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Solute Carrier SLC41A1 "A MINI REVIEW"

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ABSTRACT : **The human solute carrier, SLC41A1, is a Mg^{2}+ transporter that is regulated by extracellular magnesium. Although intracellular magnesium plays a fundamental role in cellular metabolism, little is known about how Mg^{2}+ is taken up and controlled by cells. Magnesium plays a fundamental role in cellular metabolism so that its control within the body is critical. Magnesium homeostasis is principally a balance between intestinal absorption of dietary magnesium and renal excretion of urinary magnesium. The kidney, mainly the distal convoluted tubule, controls magnesium reabsorption. Although renal reabsorption is under the influence of many hormones, selective regulation of magnesium transport is due to intrinsic control involving transcriptional processes and synthesis of transport proteins. Using microarray analysis, identification of the genetic elements involved with this transcriptional control has been begun. SLC41A1 (GenBank Accession No. AJ514402), comprises 10 putative transmembrane domains, two of which are highly homologous to the integral membrane part of the prokaryote transports Mg^{2}+ and other divalent cations Sr^{2}+, Zn^{2}+, Cu^{2}+, Fe^{2}+, Co^{2}+, Ba^{2}+, and Cd^{2}+ but not Ca^{2}+, Mn^{2}+, and Ni^{2}+. Transport of Mg^{2+} by SLC41A1 is rheogenic, voltage dependent, and not coupled to Na or Cl . Expressed SLC41A1 transports a range of other divalent cations: Mg^{2+}, Sr^{2+}, Zn^{2+}, Cu^{2+}, Fe^{2+}, Co^{2+}, Ba^{2+}, and Cd^{2+}. The divalent cations Ca^{2+}, Mn^{2+}, and Ni^{2+} and the trivalent ion Gd^{3+} did not induce currents nor did they inhibit Mg^{2+} transport. The nonselective cation La^{3+} abolishes Mg^{2+} uptake. Computer analysis of the SLC41A1 protein structure reveals that it belongs to MgtE protein family & suggested that the human solute carrier, SLC41A1, might be a eukaryotic Mg^{2}+ transporter closely related (60-70%) protein encoded by SLC41A2 is a Mg^{2+} transporter that might be involved in magnesium homeostasis in epithelial cells also transports a range of other divalent cations: Ba^{2}, Ni^{2}, Co^{2},Fe^{2}, or Mn^{2}, but not Ca^{2}, Zn^{2}, or Cu^{2+} that may have related functional properties.**

Key words : cation, magnesium, solute, carrier, transporter

History

Investigation of proteins and their properties had been going on since about 1800 when scientists were finding the first signs of this, at the time, unknown class of organic compounds. The first mention of the word protein, which means of first rank, were from a letter sent by Jons Jakob Berzelius to Gerhardus Johannes on 10. July 1838 where he wrote "*I propose to you the name 'protein' for the organic oxide of fibrin and albumin, which I have derived from the Greek word because it appears to be the primitive or principle substance of animal nutrition*". Proteid was defined in the 1913 Webster as "One of a class of amorphous nitrogenous principles, containing, as a rule, a small amount of sulphur; an albuminoid, as blood fibrin, casein of milk, etc. Long chains of amino acids are almost universally referred to as proteins, but shorter strings of amino acids are referred to as "polypeptides", "peptides" or very rarely "oligopeptides". The dividing line is somewhat undefined, although a polypeptide may be less likely to have tertiary structure and may be more likely to act as a hormon rather than as an enzyme or structural element. Proteomics, the study of the proteome, has largely been practiced through the separation of proteins. Protein-protein interactions play a central role in numerous processes in the cell and are one of the main fields of functional proteomics. The contact surfaces of the temporary protein complexes have unique structure and properties and they are more conservative in comparison with active site of enzymes. So they represent prospective targets for a new generation of drugs.

