茨城県立医療大学紀要　第25巻
A S V P I Volume 25

Review Article

Radiolabeled Molecular Imaging Agents for Amino Acid Transport in Tumors

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Abstract

About 50 types of amino acid transporter genes have been reported in mammals. Among these transporters, LAT1 (SLC7A5), LAT3 (SLC43A1), ASCT2 (SLC1A5), $ATB^{0,+}$ (SLC6A14) and xCT (SLC7A11) are reported as the upregulation-dependent transporter isoforms in tumors. In the current molecular imaging era, particularly over the past decade, the development of radiolabeled molecular imaging agents for amino acid transport in tumors using natural/non-natural amino acids based on gene information and biotechnology is an emerging trend. Promising molecular probes for the post-FDG are ^{18}F-3-iodo-α-methyl-L-tyrosine, *O*-(2-^{18}F-fluoroethyl)-L-tyrosine, and ^{18}F-*anti*-1-amino-3-fluorocyclobutane-1-carboxylic acid. Furthermore, development of immunoPET/SPECT agents for imaging every specific amino acid transporter is anticipated as a new strategy. This review focuses on membrane transporters belonging to the solute carrier (SLC) superfamily, which is responsible for amino acid transport activity in tumor imaging and radioactive tumor imaging agents.

Key words: amino acid transporter, Post-FDG, solute carrier, tumor

1. Introduction

In the 1990s, the genes of various transporters were cloned, thus rapidly advancing the clarification of expression, structure and function of those transporters.[1)] It is known that some types of amino acid transport systems are upregulated in tumor cells.[2-4)] The reason behind this is attributed to the fact that tumor cells require amino acids as nutrition blocks for active proliferation.

Our previous report demonstrated the selectivity of radiolabeled artificial amino acid accumulation via an upregulated transporter isoform in tumors using *Xenopus leavis* oocytes expressing isoforms of neutral amino acid transporters.[5,6)] The upregulated transporter isoforms in tumor cells gradually became clarified as an imaging target. The development of tumor radiopharmaceuticals with radiolabeled amino acid compounds using gene information and biotechnology is a new trend in the current molecular imaging era.

Table shows the classification of solute carrier transporter (SLC) transporter superfamily and ATP-binding cassette transporter (ABC) transporter superfamily by Human Genome Organization (HUGO). This review focuses on membrane transporters of the SLC superfamily responsible for amino acid transport activity in tumor cells and the radioactive molecular imaging agents involving them.

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Table. HUGO (Human Genome Organization) transporter families.

I. SLC (Solute carrier transporter) transporter super-family *
There are more than 60 families and more than 300 molecular species.
Amino acid transporters (neutral amino acid transporters: system A, system ASC, system L, etc., acidic amino acid transporters, basic amino acid transporters): Solute Carrier family 2, 7, 17, 23 and43.
II. ABC (ATP-binding cassette transporter) transporter super-family#
Transporters that use adenosine triphosphate (ATP) as the driving force for mass transport. Currently, 7 families and 49 molecular species have been identified.
ABCA: ABC I family ABCC: MDR/TAP family ABCD: ALD family ABCE: OABP family ABCF: GCN20 family ABCG: WHITE family

See a home page of HUGO Gene Nomenclature Committee at the European Bioinformatics Institute
*: https://www.genenames.org/cgi-bin/genefamilies/set/752
#: https://www.ncbi.nlm.nih.gov/books/NBK3/table/A145/

2. Amino acid transport

2.1 Amino acid metabolic pathways.

In addition to sugars and lipids, amino acids are very important cellular nutrition sources.[7] Figure 1 is a scheme showing amino acid metabolic pathways and the synthetic precursors of important substances such as proteins and neurotransmitters (biogenic amines). It is known that large amounts of amino acids accumulate in cells with active proliferation and metabolic processes via membrane transport systems.[8] Moreover, amino acid transporters and their substrates interact with the mammalian target of rapamycin pathway, which regulates protein synthesis and cell proliferation.[9]

