Amino Acid Metabolism as a Target for Breast Cancer Imaging

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KEYWORDS

• Breast cancer • PET/CT • Amino acid • Methionine • Fluciclovine

KEY POINTS

- Amino acids are an alternate energy source to glucose, and amino acid metabolism is up-regulated in multiple malignancies, including breast cancers.
- Multiple amino acid radiotracers have been used 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-fluorodeoxyglucose. Thus, different histologic subtypes of breast cancer may utilize diverse metabolic pathways and may be better imaged by different tracers.

INTRODUCTION

Cellular metabolism has been a major target of nuclear imaging, with the glucose analog fludeoxyglucose F 18 (^{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 PET has led to important advances in the care of patients with breast cancer (See Dhritiman Chakraborty and colleagues' article, "Diagnostic Role of FDG PET in Breast Cancer: A History to Current Application," and David Groheux's article, "Role of FDG in Breast Cancer: Treatment Response," in this issue). ^{18}F-FDG has multiple limitations, however, including difficulty distinguishing malignant from benign primary breast lesions,[2] limited utility in the evaluation of the breast and axilla compared with other imaging methods,[3–5] and variable sensitivity and specificity of breast cancer lesions, depending on 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 invasive ductal carcinoma (IDC) in both primary and metastatic lesions.[11–14] Therefore, multiple opportunities remain for novel metabolic imaging agents in breast malignancies.

Although 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

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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 past 2 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, alanine-serine-cysteine (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 up-regulation 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 up-regulated in breast cancer cells, including L-type amino acid transporter (LAT1), ASC transporter 2 (ASCT2), $ATB^{0,+}$ SNAT1, and x_c^-.[18,23–27] 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[28] have described LAT1 transporter expression with CD98 as an independent prognostic factor in triple-negative breast cancer. The ASCT2 and system A component SNAT1 have been shown up-regulated 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 up-regulated in some breast cancer tumors, as demonstrated by the PET radiotracer (4S)-4-(3-[^{18}F]fluoropropyl)-L-glutamate (^{18}F-FSPG).[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 nonresponders of endocrine or combination endocrine and chemotherapy after as little as 1 cycle of treatment.[30,32] In some cases, 11C-methionine even outperformed ^{18}F-FDG.[31] These studies included only a small number of patients—51 patients among the 4 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-min) half-life and nonprotein metabolites, which may interfere with imaging. More recently, 99m-technetium-labeled methionine has been developed and used with dedicated breast scintigraphy equipment for the detection of primary breast malignancies.[33] This radiotracer, 99mTc-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]

^{18}F-FLUCICLOVINE

^{18}F-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, ^{18}F-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 after prior treatment.