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Introduction

Between the two facilitated types of transport, carrier type usually exhibit rates of transport that are several

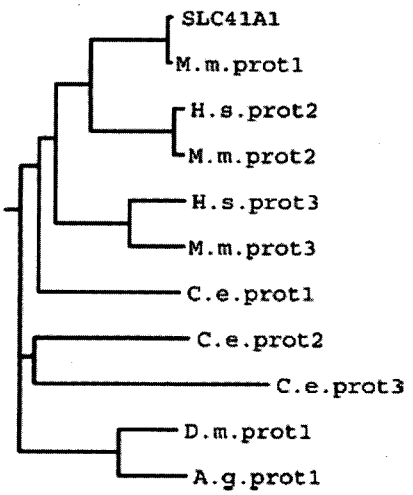

Fig. 1. Phylogenetic presentation of homologous proteins. A dendogram presenting the phylogenetic analysis that demonstrates the evolutionary relationship between SLC41A1 and its identified homologs in five different species. The dendogram was generated based on the amino acid sequence no. 138-499 in SLC41A1.(M.m. = Mus musculus, H,s = Home sapiens C.e. = C.elegans D.m. = Drosophila melanogaster, A.g. = Anopheles gambiae) (Troels wabakken *et al*).

orders of magnitude lower than those of channels. Moreover, in contrast to most channels, carriers exhibit stereospecific substrate specificities. Although both channels and carriers may exhibit the phenomenon of saturation kinetics, this is a more common characteristic of carriers. Very few carriers have been shown to be capable of functioning by a channel-type mechanism, and the few that exhibit this capacity generally do so only after the protein has been modified, either by covalent or non-covalent ligand binding or by imposition of a large membrane potential. A few carriers modify their substrates during transport. Moreover, while most channels are oligomeric complexes, many carriers can function as monomeric proteins. These observations led to the suggestion that channels and carriers are fundamentally, not superficially, different.

The human solute carrier super family as defined by the *Human Genome Organization Nomenclature Committee* (*http://www.gene.ucl.ac.uk/nomenclature/*) currently comprises 43 families and 319 (*bioparadigms.org*) transporter genes that encode mammalian passive transporters,

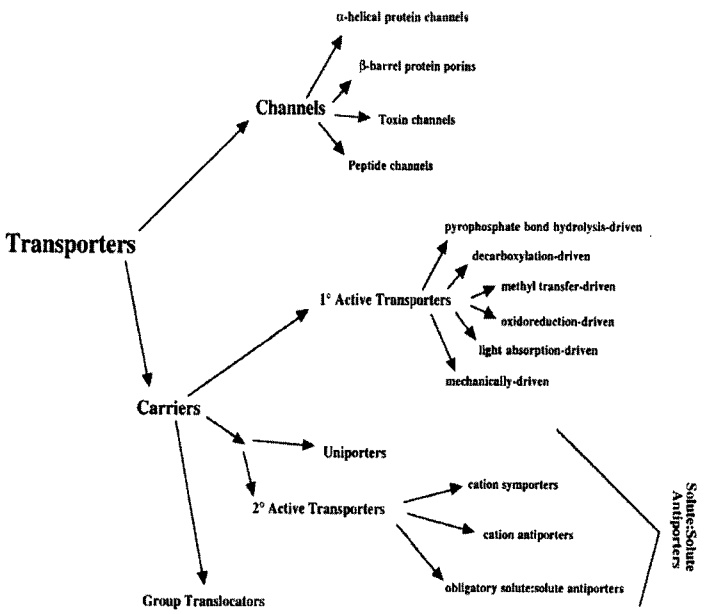

Fig. 2. Scheme illustrating the currently recognized primary types of transporters found in nature. These proteins are initially divided into channels and carriers. Channels are subdivided into a-helical protein channels, b-barrel protein porins (mostly in the outer membranes of gram-negative bacteria and eukaryotic organelles), toxin channels, and peptide channels. Carriers are subdivided into primary active carriers, secondary active carriers (including uniporters), and group translocators that modify their substrates during transport. Primary sources of chemical energy that can be coupled to transport include pyrophosphate bond (i.e., ATP) hydrolysis, decarboxylation, and methyl transfer. Oxidation-reduction reactions, light absorption, and mechanical devices can also be coupled to transport. Secondary active transport is driven by ion and other solute (electro) chemical gradients created by primary active transport systems. The only well-established group-translocating system found in nature is the bacterial phosphoenolpyruvate:sugar PTS, which phosphorylates its sugar substrates during transport (Milton H. & Saier JR.).

ion coupled transporters, and exchangers. A transporter is assigned to a specific SLC family if it has at least 20 -25% amino acid sequence identity to other members of that family. One of these families, SLC41, has a small similarity to the bacterial MgtE magnesium transport family. SLC41 includes three members SLC41A1, SLC41A2, and SLC41A3. SLC41A1 functions as a Mg^{2}+ channel when expressed in Xenopus oocytes. Query of GenBank revealed genomic sequences that were identical to SLC41A2 (GenBank Accession No.NM_177388), and alignment with SLC41A1 cDNA predicts the gene structure. The coding sequence possesses 12 exons each of which is about 200 base pairs in length. The mouse SLC41A1 gene is localized to chromosome 1E4. The human genomic sequence of SLC41A1 (GenBankTM accession no. NM.173854) was assigned to chromosome band 1q31-32.

