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Amino Acid Metabolism as a Target for Breast Cancer Imaging

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SYNOPSIS

Amino acids are an alternate energy source to glucose and amino acid metabolism is upregulated in multiple malignancies, including breast cancers. Multiple amino acid radiotracers have been utilized to image breast cancer with unique strengths and weaknesses. ^{11}C -Methionine uptake correlates with S phase fraction in breast cancer and may be useful for evaluation of treatment response. Invasive lobular breast cancers may demonstrate greater ^{18}F -fluciclovine avidity than ^{18}F -FDG avidity. Thus, different histologic subtypes of breast cancer may utilize diverse metabolic pathways and may be better imaged by different tracers.

Keywords

Breast Cancer; PET/CT; Amino Acid; Methionine; Fluciclovine

Introduction

Cellular metabolism has been a major target of nuclear imaging, with the glucose analog ^{18}F -fluorodeoxyglucose (^{18}F -FDG) serving as the prototype metabolic imaging radiotracer. This successful ^{18}F -FDG paradigm has focused on the increased metabolism of glucose in malignancy.¹ ^{18}F -FDG positron emission tomography (PET) has led to important advances in the care of patients with breast cancer (Cite articles earlier in this issue of PET CLINICS by Basu et al, Hildebrandt et al, and Groheux et al.) However, ^{18}F -FDG has multiple limitations, including difficulty distinguishing malignant from benign primary breast lesions,² limited utility in the evaluation of the breast and axilla compared to other imaging methods,^{3–5} and variable sensitivity and specificity of breast cancer lesions depending on

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tumor and patient characteristics.^{6–10} In particular, invasive lobular carcinoma (ILC) is a histologic subtype of breast cancer with lower FDG avidity than the more common ductal breast cancer (IDC) in both primary and metastatic lesions.^{11–14} Therefore, multiple opportunities remain for novel metabolic imaging agents in breast malignancies.

While glucose metabolism is recognized as a key metabolic pathway for imaging, less well known to imaging specialists are the multiple other intermediary metabolic pathways of cellular metabolism.¹⁵ In addition to glycolysis, the citric acid cycle, amino acid metabolism, and lipid metabolism are also altered during neoplasia.¹⁵ This can be demonstrated at the genomic level, as well as at the level of messenger ribosomal nucleic acid transcription, protein expression, and metabolic phenotypes.¹⁶ Exploiting these metabolic pathways for imaging malignancy has been a focus of research over the last two decades. In particular, multiple radiotracers have been designed and tested for imaging of amino acid metabolism with initial successes and potential future opportunities.

This review focuses on basic amino acid metabolism, the radiotracers that have thus far been central to amino acid metabolism imaging in patients with breast cancer, and possibilities for future development of these agents.

Basics of Amino Acid Metabolism in Normal Cells and Malignancy

Although hundreds of amino acids have been described, 20 are encoded in the human genome and serve as the basic building blocks for proteins.¹⁶ These amino acids are the components of multiple metabolic pathways that are essential for cellular maintenance. Amino acids are transported into the interior of the cell by amino acid transporters in the cell membrane. There are more than 20 amino acid transporter families, including the major amino acid transport systems L, ASC, and A.

Increased levels of methionine, glutamine, cystine, tryptophan, tyrosine, and other amino acids have been noted in many malignancies, including breast cancers.^{16–20} Cancer cells with upregulation of amino acid metabolism stimulate increased transport of amino acids into the cell.^{16,21} The increased consumption of amino acids and overexpression of amino acid transporters in malignancies make radiolabeled amino acids attractive oncologic imaging agents.²²

