

Novel therapeutic approaches targeting L-type amino acid transporters for cancer treatment

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Abstract

L-type amino acid transporters (LATs) mainly assist the

uptake of neutral amino acids into cells. Four LATs (LAT1, LAT2, LAT3 and LAT4) have so far been identified. LAT1 (SLC7A5) has been attracting much attention in the field of cancer research since it is commonly up-regulated in various cancers. Basic research has made it increasingly clear that LAT1 plays a predominant role in malignancy. The functional significance of LAT1 in cancer and the potential therapeutic application of the features of LAT1 to cancer management are described in this review.

Key words: LAT1; Amino acid transporter; Molecular target drug; Amino acid starvation response; Signal transduction

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Core tip: The discovery of molecules preferentially expressed in cancer cells is extremely valuable for the development of molecular target drugs in cancer therapy. Amino acid transporters have been receiving a great amount of attention as a candidate of such molecular targets. This review summarizes new initiatives for clinical applications of the basic research relative to L-type amino acid transporters, which are commonly expressed in cancers.

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INTRODUCTION

Cancers consume a huge amount of materials for biochemical reactions, and a continuous supply of sufficient nutrients is essential for their survival. Hydrophilic nutrients are delivered into cells by transporters.

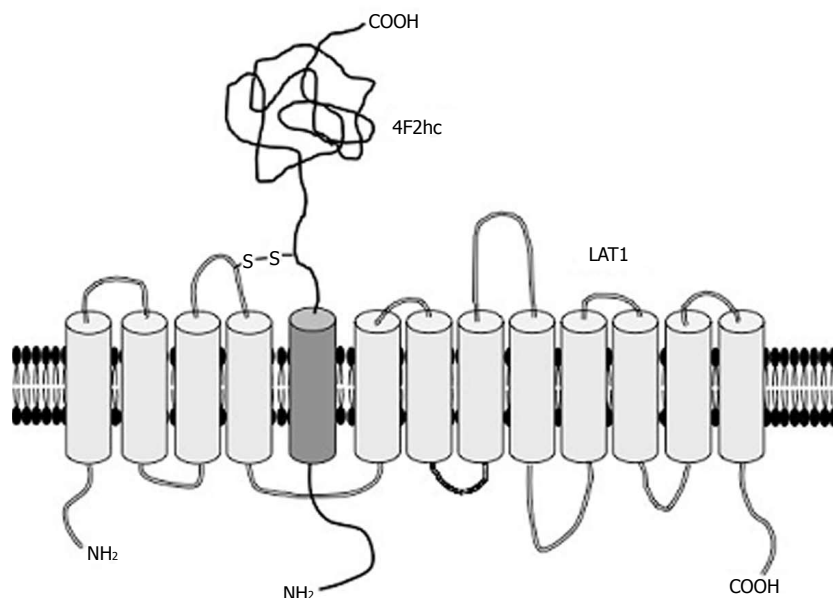


Figure 1 Structure of LAT1. LAT1 is composed of 12 transmembrane helices that are predicted to form a cylindrical conformation penetrating the cellular membrane. LAT1 associates with 4F2hc for stable localization at the cellular membrane. LAT2 is similar in structure to LAT1, whereas LAT3 and LAT4 function independently of 4F2hc.

Recent studies have revealed several transporters preferentially expressed in cancers. Inhibition of cancer specific-nutrient transporters would be a good strategy for cancer management with minimal side effects. Indeed, a therapeutic approach using transporter inhibitors for cancer prevention has been proven to be efficacious in cell lines and animal experiments and is now under evaluation in a clinical trial.

L-TYPE AMINO ACID TRANSPORTERS

Many cells take advantage of transporters to incorporate what is necessary at the time of need. Transporters fall into two broad categories based on ATP dependency for their transport form^[1]. ATP-dependent transporters, known as ATP-binding cassette, hydrolyze ATP to obtain the energy for translocation of their substrates across the membrane (active transport). Transporters with no ATPase, called solute carriers (SLCs), facilitate diffusive transport. Each SLC transporter is named in combination with the family numeral based on the sequence similarity and individual number with letter A between them (e.g., SLC3A2), with a few exceptions. Most of the amino acid transporters were formerly categorized into several groups ("System") on the basis of their substrates and sodium dependency (e.g., System L, which incorporates neutral amino acids without sodium), but they are currently classified into SLCs according to their protein homology.