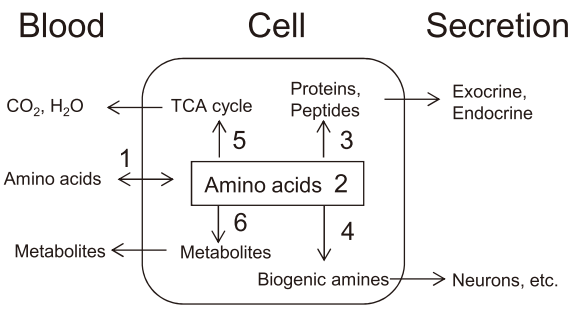


Fig. 1. Scheme showing amino acid metabolic pathways. 1. Membrane transport, 2. Free amino acid pool, 3. Protein synthesis, 4. Biogenic amine synthesis, 5. Energy-producing metabolism, and 6. Catabolism.

Radiolabeled amino acids have the potential to be used not only for amino acid transport imaging, but also for imaging various amino acid metabolic pathways. For example, L-[2-^{18}F]fluorotyrosine (2-^{18}F-Tyr) was evaluated as a tracer of cerebral protein synthesis for positron emission computed tomography (PET) by Coenen HH *et al*..[10] The authors reported that 2-^{18}F-Tyr is a promising tracer for quantification of protein synthesis rates with PET.[10] Hustinx R *et al*. evaluated the ability of PET with 2-^{18}F-Tyr to visualize cancer lesions in patients.[11]

Amino acid transport imaging for tumor diagnosis is one of the clinical applications, in addition to its fundamental importance as the first step in elucidating the underlying metabolic and signaling pathways.

2.2 Amino acid transport systems.

Amino acid transport across the plasma membrane is mediated via amino acid transporters localized in the plasma membrane.[12] Since the 1960s, studies on amino acid transporters have been performed with cell lines or tissues, using natural and artificial amino acids that inhibit specific aspects of amino acid transport in the so-called "amino acid transport system".[13,14]

Amino acids are classified into neutral amino acids, acidic amino acids and basic amino acids. For neutral

amino acid transport, according to the classification as neutral amino acid transport systems, the three main transport systems are system A, ASC and L. System A (alanine preferring: specific inhibitor is *N*-methylated-α-aminoisobutyrate (MeAIB)) and system ASC (alanine, serine and cysteine preferring: specific inhibitor is not known) are Na^+-dependent systems that transport amino acids with relatively small residues. System L (leucine preferring: specific inhibitor is 2-aminobicyclo[2.2.1]heptane-2-carboxylic acid (BCH)) is a Na^+-independent system that transports amino acids with bulky and relatively large residues.[14] Among the amino acid transport systems described, system L is a major route for providing cells with large neutral amino acids including branched or aromatic amino acids.[1,13]

Previously, we examined amino acid transport system L selectivity of ^{14}C(U)-L-tyrosine (^{14}C-Tyr), ^{125}I-4-iodo-L-meta-tyrosine (4-^{125}I-mTyr), ^{125}I-6-iodo-L-meta-tyrosine (6-^{125}I-mTyr), ^{125}I-3-iodo-α-methyl-L-tyrosine (^{125}I-IMT) and ^{125}I-3-iodo-L-tyrosine (3-^{125}I-Tyr) using Chinese hamster ovary cells (CHO-K1)[15] and *Xenopus* oocytes. We reported that ^{125}I-4-iodo-L-meta-tyrosine exhibited the greatest system L specificity (93.46 ± 0.13%) of five tested amino acids, and it could be used as a system L-specific ^{123}I-labeled system L imaging probe for single photon emission computed tomography (SPECT) (Figure 2).