SLC41A1 contains five possible protein kinase C phosphorylation sites at residues T-10, S-77, S-107, S-148, and S-304. There are also four predicted casein kinase II motifs at residues S-138, S-229, S-340, and S379, and three myristoylation consensus sequences at G-68, G-337, and G-461. The presence of these consensus sequences might indicate post-translational modification and regulation of localization and function. Recently it has been reported that the human SLC41A1 has a homology to $MgTEMg^{2+}$ transporters found in certain bacteria (Wabakken and co-workers).

Genomic sequence

* Open reading frame of 1539-base pairs that predicts a protein of 513 amino acids with a calculated molecular mass of 56 kDa.

* Integral membrane protein containing 10 hydrophobic transmembrane-spanning (TM) regions

* The mouse SLC41A1 cDNA is similar (98%) to the human sequence.

* The mouse SLC41A1 gene is localized to chromosome 1E4.

* The human genomic sequence of SLC41A1 (GenBank TM accession no. NM.173854) was assigned to chromosome band 1q31-32.

* Genomic sequence that was identical to SLC41A1 (GenBankTM accession number NM-173865), and alignment with SLC41A1 cDNA predicts the gene structure. The coding sequence possesses 11 exons each of which is about 200 base pairs in length.

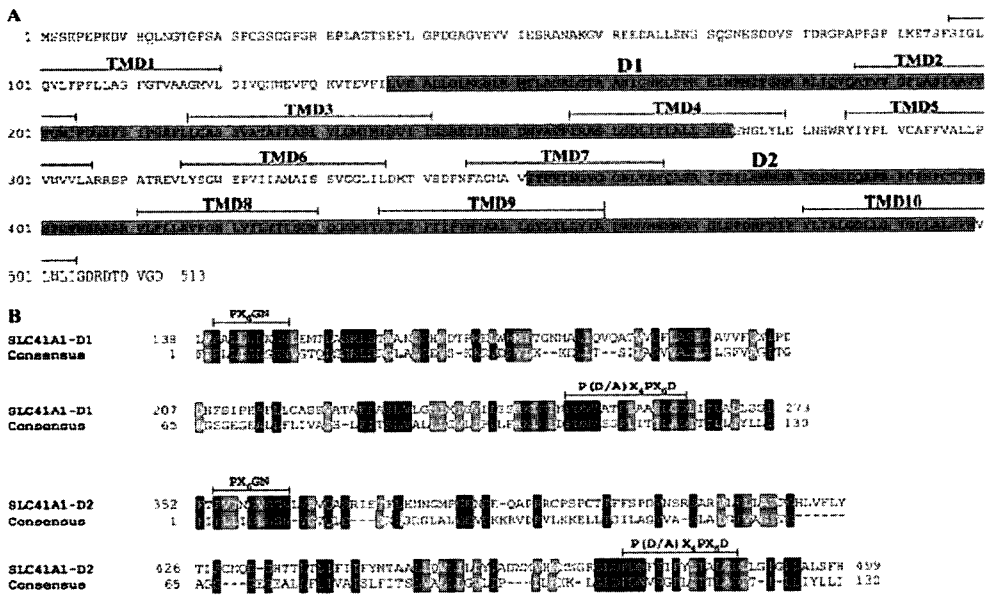

Fig. 3. Presentation of the SLC41A1 amino acid sequence and homology to MgtE domains. (A) The deduced amino acid sequence of SLC41A1. Shaded amino acids (gray) represent the SLC41A1 D1 and D2 domains homologous to the Pfam01769 MgtE consensus sequence. Ten transmembrane domains (TMDs) with their consecutive numbers are indicated. (B) Comparison of the D1 and D2 domains from SLC41A1 with the Pfam01769 MgtE consensus sequence. Dark gray shading, identity; light gray shading, similarity. The two regions are 52% and 46% homologous to the MgtE family consensus sequence, respectively. The flanking numbers correspond to positions of the amino acids of the SLC41A1 and MgtE consensus sequences (Troels wabakken *et al*).