L-type amino acid transporters (LATs) are categorized as system L transporters. LATs mainly deliver neutral amino acids into cells in a sodium-independent manner. So far, four LATs have been identified.

LAT1 (SLC7A5) was identified as the first LAT by

two groups in 1998^[2,3]. The major substrate of LAT1 is large neutral amino acids as typified by leucine. The expression of LAT1 in normal adults is detected in proliferative zones of gastrointestinal mucosa, testicular sertoli cells, ovarian follicular cells, pancreatic islet cells, and some endothelial cells that serve as a barrier between tissues (blood-brain, blood-retinal and blood-follicle barrier)^[4]. Recent studies revealed a crucial role of LAT1 in activated T cells^[5,6]. As described below, LAT1 expression is commonly up-regulated in various cancers.

LAT2 (SLC7A8) was subsequently isolated on the basis of sequence similarity to LAT1^[7-9]. LAT2 has broader specificity of its substrates including polar uncharged and small neutral amino acids than that of LAT1^[8]. LAT2 is ubiquitously expressed in normal body^[4], though LAT2 knockout mice show a mild phenotype and almost no visible symptoms except aminoaciduria^[10]. Both LAT1 and LAT2 are composed of 12 transmembrane domains that form the pathway of their substrates^[11] (Figure 1). They associate with the heavy glycoprotein subunit 4F2hc (SLC3A2) by sulfur bond^[11]. Although 4F2hc does not seem to have a function to directly transfer the substrates, it makes the localization of its partner LATs more stable at the plasma membrane^[12].

LAT3 (SLC43A1) was isolated by expression cloning from hepatocarcinoma cells^[13]. Sequence analysis revealed that LAT3 was identical to POV1, which was originally identified as a cancer-up-regulated gene^[14,15]. The substrate selectivity of LAT3 was similar to that of LAT1. LAT3 mRNA is expressed in the liver, skeletal muscle, and pancreas^[16]. The physiological role of LAT3 in normal individuals of mammals remains unknown,

but it was shown that LAT3 functions for podocyte development in zebrafish^[17].

LAT3 appears to behave as a critical transporter in several cancers. LAT3 is up-regulated in response to androgen and knockdown of LAT3 expression by RNA interference (RNAi) significantly inhibits the leucine uptake and cell proliferation in human prostate cancer cell lines *in vitro*^[18]. Furthermore, high expression of LAT3 is detected in prostate cancer patients, and stably knockdown of LAT3 by RNAi in human prostate cancer cell lines results in decrease of their growth and metastatic potential with alteration of cell cycle gene expression after xenografts into mice^[19].

LAT4 (SLC43A2) was identified by searching for sequence homology to LAT3^[20]. LAT4 is expressed in the basolateral membrane of the small intestine, kidney proximal tubule and thick ascending limb epithelial cells. LAT4 knockout mice are smaller than their controls and die within 9 d, presumably because of defective amino acid absorption^[21]. Unlike LAT1 and LAT2, LAT3 as well as LAT4 functions independently of heavy chain.

LAT1

LAT1 is the most extensively studied transporter among LATs. The interest in LAT1 is because of its extremely high expression in diverse human cancers. LAT1 was originally cloned from mRNA of C6 glioma cells^[2]. Subsequent studies have shown that LAT1 is highly expressed in many cancer cell lines. Histological analysis with qualitatively enhanced antibodies confirmed potent expression of LAT1 in human cancers in a broad range of tissues. The number of cancer types that were reported to express a high level of LAT1 is well above twenty (Table 1). LAT1 is thus a commonly up-regulated amino acid transporter in multiple human cancers. Furthermore, LAT1 expression level appears to be associated with prognosis of cancer patients. For example, elevated expression of LAT1 correlates with an adverse prognosis in prostate^[22], gastric^[23], and pancreatic cancers^[24], suggesting that higher-grade tumors are more dependent on LAT1. Not only the expression of LAT1 but also the functional significance of LAT1 in cancers has been verified by use of its inhibitors, by knockdown with RNAi and by gene disruption. 2-Aminobicyclo (2,2,1) heptane-2-carboxylic acid (BCH) is an inhibitor of system L transporters. BCH inhibits leucine uptake and strongly suppresses the proliferation of many cancer cells (Table 1). Genetic manipulation confirmed the functional significance of LAT1 in cancer cells. Knockdown of LAT1 with RNAi^[25-29] as well as genetic disruption of *LAT1* by zinc fingers nucleases-mediated gene knockout^[12] in cancer cells reduces leucine uptake and cell proliferation, indicating that LAT1 is a predominant transporter that is essential for growth of cancers. The reason that so many cancers use LAT1 despite the presence of many other amino acid transporters might be that LAT1 has a prominent capability for substrate transport. Indeed,

