]. Of particular relevance to the etiology of cancer is the dysregulation of leucine and/or glutamine. Leucine serves as the main regulatory mechanism for mTOR in many tissues [199]. Cancer cells often overexpress leucine transporters, leading to higher intracellular leucine concentrations, mTOR activation, and the subsequent

proliferation of cancer cells [199,200]. Glutamine on the other hand serves a multitude of different roles within cells as a carrier for ammonia in tissues, a regulator of the acid/base balance in kidney cells and as the precursor of compounds like glutathione, glutamate, and GABA [201]. It is used as a building block for nucleotides and other amino acids, provides a source of  $\alpha$ -ketoglutarate for the TCA cycle (as a precursor of glutamate), and helps regulate the redox balance in cells [200]. These roles make glutamine a critical metabolite for cancer cells. Five of the major contributors to aberrant leucine and glutamine transport in cancer cells are SLC1A5, LAT1, xCT, SLC6A14, and SLC43A1 [131].

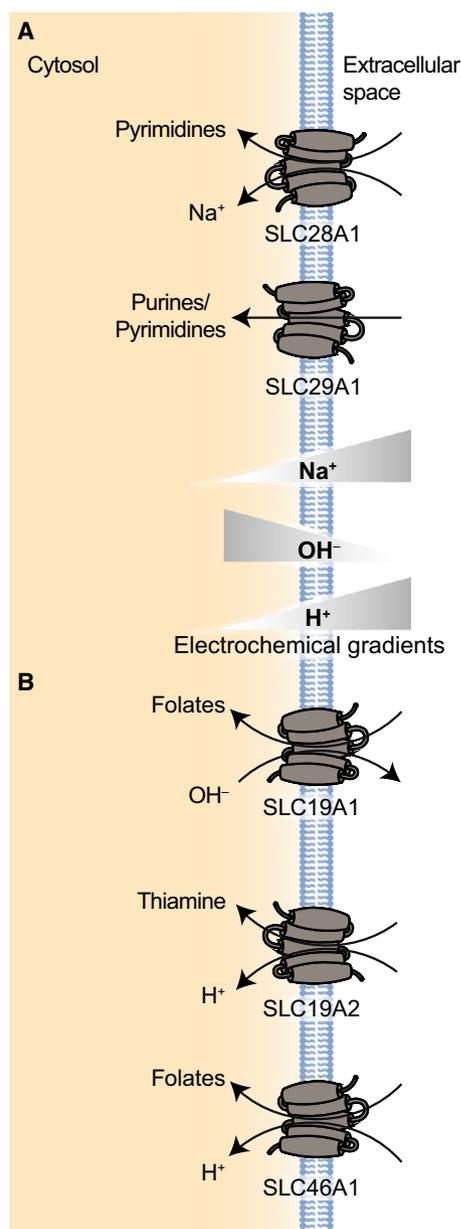
SLC1A5 serves as the primary source of glutamine uptake in cancer cells [131]. Its activity controls the rate of tumor growth in breast cancer and blocking this transporter's activity has been shown to prevent tumor cell proliferation in different tissues [77,201]. The function of LAT1 (the heterodimer of SLC7A5 and SLC3A2) is linked to that of SLC1A5, as it uses the efflux of glutamine to drive the uptake of leucine, which subsequently activates mTOR signaling. These two proteins can cooperatively drive the proliferation of tumor cells [201]. xCT (the heterodimer of SLC7A11 and SLC3A2) is essential for maintaining the redox balance of cells and the increased expression of xCT in cancer cells allows cells to reduce their oxidative stress and avoid apoptosis [158,200]. This dimer has upregulated expression in breast cancers that metastasize and inhibition of SLC7A11 (the functional subunit of xCT) delays lung metastasis, suggesting that xCT plays a significant role in cancer metastasis [202,203].

SLC43A1, similarly to LAT1, has upregulated expression in cancers as a source of essential amino acids (in particular leucine) [191,204]. SLC43A1 has also been implicated in cell proliferation and is particularly implicated in the severity of prostate cancers [194].

SLC6A14, a highly concentrative amino acid transporter, is expressed at higher levels in cancers in various tissue systems (e.g., breast, colorectal, cervical) [131,200]. Owing to the fact that SLC6A14 is generally expressed lower in healthy tissues than in cancerous tissues, it serves as a promising drug target.

## Transport of vitamins

Vitamins like ascorbic acid, folates, and thiamine are used in cells as the precursors of various compounds, as cofactors in metabolism and regulators of oxidative stress. Three SLC families drive the transport of these compounds, SLC19, SLC46, and SLC23 (Fig. 3A).



**Fig. 3.** (A) Examples of SLC proteins transporting vitamins (SLC19 and SLC46). SLC19A1 is the folate transporter, while SLC19A2 represents the thiamine transporters. SLC46A1 is a functionally related protein that drives the absorption of folate. (B) Examples of SLC proteins transporting nucleotides and nucleosides (SLC28 and 29). SLC28A1 is shown as an example of a concentrative nucleoside transporter (CNT), while SLC29A1 is shown as an example of an equilibrative nucleoside transporter (ENT).

### SLC19/ SLC46

The SLC19 family of proteins contains three members that transport either reduced folates (SLC19A1 [RFC]) or thiamine (SLC19A2 [ThTr1] and SLC19A3

[ThTr2]), driven by the antiport of organic anions [205]. These proteins are expressed throughout the body, ensuring proper levels of these critical vitamins in tissues [206]. The term folates refers to a larger group of water-soluble B vitamins that are the precursors and substrates for many different compounds related to cell and tissue growth and development [207]. Thiamine, also known as vitamin B1, also plays a critical role in cells as a cofactor in energy metabolism and also as a regulator of oxidative stress [208]. All three proteins perform the most efficient transport at a neutral extracellular pH (around 7.4), with efficiency dropping as pH does [206,207]. This may be due in part to the changing  $H^+/OH^-$  gradient across cell membranes [205].

SLC19A1 has a MFS structure and consists of 12 TM segments, with both N and C termini localizing to the cytoplasm [209]. The concentrative transport of SLC19A1 is driven by the export of anionic cellular metabolites down their concentration gradients [207]. SLC19A1 was identified in a recent study to also transport a cyclic dinucleotide that is produced when cytosolic DNA binds to cyclic GMP-AMP synthase, thus playing a role in triggering larger immune responses [210].

SLC19A2 and SLC19A3 share 48% identity and have different expression patterns within cells and affinities for thiamine. SLC19A2 is expressed primarily at basolateral membranes while SLC19A3 localizes to the apical membrane of cells. This localization suggests that SLC19A2 plays a role in thiamine export while the higher affinity transporter SLC19A3 directs the accumulation of thiamine into the cell [211,212].

A functionally related family of proteins is the SLC46 proteins. This family of proteins contains three members, two of which remain largely orphan transporters (SLC46A2, SLC46A3) [206]. SLC46A1 (PCFT) is a proton-coupled folate transporter that mediates the absorption of folate in the intestine, as well as transporting it into the CNS [206,213,214]. SLC46A1 performs electrogenic transport at a low pH, where it has an affinity for both folic acid and reduced folates [206].

### SLC23

The SLC23 family of transporters contains three members that regulate intracellular ascorbate concentrations [215]. SLC23A1 (SVCT1) and SLC23A2 (SVCT2) are both well characterized, while SLC23A3 (SVCT3) remains an orphan transporter [216]. Both characterized transporters are highly selective for L-ascorbic acid, with SLC23A1 having slightly higher

capacity but lower affinity than SLC23A2 [217]. SLC23A1 and SLC23A2 are both sodium-dependent transporters that have a stoichiometry of  $2 \text{ Na}^+ : 1$  ascorbic acid down sodium's electrochemical gradient [216]. Interestingly, SLC23A2 is also dependent on the presence of  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  in order to function, with the cations switching the transporter into an active form [218]. SLC23A1 is expressed mainly in intestinal and renal proximal tubule epithelial cells at the apical membrane [215]. SLC23A2 is expressed throughout the body and is expressed at its highest levels in brain, lung, and bone tissue [218]. It serves as the only specific ascorbic acid transporter in neuronal and glial cells, thus far [219]. SLC23A2 has been shown to localize to both the cell membrane and the mitochondria of tissues [218,220]. Interestingly, when localized to the mitochondria, SLC23A2 does not require the presence of  $\text{Ca}^{2+}$  and  $\text{Mg}^{2+}$  in order to function [221].

### Vitamin transporters in cancer

Nutritional factors, like ascorbate, thiamine, and folates, function as critical cofactors for enzymes are intermediates in carbohydrate metabolism and regulators of the oxidative balance of cells [207,208,215,222]. Thus, the proper transport of ascorbate, folate-related nutrients, and thiamine are critical to preventing carcinogenesis [222–225]. Folate is particularly important for one-carbon metabolism, wherein 5-methyltetrahydrofolate is used in the production of S-adenosylmethionine (SAM) [225]. Thiamine is important for several metabolic enzymes [224]. Although the link between thiamine consumption and the development of cancer remains unclear, studies have shown links between carcinogenesis and lower intracellular and blood levels of these vitamins [224]. Ascorbate plays a key role in maintaining the redox balance of cells by reducing reactive oxygen species and quenching free radicals [222]. Ascorbate also helps regulate the function of  $\alpha$ -ketoglutarate-dependent dioxygenases ( $\alpha$ -KGDDs), a diverse family of proteins that (among other functions) play a role in regulating DNA methylation and are often down-regulated in cancers [222,226]. Perhaps most importantly for its relation to cancer development and progression, ascorbate is a cofactor for HIF hydroxylases, proteins which identify HIF for degradation [227].

Dysregulation of vitamin transporters, and in particular SLC19A1 and SLC19A3, has been linked to carcinogenesis, as well as therapy resistance owing to their role as important drug transporters [223,224].

SLC19A1 is the primary transport mechanism for the delivery of antifolates to tumor cells, as it is expressed ubiquitously in tumor cells [206]. Polymorphisms of this transporter have been associated with an increase in adverse drug responses [228,229]. SLC46A1 provides an intriguing opportunity to harness its concentrative transport activity in acidic environments, which are often found in the tumor microenvironment [230]. SLC46A1, which is ubiquitously expressed in solid tumors, could in principle afford a more targeted delivery of antifolate drugs to tumor cells [230]. Expression of SLC19A3 in cancerous cells has been shown to be both increased and decreased and further studies are needed to elucidate the role SLC19A3 plays in cancer cells [224,231]. SLC19A3, like other transporters that have been discussed in the review, is also regulated by HIF-1 $\alpha$  [232]. This study showed that under hypoxic conditions the expression of SLC19A3 is induced, leading to higher import of thiamine and suggesting an adaptive role for SLC19A3 in hypoxic environments [232].