2.3 Important amino acid transporters in tumor cells.

There are two superfamilies of transporter proteins, SLC and the ATP-binding cassette (ABC) transporters. Molecular cloning technology has revealed about 50 types of mammalian amino acid transporters, reflecting amino acid structural divergence. At present, the SLC genes are classified into various families, from SLC1 to SLC52, according to the standards established by the Human Gene Nomenclature Committee (http://ghr.nlm.nih.gov/geneFamily/slc). Genes encoding amino acid transporters belong to the SLC1, SLC3, SLC6 and SLC7 families. Of these, neutral amino acid transporters belong to the SLC1 and SLC3 families. Among these transporters, LAT1 (SLC7A5),[16] LAT3 (SLC43A1),[17] ASCT2 (SLC1A5),[18] $ATB^{0,+}$ (SLC6A14)[19] and xCT (SLC7A11)[20] are reported as the upregulation-dependent transporter isoforms in tumors. Figure 3 shows the mechanisms and main substrates of those important transporter isoforms.

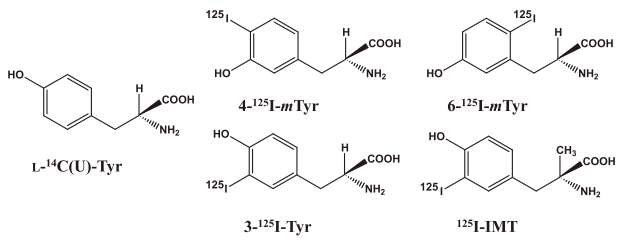


Fig. 2. Tyrosine and iodinated tyrosine analogues as candidate compounds for system L-specific imaging agents.

2.3.1 System L1: L-type amino acid transporter 1 (SLC7A5).

In 1998, Kanai *et al*. isolated a cDNA encoding a Na^+-independent transporter, subserving the amino acid transport system L by expression cloning from C6 rat glioma cells.[16] The authors examined the function of the human isoform and its expression in human tissues and tumor cell lines.[21] L-type amino acid transporter 1 (LAT1) preferentially transports large neutral amino acids such as Leu, Ile, Val, Phe, Tyr, Trp, Met and His.[16] LAT1 is a 12-segment transmembrane protein that shares about 30% homology with the cationic amino acid transporter (CAT) subfamily. This protein expresses its function by forming a heterodimer with a single transmembrane protein called 4F2hc.[16, 21]

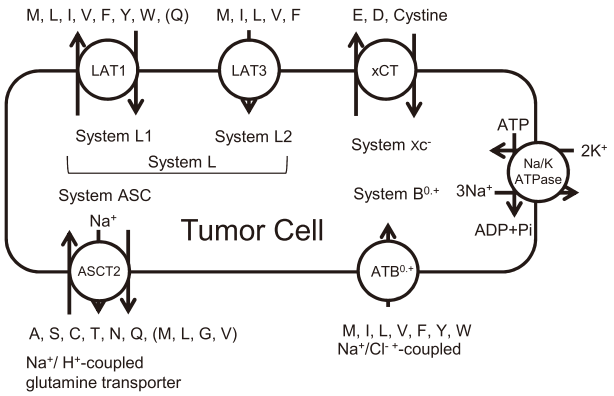


Fig. 3. Schematic depiction of important amino acid transporter isoforms in tumor imaging. Amino acid substrates are shown in one-letter code. The sodium ion gradient is maintained by the Na-K-ATPase. The system L1 and ASCT2 transporters are amino acid exchangers. ASCT2 co-transports one sodium ion into the cell, while one amino acid is removed from the cell. $ATB^{0,+}$ is a Na^+/Cl^--coupled co-transporter. LAT3 is a Na^+/Cl^--independent transporter.

Segawa *et al*. isolated L-type amino acid transporter 2 (LAT2) cDNA in 1999 from rat small intestine.[22] The encoded protein demonstrates amino acid sequence homology to the system L transporter LAT1 (50% identity). LAT2-mediated transport is not dependent on Na^+ or Cl^- and is inhibited by a system L-specific inhibitor BCH.[22]

Among the two isoforms belonging to the system L1 family, LAT2 is expressed in normal tissues including kidney and intestine, whereas LAT1 is expressed in many types of tumors as well as in normal tissues. LAT1 should be considered as a promising target of molecular imaging agents for amino acid transport in tumor cells, because LAT1 is over expressed in higher almost kind of tumor than normal tissue.