Multiple amino acid transporter families have been demonstrated to be upregulated in breast cancer cells, including LAT1, ASCT2, ATB^{0,+} SNAT1, and x_c[−].^{18,23–27} The L-type amino acid transporter (LAT1) is essential for the transport of large neutral amino acids,²¹ and is overexpressed in multiple malignant tumor types, including breast cancer.^{21,24} Furuya and colleagues have described LAT1 transporter expression with CD98 to be an independent prognostic factor in triple-negative breast cancer.²⁸ The alanine-serine-cysteine family transporter 2 (ASCT2) and system A component SNAT1 have been shown to be upregulated in a tissue microarray of 702 breast malignancies.^{26,27} Expression of ASCT2 also has prognostic associations in breast cancer.²⁹ The system x_c[−] transporter, which mediates cystine uptake, is upregulated in some breast cancer tumors, as demonstrated by the PET radiotracer (4S)-4-(3-[¹⁸F]fluoropropyl)-L-glutamate.¹⁸

Methionine imaging

¹¹C-methionine was an early agent for amino acid metabolic imaging. Methionine is a natural large neutral amino acid that is readily radiolabeled with ¹¹C. ¹¹C-methionine serves as a metabolic marker for methionine uptake by L-type amino acid transporters. Initial work has demonstrated that both primary and metastatic sites of breast malignancy are visualized by ¹¹C-methionine PET.¹⁷ In addition, ¹¹C-methionine uptake correlated with the fraction of cells in mitosis in these lesions, suggesting that amino acid uptake may correlate with proliferation rate in breast malignancies.

Subsequent work with ¹¹C-methionine extended to imaging of breast cancer treatment response.^{30–32} Uptake of ¹¹C-methionine decreased in patients before clinical objective response or regression of tumor size, and provided early evidence that radionuclide metabolic imaging could predict treatment response earlier than other methods. ¹¹C-methionine could distinguish responders from non-responders of endocrine or combination endocrine and chemotherapy after as little as one cycle of treatment.^{30,32} In some cases, ¹¹C-methionine even outperformed ¹⁸F-FDG.³¹ These studies included only a small number of patients—51 patients among the four studies^{17,30–32}—limiting the conclusions that can be drawn from the data.

Physiologic sites of uptake of ¹¹C-methionine include the liver and bone marrow, which could limit evaluation of breast cancer metastases. Other limitations of ¹¹C-methionine include its relatively short (20-minute) half-life and non-protein metabolites, which may interfere with imaging. More recently, ^{99m}Tc-labeled methionine has been developed and utilized with dedicated breast scintigraphy equipment for the detection of primary breast malignancies.³³ This radiotracer, ^{99m}Tc-DTPA-bis-methionine, could be produced with high efficiency from a single vial kit, and has demonstrated high sensitivity in the initial clinical trial.³³

¹⁸F-Fluciclovine

¹⁸F-fluciclovine (*anti*-1-amino-3-¹⁸F-fluorocyclobutane-1-carboxylic acid) is a synthetic amino acid initially developed at Emory University as a leucine analog for imaging brain malignancies,³⁴ and subsequently developed as a valuable radiotracer for prostate malignancies.^{35,36} In 2016, ¹⁸F-fluciclovine was approved by the United States Food and Drug Administration for PET imaging of patients with suspected prostate cancer recurrence based on elevated PSA levels following prior treatment.

¹⁸F-fluciclovine is transported into the cell primarily by the ASCT2 transporter with additional involvement of LAT1 in certain conditions such as dense acidic tumor environments.^{37,38} Uptake into cells is most similar to that of the naturally occurring amino acid glutamine.^{38,39} Preclinical work has demonstrated uptake of fluciclovine into breast cancer cell lines and mouse orthotopic tumor xenografts.²¹ A recent preliminary *in vitro* study reported that fluciclovine uptake into breast cancer cells occurred mostly via ASCT2 transporters.⁴⁰ As amino acid transporters, including ASC-type transporters,²⁶ are upregulated in breast cancer cells, investigators have extended clinical trials with ¹⁸F-fluciclovine to patients with breast lesions and breast cancer.^{41–43}