Various polymorphisms of SLC23A2 have been associated with an increased risk of both colorectal adenoma and gastric cancer, while SLC23A1 polymorphisms have shown conflicting results for their link to cancer risk [227,233–235]. Vitamin C has emerged as an intriguing therapeutic tool in oncology, with high concentrations of vitamin C killing colorectal cells by increasing oxidative stress in cells, inactivating GAPDH and reducing tumor size [222,236,237]. The varying localization of SLC23A2 in cells may be important for helping increase the therapeutic effect of vitamin C, as its mitochondrial localization in most cancer cell lines has allowed for mitochondria to be targeted in cancer therapeutics [238]. A recent study showed that a combinatorial therapy of doxycycline, azithromycin, and vitamin C effectively eradicates cancer stem cells [239]. Similarly, a combination treatment of vitamin C and cetuximab was recently shown to be an effective treatment to limit the development of acquired resistances in colorectal cancer, slowed the growth of cancerous cells, and impaired the structure of organoids [240].

### Transporters of nucleotides/nucleosides

As the building blocks for DNA and RNA, as well as fulfilling a multitude of different signaling roles within and between cells, the transport of nucleotides, nucleosides, and related compounds is critical for cell health. In this section, SLC families 28 and 29 are reviewed (Fig. 3B).

## SLC28/SLC29

Both SLC28 and SLC29 families provide the transport of nucleotides and nucleosides [241,242]. Both families also drive the transport of a significant number of nucleoside-analog-based drugs, including clofarabine, zebularine, and ribavirin [243]. In general, SLC28 proteins show a higher affinity for their substrates than SLC29 proteins, although SLC28 proteins have a lower turnover number in transport [241].

The SLC28 family of proteins consists of three proteins that provide the concentrative transport of nucleosides and are referred to as concentrative nucleoside transporters (CNT). These proteins link the import of nucleosides with sodium ions [241,244]. SLC28A1 (CNT1) and SLC28A2 (CNT2) have a transport stoichiometry of 1 Na<sup>+</sup> : 1 nucleoside while SLC28A3 has a stoichiometry of 2 Na<sup>+</sup> : 1 nucleoside [245]. These proteins are predicted to consist of 13 TM domains, with extracellular C terminus and an intracellular N terminus [244]. These proteins all localize primarily to the apical membrane of cells, where they provide the reabsorption of nucleosides from the extracellular milieu [246].

SLC28A1, unlike SLC28A2 and SLC28A3, does not transport adenosine, instead exhibiting a higher affinity for pyrimidine and pyrimidine-based analogs [245,247]. This protein is highly expressed in epithelial tissues, where levels vary as cell progress through the cell cycle [248]. In general, SLC28A1 tends to be upregulated in highly proliferating cells, possibly compensating for insufficient enzymatic synthesis of certain nucleosides with higher uptake [248,249].

SLC28A2 has a higher affinity for purine nucleosides than SLC28A1 and SLC28A3 [241]. In proliferating cells, this protein has been shown to salvage extracellular adenosine, triggering the activation of AMP-dependent protein kinase [250]. SLC28A2 has a varied subcellular distribution, localizing to both the cell membrane and intracellular vesicles in certain cell lines. This localization has been shown to be regulated by bile acids (BA), with extracellular BA triggering translocation to the cell membrane [251].

Unlike SLC28A1 and SLC28A2, SLC28A3 has coupled transport of substrates to both Na<sup>+</sup> and H<sup>+</sup> [243]. Interestingly, the affinity of SLC28A3 toward substrates changes depending on which cation is being cotransported [252]. Na<sup>+</sup>-coupled SLC28A3 transports a wider spectrum of pyrimidine and purine nucleosides/nucleoside drugs while H<sup>+</sup>-coupled transport is more selective and does not transport guanosine or zidovudine (an antiviral nucleoside drug) [243,252].

The SLC29 protein family encodes four transport proteins that are referred to as equilibrative nucleoside transporters (ENTs) [242]. These proteins provide the facilitative transport of nucleosides and nucleobases (and monoamines in the case of SLC29A4 (ENT4)), a function that is critical for nucleotide synthesis [241]. SLC29 members are expressed in all tissues [242]. These proteins are predicted to have 11 TMs, with a cytoplasmic N terminus and an extracellular C terminus [241,253]. These proteins also mediate the transport of nucleoside drugs like gemcitabine and didanosine and are predictors of treatment responses in diseases like pancreatic cancer and gallbladder adenocarcinomas [243,254,255].

SLC29A1 (ENT1) and SLC29A2 (ENT2) transport similar substrates across the plasma membrane, although their affinities to purine and pyrimidine nucleosides differ [242]. Through their role in controlling the nucleotide pool available for DNA synthesis, these transporters play a role in regulating the progression of cells through the cell cycle [256].

SLC29A4 (ENT4) localizes to the apical membrane of renal cells, where it provides proton-driven organic cation reabsorption [257]. This protein's activity is pH sensitive, with increases in pH resulting in diminished transport and acidic environments activating the protein [257]. SLC29A4 transports mainly adenosine, although it also shows affinity for a wider range of biogenic amines [258].

## Nucleotide transporters and cancer

The uptake of nucleosides driven by SLC28 and SLC29 proteins provides cells with the building blocks for nucleotide synthesis. Thus, rapidly dividing cells often rely on these nucleoside/nucleotide transporters, resulting in increased expression of these transport proteins to provide these building blocks [241]. Yet, decreased expression of SLC28 and SLC29 proteins has also been found in hypoxic environments [259]. There, HIF-1 $\alpha$  signaling decreased the expression of SLC29A1 and SLC29A2, resulting in higher extracellular adenosine concentrations [260]. Increased expression of SLC28A1 has also been linked to a decreased proliferation of cancerous cells [261,262]. A recent study showed that restoring the expression of SLC28A1 reduced the growth of tumors in mice. However, this study showed this effect occurred independent of transport, suggesting that SLC28A1's antiproliferative effect was signaling related [261].

SLC28 and SLC29 proteins also transport a significant amount of different nucleoside analogs like clofarabine, zebularine, and ribavirin, whose

pharmacokinetics are relevant to a wide variety of different diseases (e.g., viral infections, cancer, inflammatory diseases, autoimmune disorders) [243,263,264]. Variances in transporter distribution and expression are also linked to differing treatment outcomes, with higher expression of transporters generally resulting in higher sensitivity to nucleoside analogs [264].

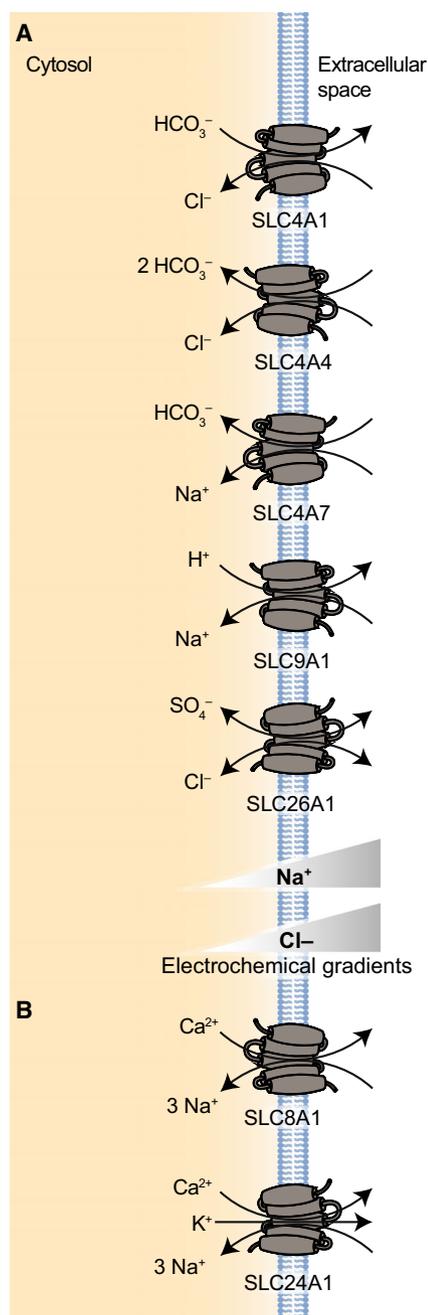
## Transporters of bicarbonate ions and protons

Through the transport of bicarbonate ions and protons, SLC families 4, 9, and 26 play a major role in the regulation of cellular pH, along with signaling events related to the transport of these compounds (Fig. 4A).

### SLC4

The SLC4 family has 10 different members that have linked the transport of bicarbonate (or carbonate) with the transport of at least one other ion,  $\text{Na}^+$  and/or  $\text{Cl}^-$  [265]. These proteins play a critical role in the acid–base homeostasis of the body by acting as either acid loaders or acid extruders, thus regulating both intra- and extracellular pH [266–268]. SLC4 protein topology consists of 10–14 TM domains with hydrophobic N and C termini extending into the cytoplasm [269–271]. Based on structural similarities between SLC4A1 and a bacterial uracil:proton symporter, SLC4 proteins with 14 TM domains are predicted to be organized in a 7TM-inverted repeat (7TMIR), meaning that the two structurally related halves span the membrane in opposite orientations and form a functional intertwined structure [272,273]. More recently, the cryoEM structure of SLC4A4 revealed the structural details of the ion pathways that dictate transport of substrates [274]. Many SLC4 proteins form dimers and oligomers and although the functional relevance of this dimerization is not entirely elucidated, in both bacterial and eukaryotic homologues dimerization is necessary for transport function and/or proper localization to the PM [266,273,275,276].

The SLC4 family includes several functional subfamilies: (a) SLC4A1 (AE1, also commonly referred to as Band 3 protein), SLC4A2 (AE2), and SLC4A3 (AE3) are all  $\text{Cl}^-/\text{HCO}_3^-$  anion exchangers (AE); (b) SLC4A4 (NBCe1) and SLC4A5 (NBCe2) are electrogenic  $\text{Na}^+/\text{HCO}_3^-$  cotransporters (NBCs); (c) SLC4A7 (NBCn1) and SLC4A10 (NBCn2) are electroneutral NBCs [265]. For SLC4A8 (NDCBE), SLC4A9 (AE4) and SLC4A11 (BTR1), substrates have not been fully resolved.