Recently, transporter isoform selectivity of imaging probes has been reported. Shikano N *et al*. examined the isoform selectivity of 3-^{125}I-Iodo-α-methyl-L-tyrosine (^{125}I-IMT) transport of the two human L-type amino acid transporters, hLAT1 and hLAT2, with human 4F2hc-coexpressed *Xenopus* oocytes. Of the two hLAT isoforms and h4F2hc-coexpressed *Xenopus* oocytes, ^{125}I-IMT uptake via hLAT1 was 5.95-fold higher than that via hLAT2 ($P < 0.005$). ^{125}I-IMT transport was hLAT1-selective. Investigations on the isoform selectivity of ^{125}I-IMT transport with other transporters are anticipated.[23]

2.3.2 System L2: L-type amino acid transporter 3 (SLC43A1).

In 2003, a cDNA that encodes a novel Na^+-independent neutral amino acid transporter designated L-type amino acid transporter 3 (LAT3) was isolated from FLC4 human hepatocarcinoma cells by expression cloning.[17] When expressed in *Xenopus* oocytes, LAT3 transported neutral amino acids such as Leu, Ile, Val, and Phe. In addition to amino acid substrates, LAT3 recognized amino acid alcohols. The LAT3-mediated transport was Na^+-independent and inhibited by BCH, consistent with the properties of system L. Distinct from system L1, which forms a heterodimeric complex with 4F2hc, LAT3 was functional by itself. The expression of LAT3 is upregulated in prostate cancer. LAT3 is a transporter subserving system L2.

Bodoy S *et al*. reported that L-type amino acid transporter 4 (LAT4) as well as LAT3, is Na^+, Cl^- and pH-independent, and is not trans-stimulated.[24] LAT4 activity is detected at the basolateral membrane of proximal convoluted tubule (PCT) kidney cells. *In situ* hybridization experiments show that LAT4 mRNA is restricted to the epithelial cells of the distal tubule and the collecting duct in the kidney. In the intestine, LAT4 is mainly present in the cells of the crypt. Human LAT4 exhibits 57% identity to human LAT3.

In the system L2 family, LAT4 is expressed in normal tissues, and LAT3 is expressed in some types of tumors. However, a LAT3-specific imaging probe has not been reported yet.

2.3.3 System xc^-: xCT (SLC7A11).

Sato H *et al*. has isolated cDNA encoding the transporter for system xc^- from mouse activated macrophages by expression in *Xenopus* oocytes.[20] Transport system xc^- found in the plasma membrane of cultured mammalian cells is an exchanger for anionic amino acids with high specificity for anionic forms of cystine and glutamate. The expression of system xc^- activity in oocytes requires two cDNA transcripts, and the sequence analysis revealed that one is identical to 4F2hc and the other is a novel protein of 502 amino acids with 12 putative transmembrane domains. Northern blot analysis demonstrated that the expression of both 4F2hc and xCT was enhanced in stimulated macrophages and tumor cells. This transporter is regulated by intracellular reduced glutathione (GSH) levels in humans. GSH functions as a radical scavenger. The expression of system xc^- is also highly regulated in many types of cell lines. These features suggest that xCT could be a potential target in tumor imaging. Baek S *et al*. reported that (4S)-4-(3-^{18}F-fluoropropyl)-l-glutamate (^{18}F-FSPG, or BAY 94-9392) is a new tracer for assessing system xc^- transporter activity with PET. The authors investigated the tumor detection rate of ^{18}F-FSPG, compared with that of ^{18}F-FDG, in patients with hepatocellular carcinoma (HCC).[25]

2.3.4 System ASC: ASCT2 (SLC1A5).

In 1996, ASCT2 was cloned and characterized as an Na^+-

dependent neutral amino acid transporter. It transports Ala, Ser, Thr, Cys and Gln at high affinity (K_m values around 20 M), and it also transports Met, Leu, Gly, Val and Glu at low affinity (K_m = 1.6 mM).[18] A cDNA was isolated from mouse testis. The encoded protein, designated ASCT2, showed amino acid sequence similarity to ASCT1 (57% identity).[22] L-Glu transport was enhanced upon lowering extracellular pH. Northern blot hybridization revealed that ASCT2 was mainly expressed in the kidney, large intestine, lung, skeletal muscle, testis, and adipose tissue.

