Identification of a Novel System L Amino Acid Transporter Structurally Distinct from Heterodimeric Amino Acid Transporters*

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A cDNA that encodes a novel Na⁺-independent neutral amino acid transporter was isolated from FLC4 human hepatocarcinoma cells by expression cloning. When expressed in Xenopus oocytes, the encoded protein designated LAT3 (L-type amino acid transporter 3) transported neutral amino acids such as L-leucine, l-isoleucine, L-valine, and L-phenylalanine. The LAT3-mediated transport was Na⁺-independent and inhibited by 2-amino-bicyclo[2.2.1]heptane-2-carboxylic acid, consistent with the properties of system L. Distinct from already known system L transporters LAT1 and LAT2, which form heterodimeric complex with 4F2 heavy chain, LAT3 was functional by itself in Xenopus oocytes. The deduced amino acid sequence of LAT3 was identical to the gene product of P0V1 reported as a prostate cancer-upregulated gene whose function was not determined, whereas it did not exhibit significant similarity to already identified transporters. The Eadie-Hofstee plots of LAT3-mediated transport were curvilinear, whereas the low affinity component is predominant at physiological plasma amino acid concentration. In addition to amino acid substrates, LAT3 recognized amino acid alcohols. The transport of L-leucine was electroneutral and mediated by a facilitated diffusion. In contrast, l-leucinol, L-valinol, and L-phenylalaninol, which have a net positive charge induced inward current under voltage clamp, suggesting these compounds are transported by LAT3. LAT3-mediated transport was inhibited by the pretreatment with N-ethylmaleimide, consistent with the property of system L2 originally characterized in hepatocyte primary culture. Based on the substrate selectivity, affinity, and N-ethylmaleimide sensitivity, LAT3 is proposed to be a transporter subserving system L2. LAT3 should denote a new family of organic solute transporters.

System L is a plasma membrane amino acid transport system, which mediates Na⁺-independent transport of large neutral amino acids (1). It was first characterized in Ehrlich ascites tumor cells as a transport system specifically inhibited by a bicyclic amino acid, 2-amino-bicyclo[2.2.1]heptane-2-carboxylic acid (BCH) (1–3). Various subtypes with different characteristics in substrate selectivity and transport property have, subsequently, been described so far for system L (4–9). System L is a major route to provide cells with branched-chain and aromatic amino acids. In addition, system L is present in the basolateral membrane of epithelial cells and plays important roles in the absorption of amino acids through the epithelial cells of small intestine and renal proximal tubules (1). System L is also pivotal in the permeation of amino acids through the blood–brain barrier as well as blood–brain barrier and placenta barrier (1).

By means of expression cloning, we identified the first isoform of system L amino acid transporter LAT1 (L-type amino acid transporter 1) in C6 rat glioma cells (10). LAT1 is a member of the SLC (solute carrier) 7 family with putative 12-membrane-spanning domains (11, 12). LAT1 mediates a Na⁺-independent amino acid exchange and prefers large neutral amino acids such as leucine, isoleucine, valine, phenylalanine, tyrosine, tryptophan, methionine, and histidine for its substrates (10, 13–15). We and others further demonstrated that a single-membrane-spanning protein, the heavy chain of 4F2 antigen (4F2hc), is essential for the functional expression of LAT1 in the plasma membrane (10, 16). LAT1 and 4F2hc form a heterodimeric complex via a disulfide bond (13, 16–18). Following the identification of LAT1, transporters structurally related to LAT1 have been found to be associated with 4F2hc or other single-membrane-spanning subunits rBAT (related to the b₀⁺, L-type amino acid transporter), establishing the heterodimeric amino acid transporter family (11, 19). These transporters include systems asc, y¹⁺L, x₂⁺C, and b₀⁺, as well as the second system L isoform, LAT2 (11, 19). LAT2 is more ubiquitously expressed than LAT1 and transports not only large neutral amino acids but also small neutral amino acids (20–22).