**Fig. 4.** (A) Examples of SLC proteins transporting protons and bicarbonate ions (SLC4, SLC9, SLC26). SLC4A1 represents the subfamily of anion exchangers (AE), SLC4A4 represents the subfamily of electrogenic  $\text{Na}^+/\text{HCO}_3^-$  cotransporters, while SLC4A7 represents the subfamily of electroneutral  $\text{Na}^+/\text{HCO}_3^-$  cotransporters. SLC9A1 serves as the prototypical  $\text{Na}^+/\text{H}^+$  exchanger. SLC26A1 is an example of an SLC26 transporter that cotransports sulfate with  $\text{Cl}^-$ . (B) Examples of SLC proteins transporting divalent ions (SLC8 and SLC24). SLC8A1 is shown as an example of a  $\text{Ca}^{2+}/\text{Na}^+$  exchanger. SLC24A1 is shown as an example of  $\text{K}^+$ -dependent  $\text{Na}^+/\text{Ca}^{2+}$  exchangers.

SLC4A1 is the predominant transport protein in the cell membranes of erythrocytes, where it participates in clearing CO<sub>2</sub> from tissues to the lungs [265]. SLC4A1 is also highly expressed in the basolateral membrane of renal cells, where it functions to reabsorb HCO<sub>3</sub><sup>-</sup> into the blood [265]. SLC4A2 is the most widely expressed of the anion exchangers, localizing to the basolateral membrane of most epithelial cells [265]. SLC4A2 and SLC4A3 are both regulated by pH, with increases in either intra- or extracellular pH resulting in increased activity [277,278].

SLC4A4 (NBCe1) acts as an electrogenic Na<sup>+</sup>/HCO<sub>3</sub><sup>-</sup> cotransporter at the basolateral membrane of renal proximal tubules, pancreatic ducts, and epididymis and is also expressed at lower levels throughout the body [265]. SLC4A5 (NBCe2) generally localizes to the Golgi apparatus within cells, but when intracellular sodium concentrations increase, the transporter is moved to the apical cell membrane [279]. SLC4A7 (NBCn1) is an electroneutral Na<sup>+</sup>/HCO<sub>3</sub><sup>-</sup> cotransporter expressed throughout the body but particularly in the spleen and testis [280]. SLC4A10 (NBCn2) is primarily found in the brain, where it functions as an electroneutral Na<sup>+</sup>/HCO<sub>3</sub><sup>-</sup> cotransporter [265]. SLC4A10 is expressed on the basolateral membrane of the choroid plexus epithelium, where its activity contributes to CSF secretion [281].

SLC4A8 encodes a Na<sup>+</sup>-driven Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> exchanger (NDCBE), importing Na<sup>+</sup> and HCO<sub>3</sub><sup>-</sup> in exchange for intracellular Cl<sup>-</sup> [282]. However, the substrate specificity is not entirely clear, as some data suggest Cl<sup>-</sup> is not necessary for transport [266,283]. This protein is primarily expressed at the plasma membrane throughout the CNS, where it may play a role in the pH regulation of neurons [284]. Although the protein encoded by SLC4A9 is called AE4, it was recently found to be an electroneutral Na<sup>+</sup>-dependent Cl<sup>-</sup>/HCO<sub>3</sub><sup>-</sup> exchanger that localizes to the basolateral membrane in cortical collecting ducts [285,286].

Finally, SLC4A11 (BTR1) is expressed throughout the body and does not transport bicarbonate. Rather, it was recently proposed to be an NH<sub>3</sub>/2H<sup>+</sup> cotransporter, as well as acting as a sodium-independent borate transporter [287,288]. Of its three main splice variants, only SLC4A11-B and SLC4A11-C are expressed as plasma membrane proteins, with SLC4A11-A localizing intracellularly [288].

## SLC9

The SLC9 family of proteins consists of 13 proteins that mainly act as Na<sup>+</sup>/H<sup>+</sup> exchangers, using the Na<sup>+</sup> gradient to transport H<sup>+</sup> (or Li<sup>+</sup>) across membranes

and thus contribute greatly to the pH homeostasis of both cells and organelles [289,290]. These 13 proteins are organized into three different families, SLC9A (the Na<sup>+</sup>/H<sup>+</sup> exchangers), SLC9B (two Na<sup>+</sup> or Li<sup>+</sup>/H<sup>+</sup> exchangers), and SLC9C (two Na<sup>+</sup>/H<sup>+</sup> exchangers expressed primarily in sperm tissue) [290,291]. Interestingly, this family of proteins has relatively large differences in their protein sequences, with the two most disparate transporters (SLC9A1 and SLC9A9) having only 12% amino acid identity [292]. Despite these differences in sequence however, these proteins are predicted to have relatively similar architecture, with 10 to 12 TM segments and a cytoplasmic C-terminal tail that acts as a regulatory domain [289,293]. Although all SLC9 members are functional monomers, these proteins contain dimerization domains and some members of the SLC9 family have been shown to form homodimers as a way to increase their stability [289,290,294,295]. Studies investigating the dimerization of SLC9A1 (NHE1) showed that this dimerization is critical to the proper transport function of these proteins [296]. Expression patterns of these proteins vary greatly between the 13 proteins. SLC9A1 is expressed in almost every tissue in the body, although the transporter is often localized to specialized membrane domains in tissues [297,298]. Other SLC9 transporters are expressed in a more tissue or temporally dependent manner, like SLC9A4, which is expressed primarily in the stomach [292]. Cellular localization of these proteins varies greatly within the family as well, with SLC9A1, SLC9A2, and SLC9A4 (NHE4) all localizing to the plasma membrane of cells [289]. SLC9A3 and SLC9A5 (NHE5) are both trafficked between the plasma membrane and endosomes [299]. SLC9A5 regulates the pH of both endolysosomes (when it is internalized) and locally at the cell membrane, which regulates cell motility, neuronal differentiation, and synaptic plasticity [300,301]. SLC9A6 (NHE6) is primarily an endosomal transporter, although it localizes to cell membranes after certain stimuli [290]. This Na<sup>+</sup> or K<sup>+</sup>/H<sup>+</sup> exchanger helps regulate intraluminal pH and dysfunction of this transporter has been associated with severe neurological disorders like Christianson syndrome, X-linked intellectual disability, and Angelman-like syndrome [302,303]. The transport activity of the two SLC9B proteins, SLC9B1 (NHA1) and SLC9B2 (NHA2), remains relatively unclear, although they are thought to drive Na<sup>+</sup>/Li<sup>+</sup> counter-transport, as well as (Na<sup>+</sup> or Li<sup>+</sup>)/H<sup>+</sup> transport [290,291,304]. Depletion of these proteins has been linked to improper sperm motility and osteoclast differentiation, respectively [290].

## SLC26

The SLC26 family of transport proteins has 10 members that transport, with different specificity, a variety of anions, including  $\text{Cl}^-$ ,  $\text{HCO}_3^-$ , sulfate, oxalate,  $\text{I}^-$ , and formate [305,306]. The transport system of this family varies, with members being characterized as channels or electrogenic/electroneutral exchangers [307]. SLC26 proteins share similar structural features, all consisting of 14 TM segments. Like SLC4 proteins, these are arranged in a 7TMIR architecture [308,309]. These two halves have slightly different functional roles, with one being the core, substrate-binding domain while the other acts as an elongated gate domain shielding the core binding domain [273]. As with all other 7TMIR proteins, SLC26 family members form dimers in the membrane, although the exact physiological role for dimerization is not yet clear [308].

These proteins are of particular importance in the gastrointestinal tract, where they regulate pH, moderate water absorption, and the absorption and secretion of specific substrates [310]. For example, SLC26A1 and SLC26A2 provide the largest source of  $\text{SO}_4^{2-}$  uptake in the intestine, localizing to the basolateral and apical membranes of cells, respectively [306,311]. SLC26A3 meanwhile is a  $\text{Cl}^-/\text{HCO}_3^-$  transporter that is critical to the formation of mucus membranes and epithelial tissues [312–314]. The role of SLC26 proteins in the gut environment has also implicated these proteins in the composition of the microbiome [315,316].

## pH regulation and cancer

Aberrant regulation of pH in cells has long been linked to the development and progression of cancer [317–319]. The ability of cell to regulate their pH balance is critical to maintaining a healthy metabolic balance in cells. The regulation of pH can also be weaponized as a way to treat cancerous cells in a more targeted fashion [317]. Understanding the role these transporters play in the development and progression of cancer could potentially unveil vulnerabilities allowing for more targeted treatments. SLC9A1, SLC4A7, and SLC26A3 are particularly well-studied examples of proton or bicarbonate transporters having an influence on cancer development and progression. SLC9A1, as the primary proton transporter of cells, has been extensively studied as the target of cancer therapeutics [320,321]. In brief, the over activity of SLC9A1 leads to both cellular alkalinization and the acidification of the microenvironment around cells. These changes in cellular state and environment result in increased cellular proliferation and loss of cell–cell contact, which

increases the possibility of cellular migration, invasion, and metastasis [322]. SLC9A1 and SLC4A7 have been suggested to work in conjunction to control changes in pH and thus act as cell cycle regulators [323]. SLC4A7 also contributes to the progression of cancer by driving the efflux of acidic waste products that are by-product of increased cellular metabolism, a hallmark of carcinogenesis [324]. SLC26A3 is another bicarbonate transporter studied in the context of cancer, as its expression is often downregulated in adenomas [325]. However, its specific role in relation to cancer development is not clear [326]. In healthy gut cells, this transporter has been found to interact with tight junction proteins and play a role in protecting the epithelial barrier, suggesting that this transporter may play a role in cellular growth or motility [312,327].

## Transport of calcium ions

The  $\text{Ca}^{2+}$  ion is a critical signaling compound in cells, such as playing a role in neuronal action potentials, the restructuring of cytoskeletal components and cell death. In order to lower the intracellular concentration of  $\text{Ca}^{2+}$  after a signaling event that resulted in an influx of free  $\text{Ca}^{2+}$ , cells rely on two different SLC families of proteins to return to their baseline levels: SLC8 and SLC24 (Fig. 4B) [328]. Another significant source of calcium transport is provided by ATPase pumps, but will not be covered here [329].