ASCT2 (SLC1A5), as well as LAT1, is a transporter that is ubiquitously expressed in tumor cells.

Ploessl K *et al*. reported the preparation and comparative evaluation of ^{18}F-labeled (2S,4R)-4-fluoro-l-glutamine (4F-GLN) and ^{18}F-labeled (2S,4R)-4-fluoro-l-glutamate (4F-GLU) as tumor metabolic imaging agents. 4F-GLN has demonstrated high uptake in tumor cells undergoing high growth and proliferation. Similar tumor targeting properties have also been observed for 4F-GLU, suggesting that both are useful imaging agents. Amino acid transport system ASC in particular, its subtype ASCT2 gene, and system xc^- played an important role in transporting 4F-GLN and 4F-GLU, respectively, across the membrane.[26]

2.3.5 System $B^{0,+}$: $ATB^{0,+}$ (SLC6A14).

Human $ATB^{0,+}$ is the first cloned $B^{0,+}$ amino acid transporter discovered by Sloan JL *et al*. in 1999.[19] The authors reported that human $ATB^{0,+}$ ($hATB^{0,+}$) was a member of the Na^+/Cl^--dependent neurotransmitter transporter family with the highest sequence similarity to the glycine and proline transporters. Tissue survey suggests expression in the lung, trachea, salivary gland, mammary gland, stomach, and pituitary gland. Electrophysiology and radiolabeled amino acid uptake measurements were used to functionally characterize the transporter expressed in *Xenopus* oocytes. $hATB^{0,+}$ was found to transport both neutral amino acids (e.g. Leu, Ilu, Met) and cationic amino acids (e.g. Arg, Lys), with the highest affinity for hydrophobic amino acids, moderate affinity for Phe, Tyr, Gly, Ala, Gln and the lowest affinity for Pro. Amino acid transport was Na^+ and Cl^--dependent and was attenuated in the presence of BCH, a system $B^{0,+}$ inhibitor. In colorectal and cervical tumor tissues, upregulation accompanied by nitric oxide synthase (iNOS) expression has been reported.[27] Development of $ATB^{0,+}$-specific labeled imaging probe is anticipated.

3 Radiolabeled amino acid transport imaging agents in tumors

3.1 General aspects.

The history of labeled amino acid as the imaging agent is long. Development of radiopharmaceuticals for SPECT has been ongoing since the 1960s.[28] A compound for SPECT, ^{75}Se-selenomethionine, was originally successfully developed as a labeled amino acid for SPECT analysis in the clinical setting.[29] However, its development was later abandoned because its physical properties were found to be unsuitable for clinical nuclear medicine.

Many types of ^{131}I or ^{123}I-labeled compounds have been investigated for application in SPECT analysis, due to their relative ease of use and the long half-life of isotope ^{125}I observed in laboratory experimental settings. Regarding chemical properties, the tyrosine phenyl group is readily iodinated by oxidants including chloramine-T.[30]

Kawai K and colleagues synthesized and evaluated radioiodinated tyrosine analogues as membrane amino acid transport imaging agents for the brain,[29-34] the pancreas,[35,36] the kidney[37-41] and tumors[42-44].

On the other hand, positron emitters of ^{11}C, ^{13}N, ^{15}O (biological elements) and ^{18}F (substitutable OH or H group) are used for labeling of radiopharmaceuticals for positron emission computed tomography (PET). There are two types of labeled amino acids - radioactive natural amino acids and radioactive non-natural amino acids. The use of elements such as radioactive carbon, nitrogen, and oxygen allows labeling without the change of chemical structure of natural amino acids, conferring an advantage for protein synthesis activity imaging. However, the half-lives of ^{11}C, ^{13}N and ^{15}O (20 min, 10 min and 2 min, respectively) are very short, making the process of nuclear reaction, labeling, and application as radiopharmaceuticals for patient data acquisition challenging. On the other hand, the use of the relatively longer half-life of ^{18}F (110 min) enables the transportation and commercial delivery

of radiopharmaceuticals and ^{18}F-2-fluoro-2-deoxyglucose (FDG) to hospitals with PET cameras. Therefore, the delivery of ^{18}F-labeled compounds and their use in clinical practice is of great importance.