Even after the finding of the heterodimeric amino acid transporters, some of the previously reported properties of system L still remain to be explained by the properties of LAT1 and LAT2. For example, system L2 characterized in hepatocyte primary culture exhibits narrower substrate selectivity in

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** The abbreviations used are: BCH, 2-amino-bicyclo[2.2.1]heptane-2-carboxylic acid; LAT1, L-type amino acid transporter 1; SLC, solute carrier; LAT2, L-type amino acid transporter 2; LAT3, L-type amino acid transporter 3; 4F2hc, 4F2 heavy chain; NEM, N-ethylmaleimide; TAT1, T-type amino acid transporter 1.
which it prefers leucine, isoleucine, and phenylalanine, distinct from that of LAT1 and LAT2 (5). Therefore, it has been proposed that still unidentified system L transporters should be present. During the search for culture cell lines with the amino acid transport properties distinct from those of LAT1 and LAT2, we have found that human hepatocarcinoma-derived cell line FLC4 (23, 24) exhibits a unique character in the leucine transport. In this study, we performed expression cloning to identify the system L transporter of FLC4 cells and isolated a cDNA encoding a novel amino acid transporter. The transporter is structurally distinct from the heterodimeric transporters and exhibits the properties corresponding to system L2.

EXPERIMENTAL PROCEDURES

Expression of FLC4 Cell Poly(A)’ RNA—FLC4 cells were cultured in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum (23, 24). The total RNA from the FLC4 cells was prepared by the guanidinium isothiocyanate method using cesium trifluoroacetic acid (Amersham Biosciences) following the manufacturer’s instructions. The poly(A)’ RNA was selected by oligo(dT) cellulose chromatography (Amersham Biosciences) (25). *Xenopus laevis* oocyte expression studies and uptake measurements were performed as described elsewhere (26). Dinitrofluorobenzene-treated oocytes (20 μg of poly(A)’ RNA obtained from FLC4 cells) 2–3 days after injection, the uptake of L-[14C]leucine was measured for 30 min in the Na’-free solution (choline-Cl 100 mM, KCl 2 mM, CaCl2 1 mM, MgCl2 1 mM, HEPES 10 mM, Tris 5 mM, pH 7.4) containing 100 μM L-[14C]leucine (0.5 μCi/ml). Expression Cloning—Expression cloning using a *Xenopus* oocyte expression system was performed as described previously (10, 27–30). 400 μg of poly(A)’ RNA obtained from FLC4 cells was size-fractionated by preparative gel electrophoresis (10, 29). RNA from each fraction (50 ng) was expressed in *Xenopus* oocytes. Positive fractions showing peak stimulation of L-[14C]leucine uptake were used to construct a directional cDNA library (10, 29). cRNA synthesized in vitro from pools of ~500 clones was injected into *Xenopus* oocytes (10, 29). A positive pool was sequentially subdivided and analyzed until a single clone (LAT3) was identified. The cDNA was sequenced in both directions by dye terminator cycle sequencing method (PerkinElmer Life Sciences). Transmembrane regions of proteins were predicted based on TopPred2 algorithm (31).

Functional Characterization—*Xenopus* oocytes were injected with 25 ng of LAT3 cRNA synthesized in vitro from the LAT3 cDNA in plasmid pSPORT1 (Invitrogen) linearized with NotI. (25). Three days after injection, the uptake of [14C]-labeled amino acids was measured as described above in the regular uptake solution (100 mM NaCl, 2 mM KCl, 1 mM CaCl2, 1 mM MgCl2, 10 mM HEPES, 5 mM Tris, pH 7.4) or Na’-free solution in which NaCl in the regular uptake solution was replaced by gluconate anion. To prepare uptake solution in which NaCl in the regular uptake solution was replaced by choline chloride, containing 0.5 mM of L-leucine, L-leucinol, L-valinol, or L-phenylalaninol was added to the Na’-free solution and the values were expressed as picomoles/oocyte/min.

Northern Analysis—The cDNA fragment corresponding to 1930–1936 bp of LAT3 cDNA (GenBank TM/EMBL/DDBJ accession number AB103633) was PCR-amplified and labeled with [32P]dCTP using a T7 Geneclean kit (Amersham Biosciences) (25). Multiple Tissue Northern Blots (Clontech) were hybridized with the probe and processed following the manufacturer’s instructions. FLC4 poly(A)’ RNA prepared as described above and human liver poly(A)’ RNA (Clontech) were separated on 1% agarose gel and blotted onto a nitrocellulose filter (Schleicher & Schuell) (25). Hybridization was performed for 20 h at 42 °C as described elsewhere (25). The filters were washed in 0.1 × SSC/0.1% SDS at 65 °C.