## SLC8/SLC24

The SLC8 family of proteins includes four  $\text{Na}^+/\text{Ca}^{2+}$  exchangers that consist of 10 TM domains, binding  $\text{Ca}^{2+}$  ions with a large cytosolic loop between TM5 and TM6 [330–333]. These proteins are widely expressed throughout the human body and restore calcium concentrations after a signaling cascade triggered either the release or uptake of this ion [334]. With a transport stoichiometry of  $3 \text{Na}^+ : 1 \text{Ca}^{2+}$ , these proteins perform electrogenic transport, with the direction of transport depending on the membrane potential, as well as the concentration gradient of both  $\text{Na}^+$  and  $\text{Ca}^{2+}$  [330,335]. Due to this critical role in cellular signaling and homeostasis, the SLC8 family has been implicated in different diseases, such as increased invasion of carcinomas, diabetes, and aberrant cardiac signaling [336–339]. The four characterized members of this family are SLC8A1 (NCX1), SLC8A2 (NCX2), SLC8A3 (NCX3), and SLC8B1 (NCLX) [330]. SLC8 proteins are regulated by the binding of  $\text{Ca}^{2+}$  and  $\text{Na}^+$  ions [330]. A critical component of SLC8 structure, calcium-binding domains (CBDs) have differing roles

in these transporters [332]. For example, in SLC8A1, CBD1 serves as the primary  $\text{Ca}^{2+}$  sensor and activates the protein while the second CBD stimulates higher  $\text{Ca}^{2+}$  flux when unbound intracellular calcium concentrations are at higher levels [332]. This regulation of SLC8 proteins allows cells to precisely respond to calcium concentrations by changing protein localization and function in cells [340,341].

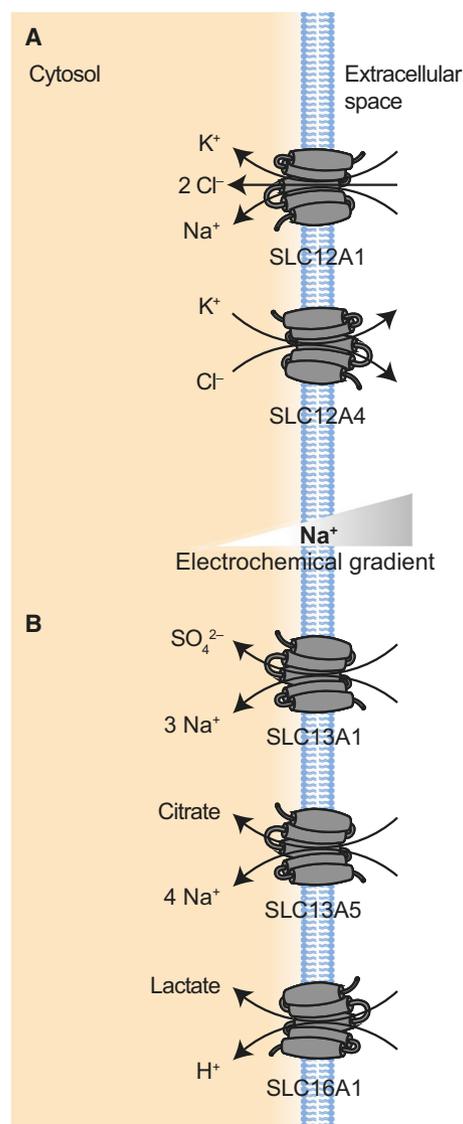
The SLC24 family of proteins contains 5 different  $\text{K}^+$ -dependent  $\text{Na}^+/\text{Ca}^{2+}$  exchangers [342]. SLC24 uses the electrochemical gradients of both  $\text{Na}^+$  and  $\text{K}^+$  to drive the efflux of  $\text{Ca}^{2+}$  [343]. These proteins are expressed in many different tissue types, although their roles are best understood in photoreceptor, neuronal, and smooth muscle cells [342,343]. Both SLC24A1 (NCKX1) and SLC24A2 (NCKX2) have been shown to transport these ions at a stoichiometry of 4 : 1 : 1 ( $\text{Na}^+ : \text{Ca}^{2+} : \text{K}^+$ ) [342]. A recent study showed that SLC24A1, SLC24A2, SLC24A3 (NCKX3), and SLC24A4 (NCKX4) all localize to the plasma membrane [344]. This study also suggested that these proteins all share similar topology, consisting of two sets of five-TM domains connected by a large intracellular loop [344].

### Transport of calcium ions in cancer

Among its many roles, calcium signaling is involved in angiogenesis (the generation of new blood vessels), neuronal signaling, and cell migration and can be altered in some cells, resulting in adaptive advantages over healthy cells and thereby promoting carcinogenesis [345,346]. SLC8A1 has been shown to play a role in angiogenesis [346,347]. As sodium and calcium concentrations change, this transporter has its transport direction reversed, resulting in ERK1/2 activation and subsequent enhanced angiogenesis [347]. Interestingly, SLC8A2 has been shown to act as a tumor suppressor in the brain, as increased expression of the transporter inhibits angiogenesis and slows tumor growth and invasion [348]. Lower expression of SLC8A1 has also been detected in certain cancers, and the resulting decrease in intracellular calcium consequently suppresses apoptosis [349]. SLC24A4, as well as SLC8A3, has been shown to be overexpressed in therapy-resistant ovarian carcinoma cells [350]. However, the specific role that SLC24 proteins may play in carcinogenesis remains unclear.

### Transport of Inorganic Ions by SLC12 transporters

In this section, SLC12 family is reviewed, a family of SLC proteins that transport ions closely related to cell volume regulation. These proteins drive the transport



**Fig. 5.** (A) Examples of SLC proteins transporting inorganic ions (SLC12). SLC12A1 represents the subfamily of  $\text{Na}^+$ -dependent cation- $\text{Cl}^-$  cotransporters (NCC), while SLC12A4 represents the subfamily of  $\text{Na}^+$ -independent cation- $\text{Cl}^-$  cotransporters (KCC). (B) Examples of SLC proteins transporting carboxylates (SLC13, and SLC16). SLC13A1 represents the subfamily of  $\text{Na}^+$ -dependent sulfate transporters (NaS), while SLC13A5 represents the subfamily of  $\text{Na}^+$ -dependent di- and tricarboxylate transporters (NaDC). SLC16A1 is shown as an example of a monocarboxylate transporter (MCT).

of  $\text{Cl}^-$  with either  $\text{Na}^+$  and/or  $\text{K}^+$ , resulting in electroneutral transport (Fig. 5A). The flux of  $\text{K}^+$  and  $\text{Cl}^-$  ions and the resulting movement of water across the membrane largely regulate changes to cell volume and concurrent cell movement [351].

## SLC12

The SLC12 family contains 9 proteins, which encode for electroneutral cation-chloride cotransporters [352,353]. This family includes two main subfamilies: transporters that are sodium-dependent and those that are sodium-independent [353]. These proteins have a common structure, consisting of 12 TM segments with intracellular N and C termini [352]. There are three sodium-dependent cotransporters—SLC12A1 (NKCC2), SLC12A2 (NKCC1), and SLC12A3 (NCC)—and four sodium-independent cotransporters, known as the Na<sup>+</sup>-independent K-Cl cotransporters (KCC)—SLC12A4 (KCC1), SLC12A5 (KCC2), SLC12A6 (KCC3), and SLC12A7 (KCC4) [55].

### SLC12 transport proteins in cancer

In tumors like gliomas, SLC12A2 takes up Cl<sup>-</sup>, creating the energetic driving force for the resulting volume increase through water uptake [351]. In addition to regulating cell volume, SLC12A2 impacts cellular migration, with higher expression of this transporter resulting in greater tumor growth, invasive phenotypes, and overall poorer clinical outcomes [354]. SLC12A6 and SLC12A7 are both upregulated in cancer, developing a more invasive phenotype of tumors [355]. Increased SLC12A6 expression plays an important role in triggering the epithelial-mesenchymal transition by downregulating E-cadherin/ $\beta$ -catenin complex formation and weakening cell-cell association, while SLC12A7 overexpression results in increased filopodia formation and can act as a cytoskeletal scaffold allowing for higher rates of invasive migration [355,356]. Thus, the increased expression of these transport proteins results in more aggressive and invasive behavior [355,356].

### Transport of carboxylates

SLC13 and SLC16 are the primarily drivers of carboxylate transport in cells (Fig. 5B). The transport of these substances is critical to regulating cellular volume and maintaining sufficient energy production.

## SLC13

The SLC13 family of proteins contains five members that perform Na<sup>+</sup>-dependent, electrogenic transport of anionic substances like sulfates and di- and tricarboxylates used in the Krebs cycle (e.g., succinate, citrate,  $\alpha$ -ketoglutarate) [357]. These transporters are expressed throughout the body in different kinds of tissue, with

the highest expression of these proteins in the kidney, liver, small intestine, placenta, or brain [357]. SLC13 proteins transport their substrates with a stoichiometry of 3 Na<sup>+</sup> : 1 substrate. This family can be separated into two subfamilies with distinctly different substrates: the sulfate transporters (SLC13A1 [NaS1] and SLC13A4 [NaS2]) and the di- and tricarboxylate transporters (SLC13A2 [NaDC1], SLC13A3 [NaDC3], and SLC13A5 [NaCT]) [358].

SLC13A1, which localizes to the apical membrane of brush-border membrane in the epithelial cells of the kidney, directs the reabsorption of 90% of filtered sulfates [359,360]. SLC13A4 is expressed at lower levels throughout the body and at higher levels in the placenta and the brain [361]. Its functional role in tissues is not yet fully understood [357].

The SLC13 di- and tricarboxylate transporters regulate and maintain the proper levels of citric acid cycle intermediates like succinate, citrate, and malate in cells [362] and have hence been considered as potential drug targets in metabolic disorders [358,362]. SLC13A2 is expressed at the apical membrane of renal proximal tubule cells and small intestine cells, which it absorbs all major dicarboxylate ions [357,363]. This protein plays a major role in facilitating cell's oxidative metabolism by taking up citric acid cycle intermediates [357]. SLC13A3 transports the same substrates as SLC13A2 across the basolateral membrane of kidney cells, although at higher affinities [358]. SLC13A5 is a Na<sup>+</sup>-dependent transporter that, unlike the other members of the SLC13 family, transports 4 Na<sup>+</sup> ions with each substrate molecule [364]. This protein drives the transport of primarily citrate and, at a lower affinity, succinate across the plasma membrane of cells [357]. This protein is most highly expressed in liver and brain tissues [358].

## SLC16

The SLC16 family of proteins contains 14 transport proteins that are also known as monocarboxylate transporters (MCTs) [365]. The characterized members of the SLC16 family passively transport protons and different groups of monocarboxylates across the cell membrane [366,367]. These proteins are predicted to be MFS structure proteins, consisting of 12 TM helices with intracellular C and N termini [368]. SLC16A1, 16A8, and 16A3 (MCT1, 3, and 4, respectively) all interact with a chaperone protein, CD147 (basigin), in order to properly translocate to the cell membrane, where the transporter and chaperone remain closely associated [369,370]. SLC16A7 (MCT2) requires a different chaperone, gp70 (embigin), to properly localize to the plasma membrane [371].