In a study of 12 women, ^{18}F -fluciclovine uptake in malignant breast lesions was more than four-fold greater than in benign lesions.⁴² The greatest uptake of ^{18}F -fluciclovine was found in the highest-grade malignancies. In another study of 27 women with breast cancer, the primary breast malignancy was visualized in all patients and in 20 of 21 pathologically confirmed axillary nodal metastases.⁴¹ In addition, ^{18}F -fluciclovine detected histologically confirmed extra-axillary nodal metastases that were previously undetected. Both of these studies identified an interesting correlation between ^{18}F -fluciclovine avidity and histologic subtypes of breast malignancy. While IDC demonstrated equal or inferior fluciclovine avidity compared to FDG avidity, the ILC histology tumors demonstrated greater fluciclovine avidity than FDG avidity^{41,42} (Fig. 1). This suggests a varying dependence of metabolic pathways between histologic subtypes of breast cancer, raising an interesting question: Could radiotracers targeting different metabolic pathways be suited for imaging specific breast cancer histologic subtypes?

A separate study evaluated the ability of ^{18}F -fluciclovine avidity to determine neoadjuvant therapy response, utilizing histology following definitive surgical management as the gold standard.⁴³ Changes in ^{18}F -fluciclovine avidity strongly correlated with the percentage of reduction of tumor seen on pathology (Fig. 2). Although as reported with ^{18}F -FDG, histologic complete response could not be accurately distinguished from non-complete responses, since small volume residual malignancy in patients with >90% tumor reduction on histology could not be readily appreciated by ^{18}F -fluciclovine PET/CT (Fig. 3).

These initial studies emphasized ^{18}F -fluciclovine avidity in local disease, with only one distal (osseous) metastasis visualized. Of importance will be future trials evaluating ^{18}F -fluciclovine avidity in patients with distant metastatic disease, where the advantages of whole body metabolic imaging will likely be greatest. Preclinical studies have demonstrated substantial success of ^{18}F -fluciclovine in the detection of osseous metastases.^{44,45} Physiologic fluciclovine avidity is seen in the liver, pancreas, and skeletal muscle. The physiologic avidity in the liver will likely limit detection of hepatic metastases, a common site of metastatic disease in patients with breast cancer. In fact, in one of the trials, hepatic breast metastases were relatively photopenic to background liver.⁴²

However, breast malignancies with ILC histology have a propensity to metastasize to nodes and bone, where ^{18}F -fluciclovine background is lower, as well as a greater propensity to metastasize to the genitourinary and gastrointestinal tracts than IDC, where background avidity with ^{18}F -FDG is more problematic. A direct comparison of ^{18}F -fluciclovine and FDG for metastatic ILC could provide evidence of where ^{18}F -fluciclovine may improve staging in ILC.

Given that amino acid transporters mediate both uptake and efflux of amino acids in cells, and ^{18}F -fluciclovine is not intracellularly metabolized and trapped like ^{18}F -FDG, the dynamics of ^{18}F -fluciclovine uptake are different than ^{18}F -FDG. While longer uptake times tend to increase ^{18}F -FDG uptake, ^{18}F -fluciclovine uptake peaks within the first 20 minutes and then often demonstrates slow washout from breast tumors.^{41,42} This phenomenon makes proper protocoling of ^{18}F -fluciclovine PET/CT studies of great importance, with radiotracer

administration followed by imaging when the patient is already positioned on the PET/CT scanner.

Cysteine transporter imaging

The amino acid transporter system x_c^- mediates cellular uptake of cystine with concurrent efflux of glutamate. Amino acid analog radiotracers have been designed to examine x_c^- activity and provide PET/CT imaging of tumors. (4S)-4-(3-(^{18}F)fluoropropyl)-L-glutamate (^{18}F -FSPG) is one such novel amino acid analog radiotracer that has demonstrated tumor visualization in small animal models⁴⁶ and in patients with lung and breast cancer,¹⁸ although uptake in breast cancer lesions was lower and not appreciated in all breast tumors. Histologic or molecular subtypes of breast cancer may influence x_c^- activity and ^{18}F -FSPG uptake. SUV of ^{18}F -FSPG on PET/CT correlated significantly with extent of immunohistochemical staining for x_c^- transporter on pathology.¹⁸ More recent preclinical studies of a cystine/glutamate analog, ^{18}F -fluoroaminosuberlic acid,⁴⁷ demonstrated tumor uptake in multiple breast cancer cell lines and breast cancer tumor-bearing mice⁴⁸ and may soon be seen in clinical trials.