When radioactive natural amino acids are injected into patients, a variety of radioactive metabolites are generated within several minutes. Thus, the analysis of biodistribution of the metabolized radioactivity is challenging. For example, a natural amino acid [*S*-methyl-^{11}C]-L-Met is mostly mediated by system L transporters,[45] but the radiolabeled *S*-methyl group is transferred to a different molecule in a cell, and the distribution of radioactivity reflects not only protein synthesis but also other metabolic processes. Protein synthesis is one of the targets in the development of these radiolabeled amino acids. But aminoacyl-tRNA synthetase recognize specific neutral amino acid structure rigidly. Aminoacyl-tRNA synthetase links an amino acid with the appropriate tRNA, thereby forming a specific neutral amino acid binding aminoacyl-tRNA structure. The incorporation of radiolabeled amino acids without a natural amino acid structure into protein is very rare, and the accumulation is mostly attributed to amino acid transport activity. For radioactive tumor imaging agents targeting amino acid transporter activity, non-metabolizable artificial amino acids that accumulate in tumors by simple pharmacokinetics are preferable to natural amino acids that generate many types of radioactive metabolites.

At the beginning of the 1960s, non-natural amino acids, 2-aminoisobutyric acid (AIB), α-aminocyclobutane-1-carboxylic acid (ACBC), α-aminocyclopentane-1-carboxylic acid (ACPC) and BCH were developed. BCH is a system L-specific substrate in Na^+-free conditions. In the 1970s, these ^{11}C-labeled non-natural amino acids with α-carboxyl groups were investigated for use in PET. AIB[46], ACBC[47] and ACPC[48] are transported into cells via membrane transport, are metabolically stable, and do not have affinity to protein incorporation processes.

Furthermore, ^{11}C-MeAIB, a system A-specific inhibitor *N*-methylated-α-aminoisobutyrate (MeAIB) labeled with ^{11}C, was synthesized and clinically evaluated.[49]

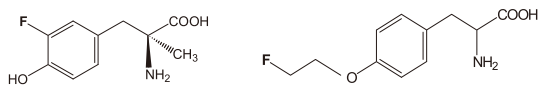
Investigation of the qualitative and quantitative differences in expression of important amino acid transporters in normal and tumor tissues may be a promising strategy for molecular design of tumor imaging agents.

3.2 Promising molecular probes for the post-FDG.

To date, more than 25 types of ^{18}F-labeled amino acids have been synthesized and evaluated. We here focus on some of these promising compounds.

Many tyrosine analogues have been tested because they have a phenyl group that can be easily labeled with radioactive halogen. Among the developed tyrosine analogues, ^{123}I-3-iodo-α-methyl-L-tyrosine (^{123}I-IAMT) has demonstrated considerable *in vivo* stability and excellent properties as an amino acid transport imaging agent for SPECT by Stöcklin G, Jager PL, Coenen HH and Langen K-J *et al*..[50] Fluorinated analogue, ^{18}F-3-iodo-α-methyl-L-tyrosine (^{18}F-L-FAMT) was also developed for PET study by Inoue T *et al*. (Figure 4).[51] The physiological accumulation of ^{18}F-L-FAMT is lower than that of ^{18}F-FDG in the brain, heart, liver, and muscle. Brain tumor image is superior to that of ^{18}F-FDG with high contrast to tumor/normal brain tissue. ^{18}F-L-FAMT has superior property in diagnosis of malignant tumors in the above-mentioned organs. ^{18}F-L-FAMT was clinically tested and reported in many papers by Kaira K *et al*..[52] D-isomer, ^{18}F-D-FAMT, is also reported.[53]

Jager PL and Langen KJ *et al*. reported the utility of *O*-(2-^{18}F-fluoroethyl)-L-tyrosine (^{18}F-FET). This agent has favorable properties for brain tumor and head/neck tumor diagnosis, because it accumulates in the kidneys and the brain, and has a lower activity than that of ^{18}F-L-FAMT or ^{123}I-IAMT. Generally, tyrosine analogues have high urinary excretion, and are not suitable for the diagnosis in the kidney and urinary tract region. ^{18}F-FET is a substrate of system L transporters, and partly accumulates in tumor cells via system ASC and A transporters. It is not incorporated into protein.