the affinity of LAT1 for leucine is much higher than that of LAT2^[30], although LAT2 is ubiquitously expressed in the normal body^[4]. Cancers may therefore be more dependent on LAT1 for rapid uptake of sufficient amino acids, whereas normal cells need less amino acid delivery that can be supported by LAT2.

The definite effect of LAT1 on the growth of various cancer cell lines prompted researchers to apply the LAT1 inhibitor in a clinical setting. However, the concentration of BCH required for suppression of cancer growth is extremely high (usually around 10 mmol/L). Moreover, the unselective effect of BCH that inhibits all LATs is another problem, since LATs other than LAT1 are considered to have functions in the normal body. It has been necessary to develop drugs that act on just LAT1 but not other transporters at a low concentration. In 2010, Endo and colleagues designed a new compound named JPH203 ((S)-2-amino-3-(4-((5-amino-2-phenylbenzo[d]oxazol-7-yl) methoxy)-3,5-dichlorophenyl) propanoic acid)^[31]. JPH203 has structural analogy to tyrosine, but it inhibits only LAT1 without affecting any other LATs. JPH203 displayed potent suppressive effects on the growth of cancers *in vitro*^[12,32,33]. Moreover, this compound has the ability to powerfully inhibit the proliferation of tumor cell lines of the colon and leukemia injected into nude mice^[31,33]. Following improvements in its specificity and pharmacological effect, JPH203 is under evaluation in a phase I clinical trial of cancer patients.

CLINICAL APPLICATION OF LAT1

Positron emission tomography

By exploiting the characteristics of LAT1 expression, an approach for the diagnosis of cancers through radiolabeled substrates of LAT1 has been attempted. [¹⁸F] or [¹¹C]-labeled compound administered into the body can be visualized by positron emission tomography (PET)^[34]. Cancers incorporating an isotopically labeled probe can be located by tracing the body with PET. In the past, 2-¹⁸F-fluoro-2-deoxy-d-glucose ([¹⁸F]FDG) was one of the most commonly used probe for diagnosis of cancer with PET. This strategy exploits the characteristic of cancers consuming a huge amount of glucose compared to that consumed by normal cells. Although [¹⁸F]FDG has been of assistance in the clinical diagnosis of many cancers, it sometimes showed false positive results, especially in brain, because even normal brain cells take up a relatively large amount of glucose. To overcome this problem, amino acids have attracted attention as alternative probes to glucose. Representative amino acids or their analogs developed as probes of PET are L-3-[¹⁸F]-fluoro- α -methyl tyrosine ([¹⁸F]FAMT), 6-¹⁸F-fluoro-L-3,4-dihydroxy-phenylalanine (¹⁸F-DOPA), L-[¹¹C-methyl] methionine ([¹¹C]MET) and O-(2-[¹⁸F]fluoroethyl)-L-tyrosine ([¹⁸F]FET). If the compounds are delivered into cells specifically through LAT1, those cells are likely to be cancers. Indeed,

