Mini-Review

DOI: 10.5582/irdr.2015.01024

The role of L-type amino acid transporter 1 in human tumors

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Summary **L-type amino acid transporter 1 (LAT1) is an L-type amino acid transporter and transports large neutral amino acids such as leucine, isoleucine, valine, phenylalanine, tyrosine, tryptophan, methionine, and histidine. LAT1 was found to be highly expressed especially in human cancer tissues, and up-regulated LAT1 can lead to dysfunction in human tumor cells. These findings suggest that LAT1 plays an important role in human tumors. This review provides an overview of the current understanding of LAT1 expression and its clinical significance and function in tumors.**

Keywords: LAT1, human tumor, proliferation, angiogenesis

1. Introduction

Cancer cells require a large amount of nutrients and amino acids for rapid growth and continuous proliferation. This situation is facilitated by the upregulation of amino acid transporters. Amino acid transporters located on the plasma membrane facilitate the movement of amino acids cross the cytoplasm. System L is a major transport system providing cells with large neutral amino acids, including branched or aromatic amino acids (*1*). To date, four L-type amino acid transporters (LATs), LAT1-LAT4, have been identified at the molecular level. LAT1 has been found in many malignant cells, while LAT2 functions in the epithelium of the kidney proximal tubules and digestive tract. LAT3 and LAT4 have been localized to the apical plasma membrane of podocytes and to the distal tubules and collecting ducts (*2*).

Among the known LATs, LAT1 has garnered particular attention because of its limited distribution and higher expression in malignant tumors. Previous studies have demonstrated that LAT1 is regulated in various tumors to increase amino acid transport (*3*). LAT1 can transport large neutral amino acids such leucine, isoleucine, valine, phenylalanine, tyrosine, tryptophan, methionine, and histidine (*4-6*). Encoded by *SLC7A5*, the 55-kD protein forms 12 putative transmembrane domains (*7*), and the functional expression of LAT1 requires covalent association of the heavy chain of 4F2 cell surface antigen (CD98) (*8*). LAT1 is also an exchanger, and it can exchange intracellular glutamine for external large neutral amino acids. The apparent affinity for large neutral and aromatic amino acids is in the physiological micromolar range on the extracellular portion and up to 100-fold higher on the cytosolic portion of the transporter (*9*).

Because of its proposed role in supplying nutrients necessary for tumor growth and proliferation, LAT1 may be a critical target for cancer intervention. The current review provides an overview of the current understanding of the clinical significance of LAT1 expression and its function in tumors.

2. Expression of LAT1 in various tumors

Although LAT1 can provide essential amino acids for normal cell growth, its expression is limited to organs such as the brain, spleen, thymus, and testes. Importantly, however, LAT1 is also highly expressed in human cancer tissues (*10,11*), including cholangiocarcinoma, multiple myeloma, malignant glioma, and lung, uterine cervical, oral, prostate, and breast cancer. The use of molecular techniques has revealed that the level of LAT1 expression in malignant tumor tissues is significantly higher than that in surrounding healthy tissues and benign tumor tissues. Moreover, the expression of LAT1

Released online in J-STAGE as advance publication September 8, 2015.

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in malignant tumor tissues with distant metastasis is higher than that in tissues without distant metastasis., LAT1 is over-expressed in human gliomas and is predominantly expressed in the vascular endothelium and the cytoplasm of tumor cells, as well as in the plasma membrane of tumor cells (*12*). In addition, the level of LAT1 expression is higher in infiltrating glioma cells than in cells located in the center of a tumor (*13*). These findings suggest that LAT1 may be associated with the metastasis of tumors in humans. Similar results were reported for uterine cervical carcinoma, in which LAT1 expression is limited to the basal layer of normal squamous epithelium, and the level of LAT1 expression in invasive squamous cell carcinoma is significantly higher than that in cervical intraepithelial neoplasia (*14*). In the lungs, LAT1 is not detected in normal epithelial cells but its expression is noted in non-small lung cancer; in addition, LAT1 expression is significantly higher in patients with mediastinal lymph node metastases than in patients without those metastases (*8*). Interestingly, non-solid tumors also display altered LAT1 expression: LAT1 acts an activation antigen in T lymphocytes and T-cell leukemia results in higher levels of LAT1 expression compared to normal activated T cells (*15*). The distribution, level of expression, and methods of detection of LAT1 are summarized in Table 1.