SLC16A1, SLC16A7, SLC16A8, and SLC16A3 can all perform either efflux or import of their substrates depending on the concentration gradients of their substrates and the pH gradient across the membrane [367]. Of these four proteins, SLC16A1 and SLC16A3 are two proteins that are closely linked in both their function and role in diseases, in particular in cancer [372]. SLC16A1 is expressed at the plasma membrane in most tissues of the body, where it provides proton-coupled passive transport of lactate, pyruvate, and ketone bodies [368]. SLC16A3, on the other hand, is expressed primarily in tissues that rely heavily on glycolysis as a source of energy and transports both lactate and ketone bodies [368]. Within a given microenvironment, primary role of SLC16A1 and SLC16A3 within cells are lactate import and lactate export, respectively [372]. Well-perfused cells have higher expression of SLC16A1, which imports lactate, helping fuel oxidative phosphorylation. Poorly perfused cells are in more hypoxic environments and rely on glycolytic pathways to generate energy and express SLC16A3 to export lactate [373].

SLC16A7 is expressed throughout the body, with high expression levels in the liver, kidneys, testis, and brain [367]. This protein localizes to the plasma membrane where it functions as an importer of lactate, although it can also transport other monocarboxylates like pyruvate or ketone bodies [374]. Among all family members, SLC16A7 has the highest affinity for monocarboxylates [375].

Unlike the more widely expressed family members, SLC16A8 is expressed primarily in retinal pigmented epithelial cells and choroid plexus epithelial cells where it transports protons and lactate, potentially inhibiting photoreceptor signaling [376,377]. SLC16A2 (MCT8) is expressed in various tissues and is a very specific high-affinity thyroid hormone (TH) transporter [378]. SLC16A10 (MCT10) shares high amino acid similarity (58%) to SLC16A2, but functions as a sodium-independent transporter of aromatic amines and localizes to the basolateral membrane [379–381].

### Transport of carboxylates in cancer

In cancerous cells, the transport of carboxylates is often dysregulated, driving more invasive phenotypes or enabling metabolic changes [131,351].

Due to the increase in anaerobic metabolism, which produces large quantities of lactate, SLC16 transporters serve as intriguing therapeutic targets [373]. Both SLC16A1 and SLC16A3 protein expression is modulated in cells via CD147, a cell surface glycoprotein often overexpressed in cancers that stimulate

cellular proliferation, invasiveness of cancer cells, and angiogenesis [373,382]. As detailed above, the two transporters work in conjunction and thus increased expression of these transporters does not usually happen in the same cells. In fact, targeting this relationship using SLC16A1 inhibitors to prevent lactate-based respiration slowed tumor growth and made cancer cells more sensitive to irradiation [383].

SLC16A7's subcellular localization has been shown to change in cancerous tissues, where there is a dramatic decrease in plasma membrane expression [384]. SLC16A7 was found to instead localize to peroxisomes, where it may increase  $\beta$ -oxidation levels and contribute to malignant transformation [385]. A recent study showed that SLC16A7 is directly involved in forming the premetastatic niche of breast cancer by inducing the activity of collagen hydroxylase enzymes, allowing for collagen remodeling [386].

### Transport of phosphate

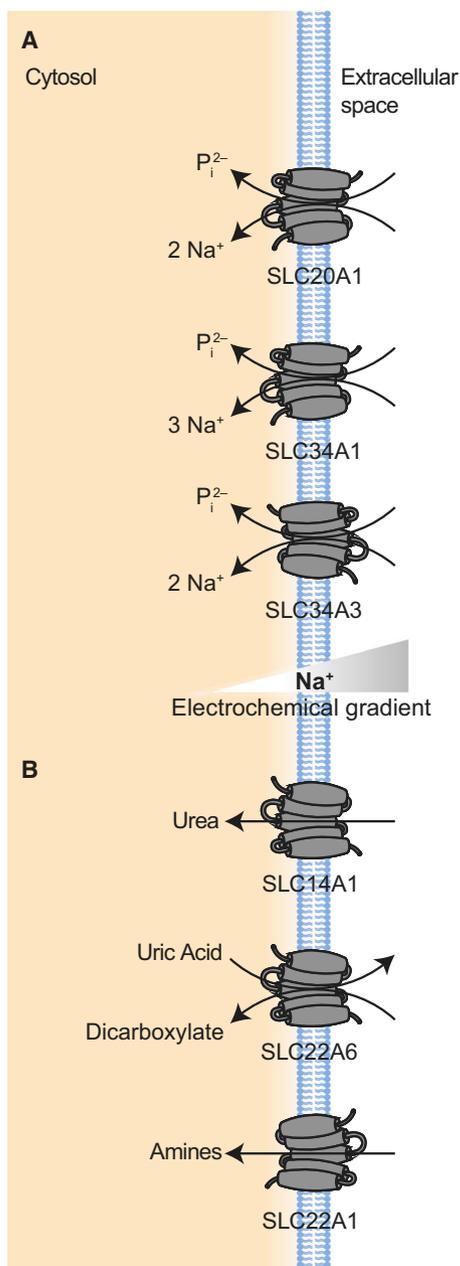
Inorganic phosphate is a substrate critical to many cellular metabolites such as nucleic acids and phospholipids and is central to metabolic processes like energy production [387]. The transport of this critical anion is driven by two SLC families, SLC20 and SLC34, which are reviewed in the following section (Fig. 6A).

#### SLC20

The SLC20 family contains only two proteins, SLC20A1 (PiT-1) and SLC20A2 (PiT-2), that are both  $\text{Na}^+$ -dependent transporters of inorganic phosphate ( $\text{P}_i$ ) [388]. SLC20 proteins preferentially transport monovalent  $\text{P}_i$  ions with a transport stoichiometry of 2  $\text{Na}^+ : 1 \text{P}_i$  [389]. These proteins are predicted to consist of 12 TM segments, with extracellular N and C termini, and are expressed at the cell membrane of most tissues [388,390]. Of note, both SLC20 proteins, through their role as phosphate transporters, also play a role in bone mineralization [391–393]. The expression of these transporters is inducible, with lower extracellular  $\text{P}_i$  concentrations resulting in an increase in expression of these proteins [394,395]. A recent study also suggested that these transporters play a role in sensing and responding to extracellular levels of  $\text{P}_i$  independently of their transport functions [396].

#### SLC34

The SLC34 family contains three proteins that couple the transport of  $\text{P}_i$  with  $\text{Na}^+$  [388]. The electrogenic SLC34A1 (NaPi-IIa) and SLC34A2 (NaPi-IIb) use



**Fig. 6.** (A) Examples of SLC proteins transporting phosphate (SLC20 and SLC34). SLC20A1 is shown as an example of a Na<sup>+</sup>-dependent transporter of inorganic phosphate (P<sub>i</sub>). SLC34A1 represents the subfamily of electrogenic Na<sup>+</sup>-dependent phosphate transporter, while SLC34A3 is the electroneutral Na<sup>+</sup>-dependent phosphate transporter. (B) Examples of SLC proteins transporting organic ions (SLC14 and SLC22). SLC14A1 is shown as an example of the SLC14 family of urea transporters. SLC22A6 represents the organic anion transporter (OAT) major clade of SLC22 proteins, while SLC22A1 represents the organic cation transporter (OCT) major clade of proteins.

three Na<sup>+</sup> ions to drive the transport of divalent P<sub>i</sub> against its concentration gradient, while the electroneutral SLC34A3 (NaPi-IIc) only uses two Na<sup>+</sup> ions [397]. These proteins have 8 TM domains with both N and C termini located in the cytoplasm [398]. Furthermore, these proteins tend to form dimers in the membrane, although they remain functionally independent [398]. These proteins play a critical role in maintaining proper levels of P<sub>i</sub> in serum, which can cause severe hypo- or hyperphosphatemic states when P<sub>i</sub> is dysregulated [399]. These clinical presentations have been linked to complications like cardiovascular diseases and higher mortality in patients with kidney disease [399,400]. Both SLC34A1 and SLC34A3 are expressed primarily in the kidneys, where they localize to the brush-border membrane of renal proximal tubule cells [397]. In mice, SLC34A1 provides about 70% of the total renal P<sub>i</sub> reabsorption while SLC34A3 performs the remaining 30% [401]. Phosphate balance is maintained by parathyroid hormone (PTH)-triggered endocytosis of SLC34A1 [402]. Although SLC34A3 internalization is similarly induced by PTH, the response is markedly slower than that of SLC34A1 [403]. SLC34A2 is expressed in many different organs, such as the small intestine, where it provides over 90% of the sodium-dependent cellular absorption of phosphate [397,398,404].

### Phosphate transport in cancer

Cancerous cells that are undergoing rapid cell proliferation require a higher amount of phosphate than healthy cells, imparting particular importance to the SLC20 and SLC34 families. Overall, tumor cells both express higher levels of phosphate cotransporters and have higher intracellular stores of inorganic phosphate [405]. SLC20A1 and SLC34A2 have been identified as particularly relevant for the development and progression of cancer [387]. SLC20A1 protein expression has been positively correlated with tumor size, invasiveness of tumor, and recurrence of tumors in somatotroph adenomas [406]. In addition to providing import of inorganic phosphate ions, SLC20A1 has been found to also have a transport-independent role in cells [407,408]. This potential transceptor plays a role in cellular proliferation and regulating TNF-induced apoptosis in cell, suggesting that SLC20A1 may have a more elaborate role in the progression of cancer [407,408]. SLC34A2 expression is similarly correlated with the tumorigenesis and development of cancers, with higher expression of the transporter serving as a prognostic marker for larger tumor size and poorer

patient outcomes [409]. Knockdowns of SLC34A2 expression results in decreased cellular proliferation and metastasis [409,410]. Interestingly, however, a separate study investigating the transporter's role in lung cancers found that SLC34A2 played a protective role in cells, preventing more aggressive phenotypes from developing [411]. Both SLC20A1 and SLC34A2 have been implicated in activation of the Wnt/ $\beta$ -catenin signaling pathway resulting in cellular proliferation and carcinogenesis [406,412].

## Transport of organic ions

SLC families 14 and 22 mediate the transport of different organic ions, including urea, amines, bile acids, and  $\alpha$ -ketoglutarate (Fig. 6B). Owing to this wide range of substrates, these two families play a significant role in a variety of processes within the human body, including helping regulate blood pressure and remote signaling between organs. SLC14 is one of the smallest SLC families while SLC22 is one of the largest.

