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The ABCs of solute carriers: physiological, pathological and therapeutic implications of human membrane transport proteins

Introduction

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Abstract The Human Genome Organisation (HUGO) Nomenclature Committee Database provides a list of transporter families of the solute carrier (SLC) gene series (see http://www.gene.ucl.ac.uk/nomenclature/. Currently, it includes 43 families and 298 transporter genes. This special issue features mini-reviews on each of these SLC families written by the experts in each field. A WEB site has been established (http://www.pharmaconference.org/slctable.asp) that gives the latest updates for the SLC families and their members as well as relevant links to gene databases and reviews in the literature. A list of all currently known SLC families, a discussion of additional SLC families and family members as well as a brief summary of non-SLC transporter genes is included in this introduction.

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Transporters are the gatekeepers for all cells and organelles, controlling uptake and efflux of crucial compounds such as sugars, amino acids, nucleotides, inorganic ions and drugs. Transporters can be divided into passive and active transporters (Fig. 1). Passive transporters, also known as facilitated transporters, allow passage of solutes (e.g., glucose, amino acids, urea) across

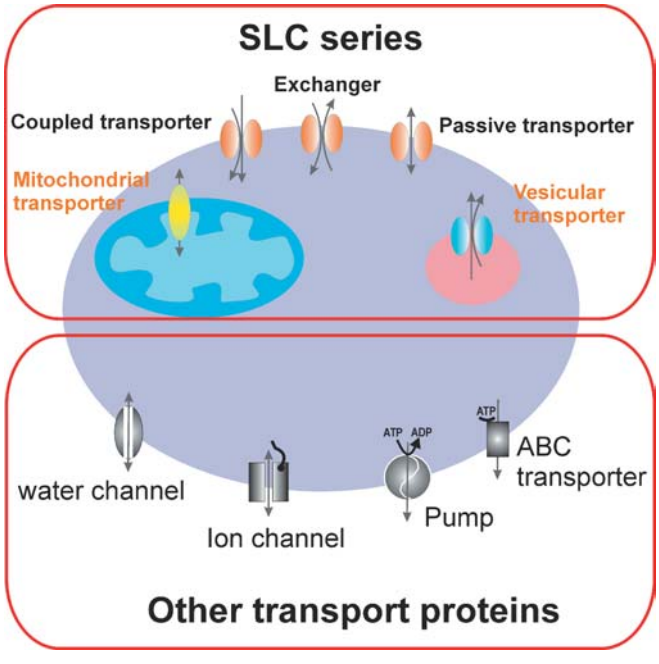

Fig. 1 Cartoon showing a cell with solute carrier (*SLC*)- and non-SLC-transporters expressed in the plasma membrane or in intracellular compartment membranes. Note that the non-SLC transporters can also be expressed in intracellular compartments

membranes down their electrochemical gradients. Active transporters create ion/solute gradients across membranes, utilizing diverse energy-coupling mechanisms. These active transporters are classified as primary- or secondary-active transporters according to the directness of coupling to cellular energy (e.g., ATP hydrolysis).

Primary-active, ATP-dependent transporters include members of the ATP-binding cassette (ABC) transporter family and ion pumps (ATPases). Mammalian ABC transporters [e.g., P-glycoprotein/multi-drug resistance (MDR) proteins and transporter associated with antigen processing (TAP)], bind or hydrolyze ATP as a control gate for the transport of a variety of substances such as ions, carbohydrates, lipids, xenobiotics and drugs out of cells or into cellular organelles [3]. Ion pumps hydrolyze ATP to pump ions such as Na^+, K^+, H^+, Ca^{2+} and Cu^{2+} out of cells or into organelles [5, 8, 11]. These pumps also generate and maintain electrochemical ion gradients across membranes, and thus are called active transporters. Such ion gradients are used in turn by secondary-active, ion-coupled transporters to drive uphill transport of nutrients across biological membranes.

Similar to transporters, channels allow movement of solutes down their electrochemical gradients [1, 4, 6, 9, 10, 14, 20]. Transporters typically have a fixed stoichiometry of ion/solute movement per translocation cycle. Ion or solute flow through channels, on the other hand, is controlled by the open probability of the channels via gating mechanisms and the single channel conductance (number of charges per second at a given voltage).