Table 1 Summary of studies for expression and functions of LAT1 in cancers

Cancer	Expression (method of detection)	Inhibition of amino acid uptake by	Growth inhibition by	Ref.
Biliary tract	Immunohistochemistry	BCH	BCH	[71]
Bladder	Northern blot (cell line)	BCH		[72]
Bone	Immunohistochemistry			[73]
Brain	Immunohistochemistry, RT-PCR (cell line), Western blot (tissue, cell line)	BCH	BCH	[74,75]
Breast	Immunohistochemistry, RT-PCR (cell line)	BCH	RNAi, BCH	[29,76-78]
Colon	Western blot (cell line)	Knockout (cell line)	Knockout (cell line) JPH203	[12]
Esophagus	Immunohistochemistry			[79,80]
Hepatocyte	Immunohistochemistry			[81]
Gastrointestine	Immunohistochemistry, Western blot (cell line)		RNAi	[23,45]
Laryngeal	Immunohistochemistry			[82]
Leukemia	RT-PCR (cell line)		BCH, JPH203	[33]
Lung	Immunohistochemistry			[41,83-85]
Melanoma	Immunohistochemistry, Microarray (tissue), Western blot (cell line)	BCH		[86,87]
Myeloma	RT-PCR (cell line)	RNAi		[88]
Neuroendocrine	Immunohistochemistry, RT-PCR (tissue), Western blot (tissue)			[89]
Ovarian	Immunohistochemistry, RT-PCR (cell line), Western blot (tissue, cell line)	BCH	BCH	[47,65,90]
Oral	RT-PCR (cell line)	RNAi	RNAi	[25]
Pancreas	Immunohistochemistry Western blot (cell line)	RNAi	RNAi	[24,27,91]
Pleura	Immunohistochemistry			[92]
Prostate	Immunohistochemistry, Western blot (cell line)	RNAi, BCH	RNAi, BCH	[18,19,22,28]
Tongue	Immunohistochemistry			[93]
Thymus	Immunohistochemistry, Western blot (cell line)	JPH203	JPH203	[94,95]
Urinary tract	Immunohistochemistry			[96]

RT-PCR: Reverse transcription polymerase chain reaction; BCH: 2-aminobicyclo (2,2,1) heptane-2-carboxylic acid.

[¹⁸F]FAMT images accord well with LAT1 distribution^[35]. Moreover, FAMT is incorporated by LAT1 but not by other amino acid transporters^[35]. Although there is still room for improvement in its specificity, this method is powerful tool for diagnosis of cancers including microcarcinoma.

Boron neutron capture therapy

LAT1 is an attractive molecular target for boron neutron capture therapy (BNCT). BNCT is an anticancer therapy that utilizes high linear energy transfer alpha particles. Particle radiation is produced by fission reaction when irradiated thermal neutrons collide with boron incorporated by a malignant tumor. The traveling distance of particle radiation is limited (5-9 μm), and it therefore disrupts only cancer cells incorporating boron without damage to other cells around target cells^[36,37]. A key component of BNCT success is accumulation of boron specifically in cancer cells. This difficult task could be achieved by the synthesis of a boron compound that is selectively delivered by LAT1. Indeed, p-boronophenylalanine (BPA), a boron compound commonly used in BNCT, is incorporated by LAT1^[38-40], suggesting that LAT1 is an optimal mediator for delivery of boron in BNCT. However, since we cannot still completely rule out the possibility of BPA uptake by other transporters, it is necessary to develop compounds that exhibit strict selectivity to LAT1. BNCT has accomplished certain clinical outcomes so far, but the problem in the

past was that it required a large-scale nuclear reactor to generate neutrons. However, a compact accelerator has been developed as an alternative to a nuclear reactor and it can be installed in a hospital, making BNCT easier to perform. Such technology will expand the applications of BNCT in the future.

LAT1 AND METASTASIS

It has been suggested that LAT1 is involved in cancer metastasis. A number of studies have shown a correlation of increase in LAT1 expression with metastasis of multiple cancers. Lymph node metastasis-positive squamous cell carcinomas express LAT1 whereas there is no positive signal of LAT1 in metastasis-negative cells^[41]. LAT1 mRNA level was significantly higher in renal cell carcinoma with metastasis^[42]. A group of cells with high LAT1 expression showed a larger size of the metastatic lesion of gastric carcinoma^[43]. LAT1 expression in neuroendocrine tumors was significantly associated with lymph node metastasis^[44]. The potency of the functional significance of LAT1 in metastasis has been shown. Knockdown of LAT1 by RNAi inhibited the migration and invasion of gastric cancer^[45] and a cholangiocarcinoma cell line^[46]. BCH inhibited the proliferation and migration of a human epithelial ovarian cancer cell line^[47]. On the basis of these findings, inhibition of LAT1 will be good strategy to prevent metastasis of cancer. However, it remains to