### SLC14

Although the SLC14 family contains only 2 distinct genes, SLC14A1 and SLC14A2, these genes are spliced into a total of eight different isoforms that perform different functions within cells [413]. SLC14A1 encodes for transporter proteins also known as UT-B1 and UT-B2, while SLC14A2 encodes for proteins known as UT-A1 through UT-A6 [414]. The primary function of these transporters is to concentrate urea in the kidneys, allowing for the excretion of urea and also reabsorption of water through passive movement of urea across cell membranes [413]. The majority of these transporters consist of 10 transmembrane segments with intracellular N and C termini [413]. Based on the crystal structure of a bacterial homologue, the selectivity of these transporters is suggested to be driven by a group of phenylalanines surrounding the transport pore [31]. A characteristic property of this family of transporters is their rapid regulation by vasopressin, a hormone synthesized in the hypothalamus [415]. In response to vasopressin signaling, transporters increase their permeability to urea, resulting in increased water resorption and thus increased blood volume, which in turn increases arterial blood pressure [415].

### SLC22

The SLC22 family is one of the larger families of SLC transporters, containing roughly 30 members, 13 of

which have been localized to plasma membrane [416–418]. The proteins within this family transport a wide variety of metabolites and signaling molecules with different affinities, resulting in different physiological functions for this family [418,419]. As examples, substrates include urate, prostaglandins, bile acids,  $\alpha$ -ketoglutarate,  $\beta$ -hydroxybutyrate, and various amines [416]. SLC22 proteins have been grouped into two major subfamilies (referred to as clades) and based on their phylogenetic history in multiple different subclades [420]. The two major clades are called the organic anion transporter (OAT) major clade and the organic cation transporter (OCT) Major clade, both of which are further subdivided into subclades resulting in six final groupings [416]. These groupings are defined by their evolutionary relatedness, apparent common ancestral genes and/or sequence homology [416]. The OAT Major clade is subdivided into the Oat (exemplified by SLC22A6 (OAT1)), Oat-like (exemplified by SLC22A13 (OAT10)), and Oat-related (SLC22A17 (BOCT1)) subclades. The OCT Major clade is subdivided into the Oct (exemplified by SLC22A1 (OCT1)), Octn (exemplified by SLC22A5 (OCTN2)), and Oct-related (exemplified by SLC22A16 (FLIPT2)) subclades [416]. These proteins are predicted to all have similar structural features, consisting of 12 TM domains and have been found to form homo-oligomers in some cases, although this oligomerization process does not seem to be required for transport function [418,421].

SLC22A6 is a sodium-independent organic anion/dicarboxylate exchanger and is one of the most highly expressed proteins in the adult kidney [418]. In the kidney, this protein localizes to the basolateral membrane of the proximal tubules, where it excretes urate, other endogenous anions and anionic drugs [418,422]. As a urate transporter, this and several other members of the SLC22 family (particularly SLC22A8 but possibly also SLC22A11 and A13) are thought to be involved in remote signaling between the kidney and intestine by regulating uric acid levels in the blood [423,424]. This transporter has been implicated in the transport of drugs such as nonsteroidal anti-inflammatory drugs, and differential activity of the protein has been implicated in the efficacy of imatinib in chronic myeloid leukemia patients [425,426].

SLC22A13 is expressed in the kidneys, as well as in the brain, heart, and intestine, where it localizes to the basolateral membrane [427,428]. This transporter drives the unidirectional efflux of organic anions like nicotinate, aspartate, and glutamate [427,428].

SLC22A17 assists in the uptake of iron and does not seem to drive the transport of other usual substrates of the SLC22 family [429]. It also acts as a

receptor for lipocalin-2, a secreted protein that can trigger apoptosis in cells with reduced intracellular iron concentrations [430]. Furthermore, SLC22A17 binds to and mediates the endocytosis of filtered proteins in the kidneys [431].

SLC22A1 is a cation transporter that operates by a mechanism of facilitated diffusion [417]. This protein is expressed throughout the body in epithelial cells of different tissues, at its highest in the liver, kidney, and small intestine, where it localizes to the plasma membrane [432]. SLC22A1 transports a variety of endogenous substrates, such as catecholamines, biogenic mono- and polyamines. Furthermore, SLC22A1 transports various drugs like opioids and xenobiotic compounds and hence plays important role in disease management [433].

SLC22A5 is a sodium-dependent high-affinity carnitine transporter and otherwise provides sodium-independent transport of other organic cations, with both transport systems being electrogenic [434]. One of SLC22A5's main functions within the body is to absorb dietary carnitine at the brush-border membrane of the epithelial cells in the intestine. Due to its ubiquitous expression in the body, SLC22A5 allows tissues that are unable to synthesize carnitine to take it up [435]. SLC22A5 also provides the transport of organic cations like tetraethylammonium [436].

SLC22A16 is mainly expressed at the plasma membrane of the testis and at lower levels in other tissues [418]. This protein functions as a high-affinity L-carnitine transporter and also has transport capabilities for other organic cations like spermidine or the drugs doxorubicin and bleomycin A5 [418,437,438]. Similarly to SLC22A5, SLC22A16 has a modular reliance on sodium to drive its transport, as L-carnitine is at least partially dependent on sodium, while doxorubicin transport is sodium independent [418].

## Organic ion transport in cancer

A variant of SLC14A1 (rs17674580) has been identified as a significant susceptibility gene for urinary bladder cancer [439]. The protein was also found to be expressed at significantly lower levels in lung and prostate cancers, with overexpression of the gene inhibiting further colony formation in lung squamous cell lines [440]. As a urea transporter, deficiency of this protein may cause increased DNA damage in areas where urea concentrations increase [441,442].

As one of the largest families of solute carriers, SLC22 proteins and their transport substrates have a wide range of roles in the development and progression of cancer. Members of this family have been

found to be both downregulated (SLC22A1, SLC22A2, SLC22A11) and upregulated (SLC22A3 and SLC22A18) in the tissue of pancreatic and liver cancer patients with the different transport proteins having varying effects on the long-term survival of patients [443–446]. As organic ion transporters, the SLC22 family of proteins plays a particularly important role in the transport of drugs across cell membranes [416]. The expression of transporters like SLC22A6 is also affected by cancer treatment regimens, with methotrexate downregulating the protein [447]. Similarly, the expression of SLC22A1 is altered by imatinib, a drug used to treat chronic myeloid leukemia [448]. Both SLC22A1 and SLC22A5 expression are also downregulated in carcinomas, which results in higher tumor progression and poorer patient survival [449–452].

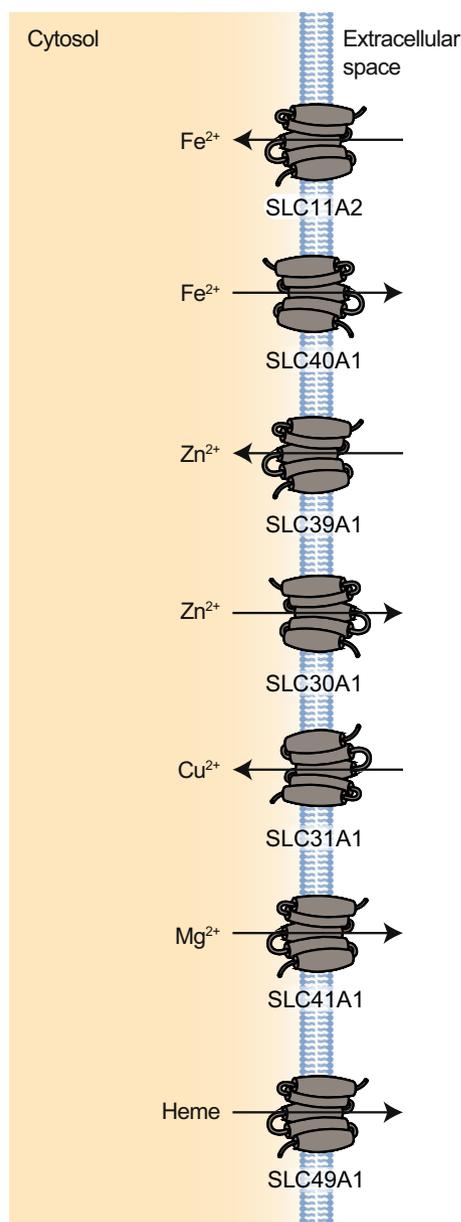
## Transport of trace metals

Although found at miniscule levels in cells, trace metals like magnesium, copper, zinc, and nickel play important roles as signaling ions and cofactors in proteins. Cells use SLC families 11, 40, 31, 30, 39, 41, and 49 to drive the influx and efflux of these components and regulate their concentrations (Fig. 7). While many of these SLCs have been studied role transporting a specific metal ion, it has become increasingly clear that these transporters have a much wider specificity to trace metals, as further detailed below.

## SLC11/SLC40

The SLC11 family consists of two proteins, SLC11A1 (Nramp1) and SLC11A2 (DMT-1), that perform the proton-dependent transport of divalent metal ions and share 66% identity in their amino acid sequence [453]. While SLC11A1 localizes to the membrane of lysosomes and endosomes, SLC11A2 is a plasma membrane transporter [454].

SLC11A2 is expressed throughout the body, as four different cell-type-specific splice variants [455,456]. Expression is found at particularly high levels at the apical plasma membrane of the duodenum, where SLC11A2 is responsible for the absorption of iron [456]. Apart from iron, this protein transports other divalent metal ions ( $\text{Zn}^{2+}$ ,  $\text{Mn}^{2+}$ ,  $\text{Cu}^{2+}$ ,  $\text{Co}^{2+}$ ,  $\text{Cd}^{2+}$ ,  $\text{Ni}^{2+}$ , and  $\text{Pb}^{2+}$ ), with highest affinity for  $\text{Mn}^{2+}$  [457,458]. Transport is both proton and membrane potential dependent [457]. In order to avoid the release of free ferrous iron into the cytosol, SLC11A2 has been shown to interact with PCBP2 (poly(rC)-binding protein 2), which removes the iron from the



**Fig. 7.** Examples of SLC proteins transporting trace metals (SLC11, SLC30, SLC31, SLC39, SLC40, SLC41, and SLC49). SLC11A2 is shown as an example of a proton-dependent transporter of metal ions (primarily  $\text{Fe}^{2+}$ ). SLC40A1 is an iron exporter. SLC39A1 is shown as an example of a zinc importer, while SLC30A1 is shown as a zinc exporter. SLC31A1 is shown as an example of a copper transporter. SLC41A1 is shown as an example of a magnesium transporter. SLC49A1 is shown as an example of a heme transporter.

transporter through the formation of a PCBP2-SLC11A2 complex [60,455,459].