RESULTS

When poly(A)’ RNA from FLC4 human hepatocarcinoma cells was expressed in *Xenopus laevis* oocytes, significant augmentation of L-[14C]leucine uptake was detected. The size-fractionation of the FLC4 poly(A)’ RNA revealed that the fraction of 2.2–2.7 kb exhibited the peak activity of L-[14C]leucine uptake (data not shown). From this fraction, a cDNA library was constructed and screened for L-[14C]leucine uptake by expression in *Xenopus* oocytes. A 2.5-kb cDNA was isolated that encodes a protein designated LAT3 (L-type amino acid transporter 3).

When expressed in *Xenopus* oocytes, LAT3 induced L-[14C]leucine transport, which was not dependent on Na’ or Cl’ in the medium (Fig. 1, a and b). Although LAT3-mediated L-[14C]leucine uptake was saturable, its Eadie-Hofstee plot was curvilinear, suggesting the presence of multiple components for the L-leucine uptake induced by the expression of a single protein LAT3 (Fig. 1c). The concentration-dependent substrate uptake was fit to the two-component kinetics (see “Experimental Procedures”). The apparent Km and Vmax were estimated by best fitting and shown in Table I.

The substrate selectivity of LAT3 was investigated by inhibition experiments in which L-[14C]leucine (100 μM) uptake was measured in the presence of 10 mM amino acids. The L-leucine uptake was highly inhibited by l-isomers of isoleucine, valine, phenylalanine, and methionine (Fig. 2e). Weaker inhibition was detected when the other neutral amino acids were used as inhibitors (Table II).
inhibitors. Acidic amino acids, L-aspartate and L-glutamate, and basic amino acids, L-lysine and L-arginine, did not inhibit LAT3-mediated L-[14C]leucine uptake (Fig. 2a). Although L-amino acids less affected LAT3-mediated L-[14C]leucine uptake, D-leucine, D-histidine, and D-methionine showed relatively strong inhibitory effects on the L-[14C]leucine uptake (24.9 ± 1.7%, 47.8 ± 2.1%, and 59.2 ± 2.1% of the control L-[14C]leucine uptake measured in the absence of inhibitors, respectively; data not shown). As shown in Fig. 2a, the system L inhibitor, 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid (BCH), exhibited strong inhibition on L-[14C]leucine uptake mediated by LAT3, whereas o-aminoisobutyric acid and system

**Table I**

Kinetic parameters of amino acid substrates

In each set of experiments to determine $K_m$ and $V_{max}$ values, L-leucine uptake (100 μM) was measured to compare $V_{max}$ values between experiments. The $V_{max}$ value of each amino acid was normalized to that of L-leucine in the same experiment.

| Amino acid   | $K_m$ 1$^a$ (μM) | $V_{max}$ 1 (pmol/oocyte/min) | $K_m$ 2 (μM) | $V_{max}$ 2 (pmol/oocyte/min) |
|--------------|------------------|------------------------------|--------------|-------------------------------|
| L-Leucine    | 1024 ± 31        | 1.000 ± 0.008                | 8.42 ± 5.82  | 0.018 ± 0.004                |
| L-Isoleucine | 1418 ± 47        | 0.82 ± 0.029                 | 12.6 ± 14.1  | 0.025 ± 0.018                |
| L-Valine     | 1885 ± 107       | 0.87 ± 0.018                 | 30.6 ± 26.3  | 0.022 ± 0.019                |
| L-Phenylalanine | 1206 ± 53    | 0.98 ± 0.026                 | 6.58 ± 4.47  | 0.010 ± 0.005                |

$^aK_m$ 1 and $V_{max}$ 1 represent $K_m$ and $V_{max}$ of the low affinity component, whereas $K_m$ 2 and $V_{max}$ 2 represent $K_m$ and $V_{max}$ of the high affinity component, respectively. $K_m$ 1, $V_{max}$ 1, $K_m$ 2, and $V_{max}$ 2 values were determined as described under "Experimental Procedures."
A inhibitor α-(aminomethyl)isobutyric acid had no inhibitory effect (data not shown).