In the past, the molecular identification of transporters has lagged in comparison with other protein classes because of the former's hydrophobic nature and relatively low abundance, while physiological data for a variety of transporters was present in great abundance. Following the development of the expression cloning approach for transporters 12 years ago [15], the transporter field has undergone a renaissance, and numerous transporters of various classes have since been identified using this technique. The subsequent sequencing of multiple genomes, as well as expressed sequence tag (EST) approaches, have advanced this field further and recently facilitated the identification and characterization of many additional "missing" transporters and transporter families.

The "SLC (solute carrier) mini-review series" presented in this special issue intends to provide an overview of the different types of mammalian transport systems belonging to the SLC series. The SLC series includes genes encoding passive transporters, ion compled transporters and exchangers (see Fig. 1). A transporter has been assigned to a specific SLC family if it has at least 20–25% amino acid sequence identity to other members of that family. The mini-reviews summarizes the physiological, pathological, and pharmacological implications for each gene product of the different SLC families. The list of currently approved SLC human gene symbols is shown in Table 1. The table comprises 43 different SLC transporter families of the SLC series and the number of members in each family.

Table 1 List of currently approved solute carrier (*SLC*) families. The total numbers of members in each family are shown on the *right*

The HUGO Solute Carrier Family Series		Total
SLC1	The high-affinity glutamate and neutral amino acid transporter family	7
SLC2	The facilitative GLUT transporter family	14
SLC3	The heavy subunits of the heteromeric amino acid transporters	2
SLC4	The bicarbonate transporter family	10
SLC5	The sodium glucose cotransporter family	8
SLC6	The sodium- and chloride-dependent neurotransmitter transporter family	16
SLC7	The cationic amino acid transporter/glycoprotein-associated amino-acid transporter family	14
SLC8	The Na^+/Ca^{2+} exchanger family	3
SLC9	The Na^+/H^+ exchanger family	8
SLC10	The sodium bile salt cotransport family	6
SLC11	The proton coupled metal ion transporter family	2
SLC12	The electroneutral cation-Cl cotransporter family	9
SLC13	The human Na^+-sulfate/carboxylate cotransporter family	5
SLC14	The urea transporter family	2
SLC15	The proton oligopeptide cotransporter family	4
SLC16	The monocarboxylate transporter family	14
SLC17	The vesicular glutamate transporter family	8
SLC18	The vesicular amine transporter family	3
SLC19	The folate/thiamine transporter family	3
SLC20	The type-III Na^+-phosphate cotransporter family	2
SLC21/SLCO	The organic anion transporting family	11
SLC22	The organic cation/anion/zwitterion transporter family	18
SLC23	The Na^+-dependent ascorbic acid transporter family	4
SLC24	The $Na^+/(Ca^{2+}$-$K^+)$ exchanger family	5
SLC25	The mitochondrial carrier family	27
SLC26	The multifunctional anion exchanger family	10
SLC27	The fatty acid transport protein family	6
SLC28	The Na^+-coupled nucleoside transport family	3
SLC29	The facilitative nucleoside transporter family	4
SLC30	The zinc efflux family	9
SLC31	The copper transporter family	2
SLC32	The vesicular inhibitory amino acid transporter family	1
SLC33	The acetyl-CoA transporter family	1
SLC34	The type-II Na^+-phosphate cotransporter family	3
SLC35	The nucleoside-sugar transporter family	17
SLC36	The proton-coupled amino acid transporter family	4
SLC37	The sugar-phosphate/phosphate exchanger family	4
SLC38	The System A and N, sodium-coupled neutral amino acid transporter family	6
SLC39	The metal ion transporter family	14
SLC40	The basolateral iron transporter family	1
SLC41	The MgtE-like magnesium transporter family	3
SLC42	The Rh ammonium transporter family (pending)	3
SLC43	The Na^+-independent, system-L-like amino acid transporter family	2
Total		298

In general the genes are named using the root symbol SLC, followed by a numeral (e.g., SLC1, solute carrier family 1), the letter A (which acts as a divider between the numerals) and finally the number of the individual transporter (e.g., SLC3A1). These general rules of SLC gene nomenclature have been elaborated further for a couple of families. In the nucleotide sugar transporter

family SLC35, the letter between SLC35 and the family member number has been exploited to specify specific subfamilies, called A, B, C, D and E [21]. In another family, originally named SLC21, encoding the organic anion-transporting (OATP) proteins, the "21" and the "A" have been replaced by the letter "O", which stands for organic transporter. This modification has occurred to accommodate a unique, species-independent classification and naming system that has been introduced, because this family has been the subject of rapid evolution, giving rise to new isoforms within a given species [22].