Thus, a wealth of evidence indicates that the level of LAT1 expression is abnormally high in human cancer cells. However, the mechanism underlying this expression remains unclear. Yamauchi *et al*. reported that LAT1 can activate the mammalian target of the rapamycin (mTOR) signaling pathway, which plays an important role in protein synthesis and energy supply (*16*). However, few studies have identified the molecular mechanisms by which LAT1 may be promoting tumorigenesis.

3. The biological activity of LAT1 in tumors

Since LAT1 is overexpressed in various types of tumors, the question of whether up-regulation of LAT1 leads to the transformation of human tumor cells, or whether its overexpression is a by-product of tumorigenesis, must be considered. Previous studies have reported that LAT1 can regulate multiple biological processes, including cell growth, invasion, and angiogenesis, that primarily characterize malignant tumors.

3.1. *LAT1 and tumor cell proliferation*

Amino acids are essential for protein synthesis, which is necessary for tumor cell growth. LAT1 can mediate amino acid uptake, and its upregulation in tumor cells suggests that LAT1 may promote tumor cell growth. Importantly, many studies have demonstrated that inhibition of LAT1 can reduce tumor cell proliferation.

Apoptosis, the major form of cell death, is deregulated in tumors, allowing their continuous growth. The upregulation of LAT1 in tumor cells may affect caspase activity, thereby altering apoptosis. Kim *et al*. reported that in KB, Saos2, and C6 cell lines, down regulation of LAT1 by 2-aminobicyclo-(2,2,1)-heptane-2-carboxylic acid (BCH) inhibits cell growth by activating apoptosis through the induction of caspase-3 and caspase-7 (*17*). Similarly, Kobayashi *et al*. reported that over-expression of LAT1 in gliomas with low endogenous expression of LAT1 significantly enhanced the rates of tumor cell growth in athymic mice but that treatment with BCH promoted apoptosis through the activation of caspases (*18*).

3.2. *LAT1 and tumor cell invasion*

Tumor invasion and metastasis are the major causes of morbidity and death in cancer patients. The supply of nutrients, and especially amino acids, is critical to this process. LAT1 upregulation is associated with tumor cell invasion, and down-regulated LAT1 can suppress tumor cell invasion. Indeed, cell migration and invasion were reduced after LAT1 knockdown in cholangiocarcinoma cells (*3*). Similarly, downregulation of LAT1 expression can inhibit the invasion and migration of gastric cancer cells (*19*). However, the exact mechanism underlying this process is not fully understood.

3.3. *LAT1 and tumor angiogenesis*

Angiogenesis is critical to tumorigenesis because new blood vessels are necessary to supply nutrients and oxygen and to dispose of metabolic waste products. Moreover, an enhanced vascular supply could reflect malignant potential. Many studies have demonstrated that LAT1 is associated with angiogenesis. Indeed, the protein is observed in vascular endothelium, and its level of expression is markedly associated with glioma microvessel density (*12*). Moreover, the expression of LAT1 is correlated with tumor angiogenesis as assessed by vascular endothelial growth factor expression, microvessel density, and vascular invasiveness of tumors (*8*).

4. Clinical significance of LAT1 in tumors

Since LAT1 functions as an amino acid transporter, its clinical significance in cancer can be traced to differences in amino acid transport within tumors. Several studies have noted an increased uptake of radio-labelled amino acids, including 6-18F-fluoro-L-3,4-dihydroxy-phenylalanine (^{18}F-DOPA), L-[3-^{18}F]-α-methyl tyrosine (^{18}F-FAMT), and anti-1-amino-3-[^{18}F]fluorocyclobutane-1-carboxylic acid (anti-[^{18}F] FACBC), in human cancers (*20*). The uptake of these radio-labelled amino acids is mediated by LAT1, with a direct correlation between uptake levels and levels

Table 1. Summary of reported distribution, level of expression, and methods of detection of LAT1 in human tumors

Link to disease	Expression	Method of detection	*Ref.*
Uterine cervical carcinoma	Higher in invasive squamous cell carcinoma than in cervical intraepithelial neoplasia	Immunohistochemistry	(*14,34*)
Non-small cell lung cancer	Higher in patients with mediastinal lymph node metastases than in those without	Immunohistochemistry, quantitative real-time PCR	(*4,27*)
Oral cancer	High	Immunohistochemistry	(*22,35,36*)
Breast cancer	High	Immunohistochemistry, quantitative real time PCR, Western blotting	(*37,38*)
Renal cell carcinoma	High	Quantitative real-time PCR	(*20*)
Esophageal squamous cell carcinoma	High	Immunohistochemistry	(*37*)
Leukemic	High	Western blotting	(*15*)
Cholangiocarcinoma	High	Quantitative real- time PCR	(*4*)
Multiple myeloma	High, associated with increased proliferation	Immunohistochemistry	(*39*)
Malignant gliomas	Higher in infiltrating glioma cells than in cells located in the center of the tumor	Immunohistochemistry	(*13*)
Gastric cancer	High	Quantitative real-time PCR, Western blotting	(*40*)
Prostate cancer	High	Immunohistochemistry	(*28,31,41*)
Thymic carcinomas	High	Immunohistochemistry	(*18*)