Consistent with the results from the inhibition experiments, 14C-labeled L-leucine, L-isoleucine, L-valine, L-phenylalanine, and L-methionine (100 μM) were transported at relatively high rate by LAT3 (Fig. 2b). Among D-amino acids, D-leucine, for which a 14C-labeled compound was available, was confirmed to be transported by LAT3 (Fig. 2b). As observed for L-leucine uptake, the Eadie-Hofstee plots for the uptake of L-isoleucine, L-valine, and L-phenylalanine were curvilinear (data not shown). Kinetic parameters of these amino acid substrates are listed in Table I.

To examine the mechanisms of substrate recognition, the effects of amino acid-related compounds on LAT3-mediated L-14C-leucine uptake was examined. As shown in Fig. 3, the preincubation of the oocytes with 5 mM NEM for 15 min completely abolished L-14C-leucine transport mediated by LAT3 regardless of presence or absence of NEM in the uptake solution with L-14C-leucine. In contrast, NEM did not affect L-14C-leucine transport mediated by LAT1 (Fig. 6).

LAT3 cDNA (2525 bp) contains a single open reading frame encoding a putative 559-amino acid protein (GenBank TM/EMBL/DDBJ accession number AB103033). The cDNA includes poly(A) tail (28 As), which starts 20 nucleotides downstream from a typical polyadenylation signal AATAAA at the nucleotide 2478. Twelve transmembrane regions (residue numbers: 21–41, 78–98, 106–126, 132–152, 165–185, 191–211, 297–317, 357–377, 419–439, 457–477, 484–504, and 511–531) were predicted on the LAT3 amino acid sequence by means of the TopPred2 algorithm. LAT3 protein contains a relatively long extracellular loop with putative N-linked glycosylation sites (Asn212 and Asn229) between transmembrane domains 1 and 2. A long intracellular loop was predicted between transmembrane domains 6 and 7, which contain putative protein kinase C-dependent phosphorylation site (Thr231 and Ser262) and a tyrosine phosphorylation site (Tyr 251). An additional leucine zipper motif was predicted at Ser405 in the putative intracellular loop between transmembrane domains 8 and 9. A leucine zipper motif was predicted at Ser405 in the putative intracellular loop between transmembrane domains 8 and 9. A leucine zipper motif was predicted at Ser405 in the putative intracellular loop between transmembrane domains 8 and 9. A leucine zipper motif was predicted at Ser405 in the putative intracellular loop between transmembrane domains 8 and 9. A leucine zipper motif was predicted at Ser405 in the putative intracellular loop between transmembrane domains 8 and 9. A leucine zipper motif was predicted at Ser405 in the putative intracellular loop between transmembrane domains 8 and 9. A leucine zipper motif was predicted at Ser405 in the putative intracellular loop between transmembrane domains 8 and 9. A leucine zipper motif was predicted at Ser405 in the putative intracellular loop between transmembrane domains 8 and 9.
Northern blot analysis using human Multiple Tissue Northern Blots indicated that a 2.5-kb LAT3 message was expressed at high level in pancreas, liver, skeletal muscle, and fetal liver. Weaker signals were also detected in heart, placenta, lung, kidney, spleen, prostate, testis, ovary, small intestine, colon, lymph node, and bone marrow (Fig. 7a). In pancreas, an additional 4.4 kb message was also detected (Fig. 7a). The expression of LAT3 in FLC4 from which LAT3 cDNA was isolated was confirmed by the Northern blot using FLC4 poly(A)/H11001 RNA (Fig. 7b).