As elaborated in the articles in this issue, numerous SLC transporter gene defects have been identified and shown to be the cause of human diseases (see tables in individual articles or the SLC web-site at http://www.pharmaconference.org/slctable.asp). For example, defects in the cationic amino acid transporter SLC7A7 or the cystine/cationic amino acid transporter SLC7A9 result in lysinuric protein intolerance and cystinuria, respectively. Two different types of hypertension result from mutations in SLC12 genes: the renal Na-K-2Cl cotransporter SLC12A1 for Bartter syndrome and the renal NaCl cotransporter SLC12A3 for Gitleman's syndrome. Mutations in the SLC26A4 anion exchanger lead to deafness (Pendred syndrome). Likewise, alterations in the glucose-6-phosphate transporter SLC37A4 cause glycogen storage disease and alterations in the basolateral iron transporter ferroportin/SLC40A1 result in hemochromatosis.

Several transporters are also of great importance from a pharmaceutical perspective. Transporters can either serve as drug targets or as drug delivery systems. Recently exploited drug targets include the glucose transporters (SLC5 family), neurotransmitter transporters (SLC6 family), intestinal bile acid transporters (SLC10 family) and cation-Cl cotransporters (SLC12 family). Furthermore, the intestinal oligopeptide transporter PepT1 (SLC15A1) and transporters at the blood-brain barrier (various SLC families) are proving to be important drug delivery systems.

It is generally assumed that at least 5% (>2,000) of all human genes are transporter-related, consistent with the biological significance of transporters and their roles in cell homeostasis. The SLC families represent a considerable portion of these genes: about 300 different SLC human transporter genes exist (Table 1; http://www.pharmaconference.org/slctable.asp) and additional SLC transporters are being identified constantly. The remaining, "non SLC" human transporter-related genes include those encoding ATP-driven transporters, channels, ionotropic receptors, aquaporins, transporter and channels subunits, auxiliary/regulatory transport proteins, etc. (see Fig. 1).

In the course of the preparation of this issue, it became apparent that there are several other gene families which should be part of the SLC series. The first member of an uncharacterized family with homology to the bacterial MgtE family of potential Mg^{2+} transporters has just been reported (SLC41A1; GenBank AJ514402) [19]. Analysis of the human genome indicates that there are probably two further members of this uncharacterized family (MF Romero, unpublished observations). This gene family is uncharacterized except for bacteria [16, 17] and extends back through *Drosophila*, *C. elegans* and yeast, to prokaryotes and archae bacteria.

Another family (the putaive SLC42 family) has recently been characterized as an ammonium transporter family (see N.L. Nakhoul's article in this issue). These proteins were known previously as Rhesus-associated glycoproteins. However, hydropathy analysis indicated that they are intrinsic membrane proteins with 10–14 predicted membrane spanning domains.

Yet another gene family includes the recently reported, Na^+-independent, system-L amino acid transporter gene SLC43A1 [2]. In contrast to the heterodimeric system-L amino acid transporters of the SLC7 family (SLC7 article in this issue), the SLC43A1 transporter does not require a type-II membrane glycoprotein for functional expression.

It is becoming increasingly evident that other membrane protein families whose function has not yet been elucidated are SLC transporters. For example, there is a gene family of membrane proteins which appears to have the backbone of a transporter [18]. Although it has been speculated that these proteins are "choline transporter"-like, their function remains unknown. This family has homologous transporters in *Torpedo*, *Drosophila*, *C. elegans* and yeast [12, 13]. Unfortunately, the functional properties of these homologues have not yet been described either.

The sequencing of various mammalian genomes is rapidly approaching completion. Nevertheless, there are still many predicted open reading frames awaiting functional characterization and subsequent assignment. Algorithms predicting membrane proteins are likely to uncover more transporter genes and gene families. The future challenge for the scientific community will be the biochemical, biophysical, physiological and pharmacological assessment of all these novel gene products.

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