of LAT1 expression. In particular, LAT1 expression is significantly correlated with L-3,4-dihydroxy-(ring-2,5,6-3H) phenylalanine (^{3}H-*L*-DOPA) uptake in human gliomas *in vitro* and 18F-DOPA uptake *in vivo* (*21*). Similar, in oral squamous cell carcinoma the uptake of ^{18}F-FAMT is mediated by LAT1 expression. Moreover, ^{18}F-FAMT positron emission tomography (PET) imaging has displayed a higher specificity at detecting malignant lesions than 2-[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET (*22*). In breast cancer, over-expression of LAT1 is correlated with anti-[^{18}F] FACBC, which can serve as a potential biomarker for diagnosis of breast cancer (*23*). Thus, evidence has demonstrated that the relationship between radio-labelled amino acids and LAT1 expression can be used to diagnose cancer.

LAT1 may also be a promising molecular target for human cancer therapy. BCH, as an inhibitor of the system L amino acid transporters, suppresses cancer cell growth and migration. Specifically, inhibition of LAT1 has significant anti-tumor action on cholangiocarcinoma and augments the therapeutic efficacy of 5-fluorouracil (5-FU) and gemcitabine (GEM) (*4*). Inhibition of LAT1 by BCH also has anti-tumor action in non-small cell lung cancer. Moreover, BCH reduced mortality in a model involving C6 glioma-bearing rats (*24*). Importantly, though, BCH is not a highly specific inhibitor of LAT1. In contrast, JPH203, a novel tyrosine analog, has a high level of selectivity for LAT1. Administration of JPH203 can effectively induce suppression of cell growth and cell apoptosis in YD-38 human oral cancer cells (*25*) and also inhibit cell growth in human colon and leukemia cancer cells (*15,26*). The knockdown of human LAT1 by small interfering RNAs or stable transduction with lentivirus can also lead to the inhibition of cancer cell growth and migration (*27*). Similarly, down- regulating LAT1 can lead to decreased growth of prostate cancer cells (*28*) and human oral cancer cells (*29*). However, the over-expression of LAT1 has been suggested as a target for combination therapy with anti-proliferative aminopeptidase inhibitors to combat ovarian cancer (*30*). Recent studies have proposed that LAT1 may be useful as a targeted drug transporter (*31*). Nonetheless, further work is needed to uncover its potential utility in clinical settings.

To date, surgical resection is still the primary treatment for human cancer, but the prognosis after treatment remains poor. Therefore, clinical markers that can predict the response to a specific therapy and aid in determining prognosis should be identified. LAT1 has been used as a prognostic marker in a variety of tumors types. For example, a high level of LAT1 expression is a significant factor for predicting a poor outcome after surgical resection. Specifically, the over-expression of LAT1 is a pathological factor for predicting the prognosis for patients with surgically resectable stage III non-small cell lung cancer (*8*). Patients with hepatocellular carcinoma and a high level of LAT1 expression are reported to have a significantly shorter overall survival (*5*). Similarly, in prostate cancers, over-

expression of LAT1 can predict local progression under expectant management (*32*). Over-expression of LAT1 can also serve as a novel independent biomarker of high-grade malignancy, which can be utilized together with the Gleason score, to assess prognosis (*33*). Thus, LAT1 may be useful as a prognostic marker to predict a poor outcome after surgical resection.

5. Conclusions and perspectives for the future

In conclusion, LAT1 plays a critical role in the formation and development of cancer, and a high level of its expression apparently has clinical significance. As LAT1 is studied, new opportunities are arising to determine the mechanisms of tumor origin and progression. Thus, the potential exists to prevent, diagnose, assess, and treat malignancies by intervening in LAT1 expression or activity. Although promising, further studies are needed to discover and optimize its therapeutic uses in the future.

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(Received June 19, 2015; Revised August 14, 2015; Accepted August 18, 2015)