3-Fluoro-α-methyl-L-tyrosine　*O*-(2-Fluoroethyl)-L-tyrosine

Fig. 4. Fluorine-labeled tyrosine derivatives.

^{18}F-1-amino-3-fluorocyclobutane-1-carboxylic acid (^{18}F-FACBC) (Figure 5) with high tumor selectivity to normal tissues in a ^{11}C-labeled ACBC study was developed by Goodman's group.[54] The *anti*-isomer of ^{18}F-FACBC (^{18}F-*anti*-FACBC: ^{18}F-*anti*-1-amino-3-fluorocyclobutane-1-carboxylic acid) has higher specificity for tumor tissue than the *cis*-isomer. Because of its higher accumulation selectivity in tumor tissues and a lower accumulation in physiologically normal organs, such as the brain, muscles, heart, liver and urinary excretion via the kidney than those of FDG, ^{18}F-*anti*-FACBC is thought to be one of the most promising probes as a post-FDG radiopharmaceutical in the abdominal, prostate and brain tumor PET study. Due to its numerous superior properties, compared to FDG, ^{18}F-*anti*-FACBC is expected to be used as a post-FDG radiopharmaceutical especially in the diagnosis of glioblastoma, which can be detected by ^{18}F-FACBC with better image. Transport of ^{18}F-*anti*-FACBC originally considered to be mediated by system L has been shown to be mainly mediated by system ASC in prostate cancer.[54]

The AIB-induced ^{18}F-labeled compounds, 3-fluoro-2-amino-2-methyl-propionic acid (FAMP), 4-fluoro-2-amino-2-methyl-butyric acid (FAMB) and *N*-methyl-3-fluoro-2-amino-2-methyl-propionic acid (*N*-MeFAMP) considered to be the substrates of system A and system ASC transporters are reported (Figure 6).

Additionally, we synthesized and evaluated non-natural sulfur-containing amino acids for SPECT (Figure 7).[55] Metabolic fate and biodistribution of those compounds remain unclear.

3.3 ImmunoPET/SPECT agents for imaging specific amino acid transporters.

Radiolabeled amino acids that are transport substrates for system L amino acid transporters including LAT1 have met limited success because of the imperfect selectivity, and thus new strategies are required for imaging LAT1 protein localization in systemic cancers. We recently attempted to develop immunoSPECT agents with this type of strategy, but targeting the extracellular domain of LAT1 was challenging because a proper antibody cannot be obtained. Ikotun OF *et al*. described the first report of this kind of direct PET imaging of LAT1 and demonstrated the potential of immunoPET agents for imaging specific amino acid transporters.[56] The authors developed a novel zirconium-89-labeled antibody, ^{89}Zr-DFO-Ab2 and biologically evaluated the specificity for LAT1 *in vitro* and *in vivo* with excellent tumor imaging properties in mice using a model of colorectal cancer. This tracer showed high tumor uptake and optimal tumor/normal tissue contrast was achieved at 7 days post administration. There are still challenges to overcome in the application of immunoagents for imaging, including accumulation in the normal liver, spleen, kidney and blood, as a general property of antibodies. Development of functional imaging of transporter activity with radiolabeled substrates and transporter protein expression imaging with radiolabeled antibodies will provide additional information about tumors.