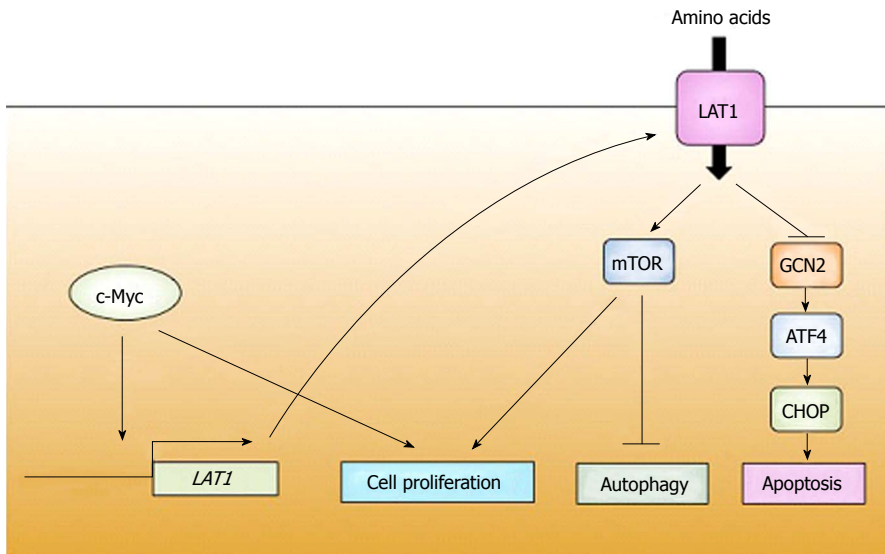


Figure 2 Schematic model of acquisition and monitoring of amino acids in cancer. c-Myc promotes expression of LAT1, which supplies amino acids necessary for growth of cancers. The availability of amino acids is constantly monitored by factors such as mTOR and GCN2. Once amino acid deficiency is detected, cancers suppress their proliferation and, as occasion demands, induce apoptosis. mTOR: Mechanistic target of rapamycin; GCN2: General control non-derepressible 2; ATF4: Activating transcription factor 4; CHOP: C/EBP homologous protein.

be determined whether the metastasis defect is derived from amino acid starvation or from other factors such as an aberrance of adhesion molecules. It would thus be valuable to investigate the relevance of LAT1 and integrin in metastasis, since they form a complex^[48].

MECHANISM OF LAT1 EXPRESSION

Although it remains unknown how LAT1 expression is facilitated in cancers, some possible molecular mechanisms have been proposed. c-Myc, a proto-oncogenic transcription factor, has been demonstrated to be an upstream of LAT1. The expression of c-Myc in normal adults is generally low^[49], but overexpression of c-Myc triggered by some cues such as gene amplification, gene translocation or other gene mutations^[50] is responsible for malignant transformation. Numerous human cancer tissues strongly express c-Myc. Target genes of c-Myc include many factors involved in progression of the cell cycle^[51]. On the other hand, the consensus binding sequence of c-Myc is also located at the *LAT1* promoter^[27]. Moreover, knockdown of c-Myc leads to reduction of LAT1 expression in cancer cell lines^[27]. These results suggest that up-regulation of LAT1 is mediated, at least in part, by c-Myc (Figure 2). Of note is that c-Myc also enhances the metabolic reprogram in cancers by promoting the expression of enzymes of glycolysis and glucose transporter^[52,53]. This is an ingenious strategy of cancers since they can coordinate multiple events required for cell growth by just one factor.