Other amino acid analogs for imaging

Multiple radiolabeled tyrosine analogs have been developed for tumor imaging, including L-[1- ^{11}C]tyrosine.²⁰ L-[1- ^{11}C]tyrosine successfully demonstrated uptake in breast malignancies and had lower uptake than ^{18}F -FDG in a limited number of benign lesions.²⁰ $^{99\text{m}}\text{Tc}$ -labeled tyrosine analogs have also been synthesized with high yield and distinguish breast malignancies from benign breast tissues.^{49,50} Propanoic acid amino acid analogs, primarily dependent on system A transport, have been developed by the same group at Emory that synthesized ^{18}F -fluciclovine.⁵¹ In preclinical studies, multiple propanoic acid derivatives demonstrated good tumor uptake in human-derived breast cancer cells, as well as in mouse tumor xenografts.⁵¹

Tryptophan analogs, primarily utilizing L-type amino acid transport, have been developed by multiple research groups, and have also demonstrated uptake in breast cancer cells and in small animal studies.^{19,52} Recently, a newer leucine analog, 5-[^{18}F]fluoroleucine, was synthesized, with primary transport via LAT1.⁵³ Both cell lines and breast cancer xenografts demonstrate 5-[^{18}F]fluoroleucine uptake. As opposed to ^{18}F -fluciclovine, 5-[^{18}F]fluoroleucine uptake progressively increases over time.⁵³ The glutaminolysis pathway is highly active in many malignancies, including triple-negative breast cancers.⁵⁴ Preclinical work with the glutamine analog [^{18}F](2S,4R)4-Fluoroglutamine^{55,56} has demonstrated the ability of this tracer to track changes in the cellular glutamine pool size and the glutaminolysis pathway following glutaminase inhibition.⁵⁴

Future applications

There is substantial interest in the synthesis of novel amino acid metabolic radiotracers and the application of promising agents for tumor imaging, with the goal of developing molecular imaging biomarkers that predict the most efficacious therapies or successfully measure response to therapy.⁵⁷ Visualization of primary breast tumors is usually the first hurdle when promising agents are translating into human studies; however, this is unlikely to

be where clinical benefit will be derived. As has been shown with ^{18}F -FDG, whole body PET/CT is not sensitive for the primary breast malignancy when compared to other available imaging modalities such as mammography, ultrasound, and MRI. Truly remarkable sensitivity of a novel amino acid tracer would be required to supplant these imaging modalities for the primary breast malignancy. Rather, PET/CT has, to date, demonstrated unparalleled utility in the evaluation of distant metastases (and to a lesser extent, extra-axillary nodal metastases) with ^{18}F -FDG as the radiotracer.

The clinical impact of amino acid analog radiotracers could be determined by identifying niches where they outperform ^{18}F -FDG, such as the potential of ^{18}F -fluciclovine in lobular breast cancer. A thorough analysis of ^{18}F -fluciclovine for the detection of unsuspected distant metastases in patients with ILC, as well as its ability to monitor ILC treatment response, seems warranted. Since LAT1- and ASCT2-mediated amino acid transport are involved in mTOR tumor signaling, therapy directed against this pathway could potentially be studied with amino acid transport imaging. Another interesting possibility is that, relative to indiscriminate ^{18}F -FDG uptake in inflammation, ^{18}F -fluciclovine is more selectively taken up by T- and B-cells, which could prove useful in imaging of immunomodulatory therapies.⁵⁸ While the ultimate goal of a highly sensitive and specific radiotracer for breast cancer will likely lie in targeted biomarker imaging directed to the breast cancer cell, metabolic agents such as amino acid analogs are ripe for nearer-term applications in specific scenarios of breast cancer.