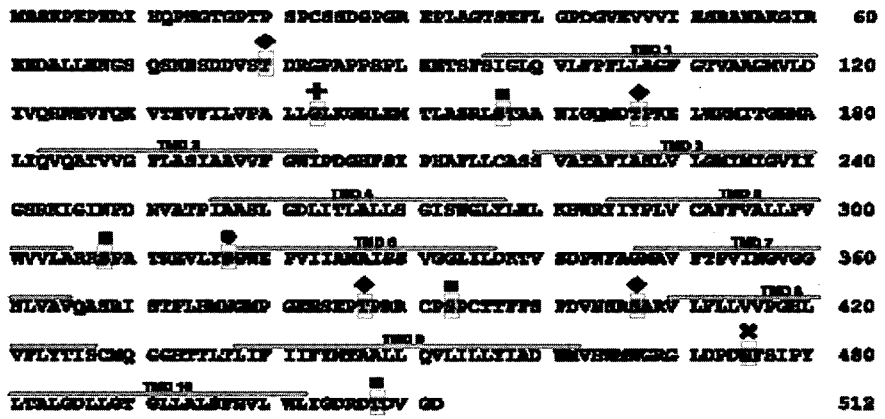

Fig. 4. Molecular characterization of SLC41A1. A amino acid sequence of mouse SLC41A1. Transmembrane segments are underlined, and predicted NH2- linked glycosylation sites (X), protein kinase A (■), protein kinase C phosphorylation (◆), casein kinase II (●), and myristoylation (+) sites are indicated (Angela Goytain and Gary A. Quamme).

Tissue distribution of SLC41A1:

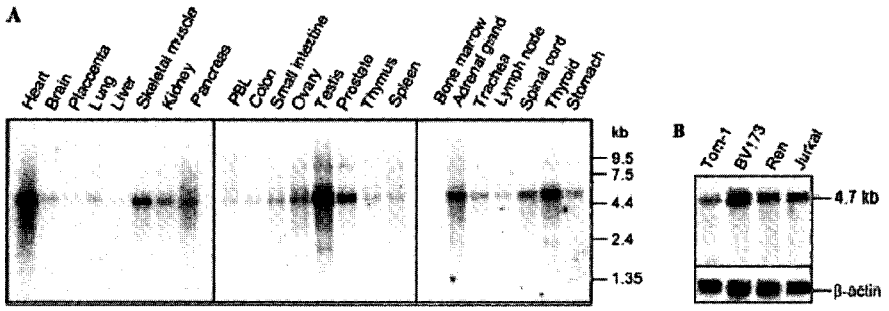

Fig. 5. Expression of SLC41A1 mRNA. (A) Expression of SLC41A1 mRNA in various human tissues. (B) Expression of SLC41A1 mRNA in various human B lymphoid (Tom-1, BV173, and Reh) and T lymphoid (Jurkat) cell lines. Lower panel shows actin hybridization of the same blot. Each lane represents the loading of 2 ug mRNA. Molecular weights in kilobase are indicated to the right.

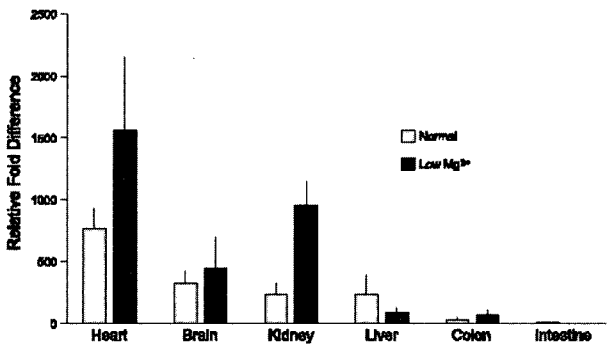

Fig. 6. Tissue distribution of mouse SLC41A1 expression and responsiveness of the SLC41A1 transcripts to Mg^{2+} (Angela Goytain and Gary A. Quamme).

Fuctions:

* Amino acid sequence by the NetNGlyc 1.0 and NetPhos 2.0 server programs reveals several consensus sites for post-translational modification.

* A possible glycosylation site at amino acid residue N-475 on the last putative extracellular loop.