Therefore, we can make a decision of the way, depending on intending imaging, amino acid transporter function using of radio-labelled substrates or expression using an immuno PET/SPECT agents. Using of radio-labelled substrates of a kind of amino acid transporter cannot always image the specific amino acid transporter

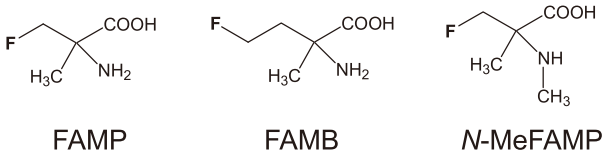


Fig. 6. Fluorine-labeled α-methylated non-natural amino acids and a *N*-Me-derivative.

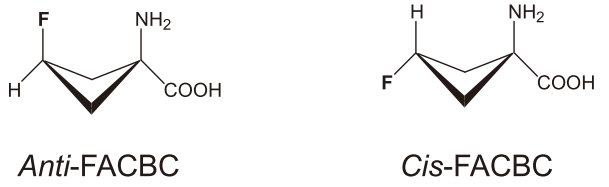


Fig. 5. Fluorine-labeled non-natural amino acids with saturated cyclic alkyl residues.

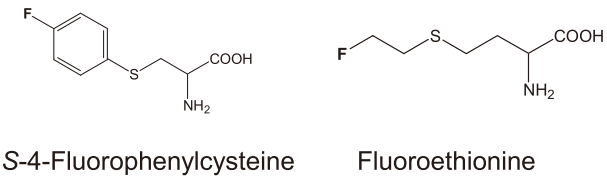


Fig. 7. Fluorine-labeled sulfur-incorporated non-natural amino acids.

because there are so many cases that those substrates are also transported via some other kinds of amino acid transporters and/or their isoforms. Although the superior point of using an immuno PET/SPECT agents is their can image a specific amino acid transporter protein expression its self, the location and the amount.

4. Conclusion

Among the genes clarified by the recent human genome project, about 3% are expected to function as membrane or intracellular transporters. Furthermore, approximately 30% of currently available clinical drugs target transporters or channels. Approximately 50 types of amino acid transporter genes have been reported in mammals. Among these transporters, LAT1 (SLC7A5), LAT3 (SLC43A1), ASCT2 (SLC1A5), $ATB^{0,+}$ (SLC6A14) and xCT (SLC7A11) have been demonstrated as upregulation-dependent transporter isoforms in tumors. Based on a strategy using recently obtained information about gene expression involved in amino acid metabolism in various organs and tumors, radiolabeled amino acid imaging agents as molecular probes in nuclear medicine are being developed. A new chapter in the field of radiolabeled molecular imaging agents for amino acid transport in tumors in the post-genomic era lies ahead of us.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

This study was supported by Grants-in-Aid for Scientific Research (Project Number: 26461801, 24659558 and 30204663) from the Ministry of Education, Science, Sports and Culture of Japan and the Japan Society for the Promotion of Science and Arteriosclerosis Research Foundation grant 2019.

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和文抄録

哺乳類では約50種類のアミノ酸トランスポーター遺伝子が報告されている。これらのトランスポーターのうち，LAT1（SLC7A5），LAT3（SLC43A1），ASCT2（SLC1A5），$ATB^{0,+}$（SLC6A14）およびxCT（SLC7A11）は，腫瘍で発現亢進するトランスポーターアイソフォームとして報告されている。最近の分子イメージングの時代において，遺伝子情報とバイオテクノロジーを用いた天然/非天然アミノ酸による腫瘍のアミノ酸輸送のための放射性標識分子イメージング剤の開発が，特に過去10年間で新しいトレンドになりつつある。 Post-FDGの有望な分子プローブは，^{18}F-3-iodo-alpha-metyl-L-tyrosine, *O*-(2-^{18}F-fluoroethyl)-L-tyrosine, and ^{18}F-*anti*-1-amino-3-fluorocyclobutane-1-carboxylic acidである。さらに，すべての特定のアミノ酸トランスポーターをイメージングするためのimmunoPET / SPECT薬剤の開発が新しい戦略として期待されている。この総説では，腫瘍イメージングと放射性腫瘍イメージング剤のアミノ酸輸送活性に関わるsolute carrier（SLC）に属するトランスポーターに焦点を当てて解説する。