Some other factors appear to regulate LAT1 expression. Hypoxia-inducible factor (Hif) is a critical regulator in response to hypoxia. Hif2 α , an isoform of the Hif family, binds to the *LAT1* promoter and enhances LAT1 expression in renal carcinoma cell

lines^[54]. Artificial manipulation to elevate Hif2 α activity induces LAT1 expression in lung and liver tissues, in which LAT1 expression is usually low^[54]. Aryl hydrocarbon receptor (AHR) is a transcription factor that is activated by interaction with its ligands such as dioxin, and it promotes tumorigenesis^[55]. AHR binds to its consensus binding sequence in *LAT1* and drives LAT1 expression in breast cancer cell lines^[56], suggesting that LAT1 contributes to tumorigenesis induced by an environmental carcinogen. As described previously, T cell activation induces LAT1 expression^[5,6]. Nuclear factor kappa B, AP-1 and nuclear factor of activated T-cells are critical transcription factors that are activated by T cell stimulation and enhance immunological reactions. The expression of LAT1 is prevented by inhibitors of these transcription factors^[5,6]. This means that LAT1 expression is induced by the common regulators that also boost immunological reaction in T cells.

DOWNSTREAM OF LAT1

Ensuring a sufficient supply of nutrients is an issue of vital importance for cancers. The majority of cancers are thought to constantly monitor the availability of amino acids. Starvation of amino acids rapidly induces a stress response that puts a brake on cellular biochemical reactions to avoid wasting energy and materials. The most extensively studied system for monitoring the amino acid availability is mechanistic target of rapamycin (mTOR)^[57], a serine-threonine kinase. Plenty of amino acids maintains mTOR kinase activity, resulting in progression of the cell cycle, protein synthesis, or inhibition of autophagy induction (Figure 2). Some mTOR regulators such as SLC38A9^[58-60], Cellular arginine sensor for mTORC1 (CASTOR1)^[61] and Sestrin2^[62] have

been demonstrated to associate with amino acids to dictate mTOR activity. Dissociation of those interactions caused by amino acid deficiency inactivates mTOR and inverses the reaction of its downstream, resulting in a halt of cancer growth. Growing evidence suggests that LAT1 disruption leads to the inhibition of mTOR. LAT1 inhibition decreases mTOR activity in many cancer cell lines^[28,33,63-65]. These findings suggest that the arrest of cell growth of cancers by a defect of LAT1 is derived from inactivation of mTOR (Figure 2). mTOR inhibitors are being used in practical trials for therapeutic management of several cancers^[66]. Application of JPH203 together with an mTOR inhibitor probably creates a synergistic effect and might be useful for maximizing the benefit of treatment with a low-dose drug, which would help to minimize adverse effects.

General control non-derepressible 2 (GCN2) is another factor for detection of amino acid starvation^[67]. GCN2 is a serine-threonine kinase that is activated by amino acid deficiency. Uncharged tRNAs caused by a decline of amino acid concentration activates GCN2, which eventually induces activity of activating transcription factor 4 (ATF4). ATF4 regulates the expression of genes responsible for coping with amino acid deficiency^[68]. Several studies have shown that dysfunction of LAT1 initiates the GCN2 signal. JPH203 promotes the expression of C/EBP homologous protein [CHOP, also known as DNA damage inducible transcript 3 (DDIT3)], which is up-regulated by ATF4^[68] and probably takes part in apoptosis in leukemia^[33]. Gene disruption of LAT1 in cancer cell lines activates the GCN2-ATF4 cascade^[12]. Activation of ATF4 by LAT1 defect was also shown in cells other than cancer. JPH203 triggers the expression of CHOP^[5,69] and homeobox B9^[70], a novel target of ATF4, in human T cells to repress cytokine production. These findings suggest that GCN2-ATF4 is another critical system for detecting amino acid deficiency evoked by LAT1 inhibition (Figure 2).

CONCLUSION

After the importance of LAT1 in cancer cells had been established, basic studies on LAT1 have progressed with remarkable speed. Better still, research achievements are potentially capable of technical developments for the use of LAT1 as a molecular target in clinical practice. However, although JPH203 is more effective and specific than BCH, it still requires a high concentration for sufficient suppression of the growth of cancers, and wariness of adverse effect persists. Nevertheless, such concerns might be overcome, at least for the time being, by virtue of the proper combinational use of multiple drugs with different action points in cellular metabolism (*e.g.*, mTOR inhibitor). However, further improvements in selectivity of the inhibitor, boron donor of BNCT and PET probe to LAT1 will raise the quality of cancer treatment. Besides, although not to the extent to LAT1, there are several cancers that rely on LAT3

for their growth and development of a LAT3-specific inhibitors is also encouraged. Advances in technologies are expected to resolve such issues.

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