Summary

Amino acids are central to multiple metabolic processes in the cell. Amino acid transporters and amino acid metabolism are upregulated in multiple malignancies, including breast cancers. Multiple amino acid analog radiotracers have been utilized to image breast cancer with unique strengths and weaknesses. Early work with ^{11}C -Methionine demonstrated tracer uptake, which correlates with S-phase fraction in breast cancer and may be useful for evaluation of treatment response. Invasive lobular breast cancers may demonstrate greater ^{18}F -fluciclovine avidity than ^{18}F -FDG avidity, and thus evaluation of this tracer at initial ILC staging for the detection of unsuspected distant metastases, as well as for evaluation of treatment response in metastatic ILC, is warranted. There continues to be substantial research into the development and application of novel amino acid radiotracers.

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KEY POINTS

1. Amino acids are an alternate energy source to glucose and amino acid metabolism is upregulated in multiple malignancies, including breast cancers.
2. Multiple amino acid radiotracers have been utilized to image breast cancer with unique strengths and weaknesses.
3. ^{11}C -Methionine uptake correlates with S phase fraction in breast cancer and may be useful for evaluation of treatment response.
4. Invasive lobular breast cancers may demonstrate greater ^{18}F -fluciclovine avidity than ^{18}F -FDG avidity. Thus, different histologic subtypes of breast cancer may utilize diverse metabolic pathways and may be better imaged by different tracers.

Figure 1.

Greater ^{18}F -fluciclovine avidity than ^{18}F -FDG avidity in a patient with a right breast invasive lobular carcinoma (ILC). (A) Coronal CT, PET, and fused PET/CT images from a ^{18}F -fluciclovine PET/CT demonstrate a ^{18}F -fluciclovine-avid right breast ILC (arrow, SUV 7.1). (B) Coronal CT, PET, and fused PET/CT images from a ^{18}F -FDG PET/CT on the same patient demonstrate lower FDG avidity (arrow, SUV 3.5).

Adapted from Tade FI, Cohen MA, Styblo TM, et al. Anti-3- ^{18}F -FACBC (^{18}F -Fluciclovine) PET/CT of Breast Cancer: An Exploratory Study.

J Nucl Med. 2016 Sep;57(9):1357-63. doi: 10.2967/jnumed.115.171389. Epub 2016 Apr 7; with permission.

A. ^{18}F -Fluciclovine at initial staging **B. ^{18}F -Fluciclovine following neoadjuvant therapy** **Figure 2.**

Reduction in ^{18}F -fluciclovine avidity following neoadjuvant therapy in a 52-year-old woman with breast cancer. (A) Axial PET, CT, and fused images from a ^{18}F -fluciclovine PET/CT at baseline demonstrate the ^{18}F -fluciclovine-avid primary breast mass (arrow) and ^{18}F -fluciclovine-avid axillary nodal metastases (dashed arrows). (B) Axial PET, CT, and fused PET/CT images from a ^{18}F -fluciclovine PET/CT following neoadjuvant therapy demonstrate decreased ^{18}F -fluciclovine avidity of all lesions to background. On pathology, there was a complete pathologic response, with no residual tumor.

Adapted Ulaner GA, Goldman DA, Corben A, et al. Prospective clinical trial of ^{18}F -fluciclovine PET/CT for determining the response to neoadjuvant therapy in invasive ductal and invasive lobular breast cancers. *J Nucl Med.* 2017;58(7):1037-1042; with permission.

Figure 3.

Scatterplot demonstrating a strong correlation between ¹⁸F-fluciclovine SUV and percent tumor volume reduction on pathology in 24 patients with breast cancer following neoadjuvant therapy. Note that a 100% reduction in SUV on PET correlated with a 90-100% reduction in tumor reduction. Thus, while the correlation was strong, a 100% reduction in ¹⁸F-fluciclovine SUV could not distinguish a pathologic complete response from a pathologic non-complete response. ρ = Spearman's rho.

Adapted from Ulaner GA, Goldman DA, Corben A, et al. Prospective clinical trial of ¹⁸F-fluciclovine PET/CT for determining the response to neoadjuvant therapy in invasive ductal and invasive lobular breast cancers. *J Nucl Med.* 2017;58(7):1037-1042; with permission.