**DISCUSSION**

We previously showed that L-leucine uptake by T24 human bladder carcinoma cells is almost exclusively mediated by LAT1 (39). Most of the tumor cell lines exhibit similar properties to that of T24 cells. However, we found that FLC4 hepa-tocarcinoma-derived cells (23, 24) exhibited a somewhat different character in the leucine transport. L-[14C]Leucine uptake by FLC4 cells was not inhibited by the compounds that inhibited T24 cell-mediated uptake, such as triiodothyronine and /H9251-methyltyrosine (data not shown). LAT3 was identified as a transporter responsible for the L-leucine uptake by FLC4 cells. LAT3 proved to be a gene product of /H11002POV1 reported previously as a prostate cancer-up-regulated gene whose function was not determined (38). LAT3 did not show significant sequence similarity to already identified transporters and was not classified into any established solute carrier families SLC1/H1101141 (HUGO Gene Nomenclature Committee, www.gene.ucl.ac.uk/nomenclature/). LAT3, however, shows similar transmembrane topology to that of the members of organic cation/anion transporter family (SLC22) and facilitated glucose transporter family...
does not recognize triiodothyronine and ports branched-chain amino acids and phenylalanine. LAT3 is distinct from LAT1 and LAT2. LAT3 shows narrower substrate specificity. LAT3 cRNA is sufficient for the functional expression of LAT3 and already assigned to system L (10, 16, 20). LAT1 and LAT2, which are the members of the SLC7 family, are Na+- and BCH-sensitive, showing the properties of system L (1). Distinct from LAT1 and LAT2, which are the members of the SLC7 family, LAT3 is not required for functional expression. A single injection of LAT3 cRNA is sufficient for the functional expression of LAT3 in Xenopus oocytes. Substrate selectivity of LAT3 was also distinct from LAT1 and LAT2. LAT3 shows narrower substrate selectivity compared with LAT1 and LAT2 and mainly transports noncharged-chain amino acids and phenylalanine. LAT3 does not recognize triiodothyronine and @-methyltyrosine, consistent with the properties of leucine transport of PLC4 cells (data not shown). It has, thus, turned out that more than one family of transporters contribute to system L transport activity.

We previously showed that the transport mediated by TAT1, a Na+- and BCH-sensitive, aromatic amino acid transporter for system L, was inhibited by N-acetyl- and N-methyl- derivatives of substrate amino acids but not by amino acid methylesters (30). Based on this observation, it was suggested that TAT1 recognizes amino acid substrates as anions, consistent with its structural similarity to H+/monocarboxylate transporters of SLC16 family. In contrast, LAT3-mediated transport was not prominently inhibited by N-acetyl- derivatives, N-methyl- derivatives, or methylesters. We found that L-leucinol, 1,3-dimethyl-n-butylamine, L-valinol, and L-phenylalaninol exhibited relatively strong inhibitory effects on LAT3-mediated transport. Thus, it is suggested that @-carboxyl group can be substituted by hydroxymethyl group or methyl group for the recognition by LAT3, although hydroxymethyl and methyl groups appear less suited compared with the carboxyl group. Because N-methyl-L-leucine exhibited relatively strong inhibition, it seems that the @-amino group does not have to be intact for the interaction with LAT3. It is interesting that isopentylamine, isobutylamine, and 2-phenylethylamine, which possess side chains of L-leucine, L-valine, and L-phenylalanine, respectively, and lack @-carboxyl groups, exhibited weak but significant inhibitory effects, whereas 4-methylvaleric acid, isovaleric acid, and 3-phenylpropionic acid, which lack @-amino groups, had no inhibitory effects. Therefore, the @-amino group or its modified moieties seems to be indispensable for the interaction with the substrate binding site.

A remarkable feature of the transport kinetics of LAT3 is in its curvilinear Eadie-Hofstee plots. The expression of a transporter encoded by a single cDNA into heterologous expression systems usually results in the appearance of a transport function with a single-component kinetics (14, 21, 25, 27, 30, 34, 35, 42–44). We compared the concentration-dependent transport mediated by LAT3 with that mediated by system T transporter TAT1 (30) in the same batch of oocytes. We obtained linear Eadie-Hofstee plots for L-tryptophan transport by TAT1 in contrast to curvilinear Eadie-Hofstee plots for L-leucine transport by LAT3, confirming the peculiar nature of LAT3 (data not shown). In some transporters, it has been reported that phosphorylation of the receptor proteins alter the affinity for ligand binding, so that producing heterogenic populations is receptor affinity-dependent on their phosphorylation state, which results in the apparent multicomponent kinetics (45–47). This might be considered also for LAT3, because it possesses putative phosphorylation sites, although the effect of phosphorylation on the substrate affinity is not determined yet. The low affinity component is assumed to be predominant at physiological plasma amino acid concentration based on the comparison of Vmax values (Table 1). The properties of LAT3-mediated L-leucine transport characterized by using 100 µM L-[14C]leucine as a tracer in the present study main reflect those of the low affinity component.