The SLC40 family contains only one member, SLC40A1 (FPN1) that functions as an iron exporter

[453,460]. This protein is expressed throughout the body and serves as the major iron efflux pathway [453]. Similarly to SLC11A2, SLC40A1 is also capable of driving  $\text{Mn}^{2+}$  transport, suggesting these proteins also work in conjunction to maintain manganese homeostasis [461]. Thus, the SLC11 family primarily transports iron *into* cells, while SLC40 transports iron out of cells. This is exemplified in enterocytes, where SLC11A2 absorbs dietary iron from the intestine and SLC40A1 facilitates basolateral exit of iron into the circulatory system [453].

### SLC30/SLC39

Cells have developed two primary transport mechanisms through which zinc homeostasis is regulated. The SLC30 family functions to decrease cytosolic zinc levels while SLC39 proteins increase concentrations [462,463]. The SLC30 family of zinc transporters contains 10 members that are expressed throughout the body [463,464]. With the exception of SLC30A1, these proteins are primarily expressed intracellularly, driving the compartmentalization of zinc, although some members are occasionally translocated to the plasma membrane [463,465,466]. SLC30A1 (ZnT1) is expressed at the plasma membrane, where it drives the efflux of zinc into extracellular space. The expression of this transporter is tightly regulated, with both expression and plasma membrane localization increasing in response to higher zinc concentrations in the cytoplasm [467,468].

SLC39 is a family of 14 proteins that are primarily responsible for transporting zinc across membranes and into the cytoplasm [469]. Although a transport mechanism has not been conclusively determined, kinetics studies suggest that these proteins drive their transport through a secondary active mechanism [462]. However, the driver of this secondary transport remains unclear and has ranged from bicarbonate to protons [470]. In general, these proteins contain between 7 and 9 TM segments with both N and C termini facing away from the cytoplasm, although there is some variation [462,471]. The SLC39 family is separated into 4 subfamilies based on amino acid sequence similarities [472]. The first subfamily, subfamily I, contains only one protein, SLC39A9 (ZIP9). Subfamily II contains SLC39A1 (ZIP1), SLC39A2 (ZIP2), and SLC39A3 (ZIP3) [469]. The third, and largest with nine members, subfamily is referred to as LIV-1 and is exemplified by SLC39A4 (ZIP4) [469]. The last family is called *gufA* and contains only SLC39A11 (ZIP11) [469]. Due to zinc's role as a secondary messenger molecule, the SLC39 family has also been implicated in signaling pathways, like the

PTEN-Akt signaling axis [473,474]. SLC39A1 is expressed throughout the human body, and primarily localizes to the plasma membrane [469]. In response to changing zinc concentrations, SLC39A1 can be translocated from intracellular organelles to the plasma membrane or vice versa [475,476].

SLC39A4 is expressed mainly in the intestine, where its expression and localization is tightly regulated by both transcriptional and post-transcriptional means [477]. There, SLC39A4 functions mainly to absorb dietary zinc [477].

Thus, as a general rule, the SLC30 and SLC39 families have complementary roles, similar to SLC11 and SLC40. SLC30 proteins transport zinc out of the cytosol, either into organelles or extracellular space, while SLC39 proteins transport zinc into the cytosol [462].

### Other SLC families transporting trace metals (SLC31, SLC41, and SLC49)

The SLC31 family contains two copper transporters, SLC31A1 (CTR1) and SLC31A2 (CTR2) [478]. These proteins are expressed ubiquitously and at highest levels in the liver and placenta [479]. SLC31A1 is primarily expressed at the cell membrane and drives the uptake of copper from food in a potassium-dependent manner [478,480]. Copper homeostasis is critical for cells, as many enzymes are dependent on it for proper function [481].

The SLC41 family contains three proteins that transport magnesium [482,483]. SLC41A1 is the best characterized member of the family and is expressed throughout the body [482]. This protein drives the efflux of  $Mg^{2+}$  and also to a lesser degree  $Fe^{2+}$ ,  $Zn^{2+}$ ,  $Cu^{2+}$ ,  $Co^{2+}$ , and  $Cd^{2+}$ , across the plasma membrane of epithelial cells [484,485]. The expression and localization of this protein are regulated by extracellular  $Mg^{2+}$  concentrations, which regulates its transport function through endosomal recycling mechanisms allowing for dynamic regulation of the ion [482,486].

SLC49 is a family of four proteins, two of which, SLC49A1 and SLC49A2, contribute to heme transport across cell membranes [487]. SLC49A1 functions as a heme exporter, protecting cells from heme toxicity [488]. It is expressed at highest levels in the liver and small intestine, where there are higher levels of heme transport and localizes to the plasma membrane of these cells [487].

### Transport of trace metals in cancer

Trace metals like magnesium, copper, zinc, and nickel are critical components of enzymes, regulating cellular

signaling pathways, DNA replication and repair, apoptosis and much more [489–493]. Maintaining a proper concentration of these trace metals is important to not only these processes, but also combating the formation and/or accumulation of free radicals [490,492].

SLC40A1, which as mentioned mediates iron efflux from cells, has been linked to poorer prognoses in both breast cancer and adrenocortical carcinoma [494,495]. Furthermore, a recent study showed that the downregulation of SLC40A1 results in greater cell proliferation [496,497]. This downregulation of SLC40A1 by Nrf-2 has also been shown to induce cisplatin resistance, although this was reversed by increasing iron concentrations within cells [498]. This suggests that iron metabolism plays a large role in determining drug effectiveness.

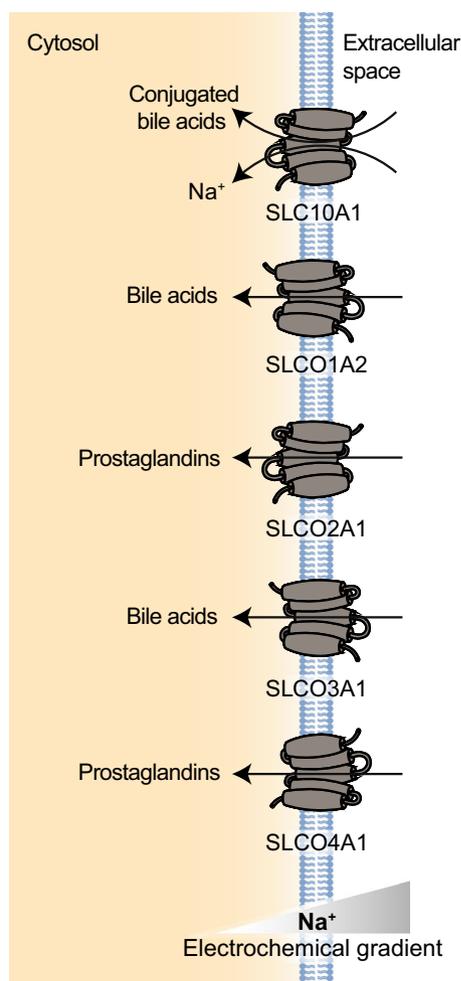
Mutations, dysregulation, or other perturbations of zinc transporters have been linked to many different diseases [499]. As the cofactor for so many enzymes, zinc deficiency is particularly detrimental to cells and is heavily linked to the development of many different cancers [500]. For example, SLC39A4 was recently shown to be overexpressed in more aggressive types of ovarian and pancreatic cancer, possibly as a response to lower levels of zinc in cancer tissues [501,502]. For more comprehensive reviews of zinc transport in cancers, the reader is referred to Takatani-Nakase and Pan *et al.* [500,503].

Copper accumulation has been linked to the progression of different cancers and their severity [492]. The knockdown of SLC31A1, and resulting decrease in intracellular copper, has been shown to inhibit the progression of pancreatic cancer [504]. SLC31A1 is also particularly relevant to the toxicity of cisplatin and other similar drugs, as they use this copper transporter as a system to enter cells [462].

Magnesium is required for cell proliferation, membrane stability, and DNA repair/genomic stability [505,506]. Furthermore, reduced intracellular concentrations have been linked to a suppression or inhibition of Akt/mTOR signaling [505]. SLC41A1, the magnesium efflux transporter, thus acts as a tumor suppressor, with increased expression of the transporter reducing the proliferative effects of mTOR signaling while also helping drive bax-associated apoptosis [507].

### Transport of other organic compounds

The final two SLC families to be covered in this review are SLC10 and SLCO (formerly known as SLC21) (Fig. 8). These two families transport a wide array of organic compounds, including numerous drugs. As



**Fig. 8.** Examples of SLC proteins transporting other organic compounds (SLC10 and SLCO). SLC10A1 is shown as an example of the SLC10 family that transports conjugated bile acids. SLCO1A2 represents the OATP1 subfamily and transports organic anions like bile acids. SLCO2A1 represents the OATP2 subfamily and transports prostaglandins. SLCO3A1 is the only member of the OATP3 subfamily and functions primarily as a bile acid transporter. SLCO4A1 represents the OATP4 subfamily and transports various organic compounds like prostaglandins.

transporters of such diverse substrates, members of the SLC10 and SLCO families have wide-ranging physiological roles in cells.

## SLC10

The SLC10 family of proteins contains seven members. For a time, it was thought that this family's primary purpose was to transport bile acid (BA), a family of substances that play a critical role in the solubilization and/or absorption of different nutrients like vitamins

and cholesterol as well as different signaling cascades, and endocrine homeostasis [508,509]. However, it is now clear that these proteins transport a wider variety of molecules, including steroidal hormones, drugs, and other substrates [510].

The best-studied members of this family, SLC10A1 and SLC10A2, play key roles in the regulation of BA levels in the body, helping reabsorb secreted BAs in the intestine and removing BAs from the liver's portal circulation [510]. Both SLC10A1 and SLC10A2 have been found to use homo- and heterodimeric and higher order oligomers as functional units on the cell membrane [511,512]. Due to the cytotoxic nature of BAs, both the expression and activity of these two proteins are regulated by their substrates, through the nuclear receptor like farnesoid X receptor [513].

SLC10A1 (NTCP) was found to be a strictly hepatocellular protein, expressed at the basolateral membrane [514,515]. This symporter couples the uptake of taurocholate or another conjugated BA with the uptake of two  $\text{Na}^+$  ions (1 conjugated BA: 2  $\text{Na}^+$ ) [516]. The uptake of these BAs is supplemented by the actions of SLCO1B1 and SLCO1B3 (see below), two transporters that uptake BAs in an sodium-independent manner [513]. Recently, SLC10A1 has also been found to act as a receptor for human hepatitis B virus (HBV) and satellite hepatitis D virus [517,518]. SLC10A2 (ASBT) is a protein mainly expressed in the intestine, localizing to the ileal brush-border membrane [519]. SLC10A2 uses the sodium gradient to drive the transport of BA into the cell with a 2 : 1  $\text{Na}^+$  : BA stoichiometry [520]. Due to its location in the final portion of the small intestine, SLC10A2's main function is to reabsorb any BAs that were not already absorbed as a part of mixed micelles. This way, the body takes up to 95% of the BAs and minimizes the amount of BAs that must be synthesized again [512].