* Contains four putative cAMP-dependent protein kinase phosphorylation sites at residues S-157, S-308, S-393, T-508 and four possible protein kinase C phosphorylation sites at residues T-80, T-167, T-387, S-407.

* One predicted casein kinase II motif at residue S-317 and a myristoylation sequence at G-143.

SLC41A1 is widely distributed among tissues (Fig. 5 & 6) and is responsive in some organs to magnesium balance, e.g. Heart, brain, kidney, testes, adrenal gland, thyroid gland prostate gland, skeletal muscle and liver with lesser amounts in the colon and small intestine & most of other tissues. Although there is ample evidence for unique Mg^{2+} transporters in a variety of animals and tissues, only a few have been identified at the molecular level.

* The two different gene products, SLC41A1 and

SLC41A2, function as divalent metal transporters when expressed in Xenopus oocytes but each have different substrate selectivity and cationic inhibition profiles.

* The two solute transporters were permeable to many divalent cations: SlC41A1, $Mg^{2+} = Sr^{2+} = Fe^{2+} = Ba^{2+} = Cu^{2+} > Zn^{2+} = Co^{2+} > Cd^{2+} > Cd^{2+} = Mn^{2+}$ whereas SLC41A2, $Mg2+ = Ba^{2+}$, $Ni^{2+} = Co^{2+} > Fe^{2+} > Mn^{2+}$.

* The inhibition of Mg^{2+} currents by divalent cations is also distinctive; Ca^{2+} did not inhibit SLC41A1-mediated Mg^{2+} transport whereas it inhibited SLC41A2-evoked currents when measured under the same conditions.

* SLC41A1 expression increases with low magnesium but SLC41A2 mRNA will not be altered.

* The two solute carriers appear to have different functions within the cell even though both are present in most cells

* SLC41A1 transcript is up-regulated in response to low magnesium & that transcriptional changes are involved with magnesium homeostasis.

* SLC41A1 prefers Mg^{2+} as a substrate compared to other divalent cations, nevertheless it is evident that it could perform a physiological function within cells to transport Fe^{2+}, Zn^{2+}, Cu2+, Co^{2+}, and Cd^{2+}.

* SLC41A1 is responsive in some organs to magnesium balance.

* The SLC41A1 protein molecule could be the possible drug target as well as it may be taken as one of the important vector for drug delivery (*hypothetical function*).

* Heavy metal intoxication may be more severe in individuals with low magnesium. (notion)

Factors affecting magnesium absorption/ transport

* The clinical use of aminoglycosides often leads to renal magnesium wasting and hypomagnesaemia.

* Magnesium transporters that are involved with renal magnesium balance are regulated by magnesium-dependent transcriptional mechanisms.

* Mrs2 (*mitochondrial RNA splicing2*) protein may mediate Mg^{2+} transport in mammalian mitochondria (Schweyen and colleagues).

* Transient receptor potential melastatin (TRPM) ion channel family, that produces a Mg^{2+} current in a wide variety of cells (Nadler *et al*)

* Heavy metal intoxication may be more severe in individuals with low magnesium (Quamme, GA.)

* Epithelial Mg^{2+} absorption is regulated to a major degree by differential expression of genes encoding magnesium transport proteins.

Conclusion

SLC41A1 is a regulated Mg^{2+} transporter that might be involved in magnesium homeostasis in epithelial cells or in other word SLC41A1 is a Mg^{2+} transporter that is responsive to magnesium balance. SLC41A1 transcript is unregulated in response to low magnesium. The membrane protein SLC41A1 that belongs to a novel eukaryotic protein family previously described in prokaryotes. Domains of high homology define the eukaryotic family, whereas only one such domain is found in the prokaryotic proteins. These domains are likely to have functional or structural importance. SLC41A1 protein structure reveals that it MgtE protein family suggested that the human solute carrier, SLC41A1which consists of 513 amino acids and has a molecular size of 56 kDa, might be a eukaryotic $Mg^{2}+$ transporter. Until now solute carrier super family discovered 43 families and 319 (bioparadigms.org) transporter genes. Phylogeny provides the most reliable guide to structure, function, and mechanism, and it provides valuable information concerning the evolutionary history of a family. Proteomics is one of the important subjects of study in this decade and previous so that the new genes like SLC41A1, SLC41A2, SLC41A3 is being discovered which are very important to keep the life smooth. SLC41 family members may become prospective target for new generation drug as well as may be important molecule for drug delivery in particular organs.

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