Recently it has been shown that many amino acid transporters mediate the exchange of substrates (10, 14, 15, 34, 35, 48, 49). As shown in Fig. 5, however, the efflux of preloaded L-[14C]leucine was detected even in the absence of extracellular L-leucine, which is totally different from the properties of typical amino acid exchangers such as LAT1 and y-type L-type amino acid transporter 1) (10, 14, 15, 35). The L-leucine transport mediated by LAT3 was electroneutral and not dependent on Na+, Cl−, and pH around physiological pH (6.5–8.0) (Figs. 1a, 1b, and 4), suggesting that LAT3-mediated transport is not coupled to the transport of inorganic ions, including H+. These properties are similar to those of TAT1, which mediate an electroneutral facilitated diffusion of neutral amino acids (30). It is thus suggested that LAT3-mediated transport is due to the facilitated diffusion rather than the obligatory exchange of substrate amino acids.

We found that L-leucinol, L-valinol, and L-phenylalaninol, which have a net positive charge, induced inward current in the oocytes expressing LAT3 under the voltage clamp condition, although a neutral amino acid L-leucine did not generate significant currents (Fig. 4). This suggests that L-leucinol, L-valinol, and L-phenylalaninol, which inhibit LAT3-mediated L-leucine uptake, are in fact transported by LAT3. Electrogenic facilitated transport of cationic compounds was once reported for cationic amino acid transporters (50). Because L-leucinol, L-valinol, and L-phenylalaninol are positively charged, the facilitated diffusion of these amino acid alcohols via LAT3 from outside to the inside of the oocytes generates inward currents.

In primary hepatocyte culture, it was shown that system L with low affinity and narrow substrate selectivity (“system L2”) is predominant in freshly isolated hepatocytes. It is replaced by the other subtype of system L with high affinity and broader substrate selectivity (“system L1”) over the initial 24 to 48 h of culture (1, 5). It was reported that the uptake by system L1 is of high affinity (micromolar range) and substantially inhibited by cysteine, valine, isoleucine, leucine, methionine, histidine, tryptophan, tyrosine, phenylalanine, and BCH. In contrast,
system L2-mediated transport exhibited low affinity (millimolar range) and narrower substrate selectivity. The uptake by system L2 was inhibited by isoleucine, leucine, phenylalanine, and BCH (32, 51). It was noted that system L2 is sensitive to inhibition by NEM, whereas system L1 is not affected by NEM (32). In this study, we showed that L-leucine transport mediated by LAT3 was completely inhibited by NEM, whereas that mediated by LAT1 was not affected by NEM (Fig. 6). This NEM sensitivity of LAT3 is similar to that of system L2. Once the oocytes were pretreated with NEM, the presence or absence of NEM in the uptake solution with L-[14C]leucine did not affect the results. This is consistent with NEM, a thiol reagent, inhibiting the functional activity of LAT3 by reacting covalently with exposed sulfhydryl groups (32) and not by competing with substrates at the binding site of LAT3. Considering the low affinity and narrower substrate selectivity together with the NEM sensitivity, we propose that LAT3 is a transporter serving system L2. In contrast, the properties of LAT1 are consistent with those of system L1.

The Northern blot analysis of human tissues revealed the high level of LAT3 mRNA in pancreas and adult and fetal liver (Fig. 7a), consistent with the report by Cole et al. (38). Our Northern blot further showed strong signals in skeletal muscle and weaker signals in many other tissues (Fig. 7a). LAT3, the gene product of POV1, was reported to be up-regulated in prostate cancers (38). DNA microarray analyses revealed that POV1 gene is also up-regulated in testicular tumors, suggesting the possible involvement of LAT3 in a variety of malignant tumors (52). In prostate cancers, two spliced variants were reported for POV1 (38). The one that is identical to LAT3 and encoded by a shorter message (2.4–2.6 kb) was reported to be predominantly expressed in normal tissues, whereas the other encoded by a longer message (4.4–5 kb) was proposed to be primarily associated with fetal tissues and tumors (38). Because of this alternative splicing, putative transmembrane domains 11 and 12 and C terminus intracellular domains are altered. The functional significance of this alternative splicing and its roles in cancer cells remain to be clarified.

In summary, we have identified a novel Na+/H+ independent neutral amino acid transporter LAT3. LAT3 exhibits system L activity corresponding to the NEM-sensitive system L2. Because LAT3 does not exhibit structural similarity to already identified transporters, including system L transporters LAT1 and LAT2, LAT3 should denote a new family of organic solute transporters.

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