SLC10A6 (SOAT) is mainly expressed in the testis, where it localizes to the plasma membrane of primary spermatocytes [521]. Unlike other SLC10 members, this protein does not transport BAs, but mediates sodium-dependent transport of sulfated steroids like tauro lithocholic acid-2-sulfate (TLCS), estrone-3-sulfate ( $\text{E}_1\text{S}$ ), and dehydroepiandrosterone sulfate (DHEAS), compounds which can be quickly modified to create active steroids [522,523].

## SLCO

The SLCO family of proteins (formerly SLC21) mediates the transport of organic ions and are also known as organic anion transporting polypeptides (OATPs) [9]. These proteins are predicted to consist of 12 TM

segments with cytoplasmic N and C termini [9]. Eleven identified SLCOs have been subdivided into six subfamilies based on amino acid sequence similarity [524,525]. The largest is the OATP1 subfamily, which contains SLCO1A2 (OATP1A2), SLCO1B1 (OATP1B1), SLCO1B3 (OATP1B3), and SLCO1C1 (OATP1C1). The OATP2 subfamily contains two members, SLCO2A1 (OATP2A1) and SLCO2B1 (OATP2B1). OATP3, OATP5, and OATP6 all contain only one member within their families (SLCO3A1 (OATP3A1), SLCO5A1 (OATP5A1), and SLCO6A1 (OATP6A1), respectively). Finally, OATP4 contains two member proteins, SLCO4A1 (OATP4A1) and SLCO4C1 (OATP4C1) [525].

This family has become a focus of drug development and pharmacokinetics of novel drugs [526]. Expressed throughout the body, its members are important for drug absorption. Tissue distribution and polymorphisms of these transporters have a significant effect on the efficacy of different drugs such as statins, antibiotics, direct renin inhibitors, and cardiac glycosides [527,528]. SLCO1B1, SLCO1B3, and SLCO2B1 are of particular interest, contributing to the uptake of drugs across the basolateral membrane of hepatocytes [526].

SLCO1A2 is expressed widely throughout the body, localizing to the plasma membrane of most cells [529,530]. This protein transports a wide range of organic anions, including bile acids, steroids, thyroid hormones, and various drugs (including imatinib, statins, and methotrexate) [531]. As with other SLCO proteins, SLCO1A2 is trafficked to the plasma membrane and stabilized through its interactions with PDZK1 and NHERF1 [531,532].

SLCO2A1 is also ubiquitously expressed in the body, localizing to the plasma membrane to transport prostaglandins [9]. This transporter is of particular importance at the blood–brain barrier, where it facilitates the transport of Prostaglandin E<sub>2</sub>, an essential component of the body temperature regulatory network [533]. SLCO2B1 is expressed at the cell membrane of many different tissues, where it drives the transport of various organic ions like taurocholate, prostaglandins, antifolates, and tyroxine [9]. The transport activity of this protein is stimulated at lower pH levels [534].

SLCO3A1 is expressed in the testis and brain and to a lower extent in the lung, spleen, peripheral blood leukocytes, and thyroid gland [535]. This transporter has two different cell-specific splice variants. Interestingly, although expression of SLCO3A1 is generally lower in the liver, expression is elevated during cholestatic liver injury—when bile acids accumulate in the

blood and liver due to impaired bile formation. There, SLCO3A1 functions as a protective bile acid efflux transporter [536,537].

SLCO4A1 is expressed throughout the body at the plasma membrane [535]. Substrates of this transporter include prostaglandins, benzylpenicillin, taurocholate, and thyroxine [537]. SLCO4A1 is a prognostic marker for colorectal cancer, with higher expression indicating a poorer prognosis [538].

## Transport of organic compounds in cancer

The transport, release, and concentration of organic compounds like bile acids, hormones, and drugs is regulated by the activity of members of the SLC10 and SLCO family [9,508,509]. These diverse roles result in a litany of links to the development, progression, spread, and treatment of cancer [538,539].

Certain SLC10A2 polymorphisms more than double the risk of developing colorectal polyps, which supports the idea that aberrant transport of bile acids increases the risk of colorectal cancer [540]. Furthermore, SLC10A2 knockout mice had a significant two-fold increase in the amount of colon adenocarcinomas over the control mice, as well as an increased tumor number and growth rate [541]. These contributions to carcinogenesis are thought to be caused by an increase in fecal bile acids acting as tumor promoters in the colon [539,541]. The regulation of this transporter remains an intriguing topic, as treatment of solid tumors with irinotecan results in decreased expression of SLC10A2 [542].

The SLCO family of transporters has been increasingly investigated in the past years for their potential role in the transport of chemotherapeutics and their potential impact on efficacy of therapies [543]. This interest has particularly focused on SLCO1A2, SLCO1B1, SLCO1B3, and SLCO2B1 [525,526,544]. The expression of many SLCO proteins is altered (both up and down) in many different types of cancers (SLCO1A2, SLCO1B1, and SLCO1B3 tend to be expressed at lower levels, while SLCO2B1 are expressed at higher levels in cancer tissue) [525]. These changes in expression patterns of the above transporters have not been fully elucidated, with a range of, at times conflicting, results being reported [525,545]. The conflicting data on the use of SLCOs as biomarkers highlight the need for a deeper understanding of their biology, especially as expression levels seem to be associated with changes in efficacy for cancer treatments [544,545]. For more in-depth reviews of the role that SLCO proteins play in cancer development,

progression, and treatment, the reader is referred to Schulte *et al.* and Obiadat *et al.* [525,543].

## Discussion

In this review, we have provided a guide to the main families of SLCs that transport sugars, amino acids, peptides, vitamins, nucleotides and nucleosides, different subsets of ions, metals, and organic compounds into cells across their plasma membrane.

In spite of the progress in understanding SLC functions, major gaps remain in our understanding of many members in the SLC protein superfamily. In particular, while we have focused our review on documented plasma membrane SLCs, we must note that there is incomplete understanding of the localization of SLC proteins. Furthermore, some members of this superfamily translocate to different subcellular localizations, as discussed above, or when cellular states change. For example, expression of both SLC9A2 and SLC9A3 has been shown to change in mice depending on their stage in development [546,547].

As detailed in this review, SLC proteins play important roles in maintaining the proper function of cells and managing their relationship with the environment of specific cell types. The overlapping and redundant transport activity of different SLC proteins allows cells to rapidly respond to changes in their surroundings and maintain close control over their contents. For example, members of both SLC7 and SLC38 provide seemingly redundant transport of small amino acids. However, through ancillary roles like acting as transporters (SLC38A2) or regulating the redox balance of cells (SLC7A11), these proteins maintain their own unique roles within cells [158,188]. SLC34A1 and SLC34A3 are another example of the interconnected and complementary roles at the organism level, with the two transporters cooperatively ensuring complete phosphate resorption [401].

As highlighted throughout the review, members of the SLC superfamily are implicated in the development and progression of many diseases. For example, dysregulation of multiple members of the SLC6 family results in disorders related to their altered ability to transport neurotransmitters and other substrates of SLC6 proteins (e.g., mutations of SLC6A3 cause infantile Parkinsonism dystonia, SLC6A8 is linked to X-linked mental retardation; mutations of SLC6A19 causes Hartnup disorder) [161,548–550]. Changes in SLC protein expression and function are also closely linked to the development of diseases such as cancer. In fact, a comparison of healthy and cancerous cell lines suggested that SLC proteins have greater changes in their

coexpression networks than protein kinases [28]. Proteins like SLC2A1, SLC39A14, and SLC16A1 may serve as prognostic biomarkers in cancers due to their central role in the development of cancer and responses to treatments [551–553]. Thus, it is imperative to continue studying transport proteins in a comprehensive manner, focusing not only on individual transport functions, but also unraveling the complex relationships between different transporters and metabolic states.

Furthermore, when aberrant transport of metabolites occurs, entire signaling pathways may be affected due to changing electrochemical gradients and metabolic pathways. For example, the oncogene MYC can induce the expression SLC7A5 and SLC43A1, resulting in the increased transport of essential amino acids and thus supporting increased cell growth and tumorigenesis [554]. There is a critical need to study regulatory networks such as these in order to understand the relationships between transport activities and cellular states.

In the past years, as their roles in cells have been discovered, SLC proteins have increasingly become the target of drugs [8,90,92]. However, the vast potential of modulating the activity of SLCs, and in particular plasma membrane expressed SLC proteins, remains largely untapped [5]. Families like SLC39 and SLC30, whose member proteins are recognized as direct regulators of zinc homeostasis, offer great therapeutic potential in combating the progression of cancer [555]. A more complete understanding of substrates, structures, transport mechanisms, interaction networks, and secondary functions within cells may contribute in the future to drug discovery programs targeting such SLCs. A family like SLC16 provides an example for the progression of this field. After understanding the molecular mechanisms that underlie SLC16 proteins and how altered transport may contribute to the development of disease states, SLC16 inhibitors were rapidly developed [556]. Currently, there are multiple potent inhibitors of SLC16 proteins that serve as potent chemical tools to further understand the role of SLC16 proteins in cells, with at least one under clinical evaluation (NCT01791595) [557,558].

Finally, while this review covered the major classes of substrates transported by plasma membrane SLC proteins, there remain many other substances in the extracellular milieu whose transporter has not been determined or could not be described within the scope of this review. We expect that with as our understanding of the human metabolome grows, more SLCs will be reported to mediate the transport of a growing list of endogenous and exogenous metabolites, further adding to the complex network of transport proteins regulating cellular content.

## Acknowledgements

We are thankful to all the members of the Superti-Furga laboratory for discussions and feedback. In particular, we would like to thank Enrico Girardi, Kai-Chun Li, Gernot Wolf, Vitaly Sedlyarov, Utkarsh Kapoor, Ruth Eichner, Ismet Srndic, Ludwig Bauer, Vojtech Dvorak, Ben Haladik, Patrick Essletzbichler, Giuseppe Fiume, and Manuele Rebsamen for reading through the manuscript and providing with editorial input. We thank the referees for their constructive comments. CeMM and the Superti-Furga laboratory are supported by the Austrian Academy of Sciences. We acknowledge receipt of third-party funds from the European Research Council (ERC AdG 695214 GameofGates, AB, MDP). MDP is a recipient of a Fulbright Study/Research Grant.

## Conflict of interest

The authors declare a conflict of interest. Ariel Bensimon and Giulio Superti-Furga have filed patents on SLC pharmacology that will be the object of a commercialization effort in the future.

## Author contributions

MDP, AB, and GS-F conceived the review and wrote the manuscript.

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