

## Review Article

# A systemic review of PET and biology in lung cancer

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**Abstract:** Positron emission tomography imaging with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (<sup>18</sup>F-FDG) has been established as a significant molecular imaging technique in the management of lung cancer. However, <sup>18</sup>F-FDG accumulation is not specific, therefore several other radiotracers targeting hypoxia, cell proliferation and amino acid metabolism have been developed for the imaging of human cancers. This review summarizes the current data on the correlation between the underlying molecular biology and tumor PET accumulation in lung cancer.

**Keywords:** Molecular biology, <sup>18</sup>F-FDG, PET, lung cancer, molecular imaging, hypoxia, cell metabolism, proliferation

## Introduction

Lung cancer is the leading cause of cancer death and has a poor prognosis. Positron emission tomography (PET) imaging with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose (<sup>18</sup>F-FDG) as a tracer is a non-invasive diagnostic and prognostic tool that measures tumor metabolism. The usefulness of <sup>18</sup>F-FDGPET for cancer diagnosis has been investigated in many studies [1-3]. <sup>18</sup>F-FDG PET is a molecular imaging technique that is based on glucose metabolism [4]. The overexpression of glucose transporter 1 (Glut1) has been shown to be closely related to <sup>18</sup>F-FDG uptake in human cancer [5,6]. Glucose phosphorylation enzyme (hexokinase) is also known to play an important role for glucose metabolism in cancer cells [7]. Glucose-6-phosphatase is decreasing by the increased concentration of hexokinase, and the acceleration of glucose phosphorylation results in increased glucose consumption. Glut1 is thought to be a possible intrinsic marker of hypoxia, and the expression of Glut1 has been found to be regulated by hypoxia in a Hypoxia inducible factor (HIF)-1-dependent way [8,9]. HIF-1 $\alpha$  is considered to support tumor growth by the induction of angiogenesis via the expression of the vascular endo-

thelial growth factor (VEGF) and also by high and anaerobic metabolic mechanism [10]. The amount of <sup>18</sup>F-FDG uptake has been documented to be determined by the presence of glucose transporter 1 (Glut1), hypoxia (HIF-1 $\alpha$ ) and angiogenesis (VEGF) [4]. However, the underlying mechanisms for <sup>18</sup>F-FDG accumulation are still a matter of debate in various human neoplasms, because many factors can influence the extent of <sup>18</sup>F-FDG uptake.

The aim of this review is to summarize the current data on the correlation between the underlying molecular biology and tumor <sup>18</sup>F-FDG accumulation in lung cancer. Moreover, we also describe the data of the PET tracer targeting hypoxia, cell proliferation and amino acid metabolism.

## Glucose metabolism

Malignant cells show increased glucose uptake in vitro and in vivo, and this process is thought to be mediated by glucose transporters [11]. Currently, there are 14 known glucose transporter protein subtypes, and Glut1 and Glut3 are expressed in a variety of carcinomas [12,13]. The upregulation of Glut protein is com-

mon in most cancers and is negative associated with outcome [11]. The overexpression of Glut (Glut1 and Glut3) enhances tumor glucose metabolism, and  $^{18}\text{F}$ -FDG is transported into tumor cell and is phosphorylated to  $^{18}\text{F}$ -FDG-6-phosphate by the overexpression of hexokinase.  $^{18}\text{F}$ -FDG-6-phosphate cannot be metabolized further in the glycolytic pathway and becomes trapped in the cell because of its negative charge, and it leads to the tumor cell accumulation of  $^{18}\text{F}$ -FDG-6-phosphate [14].

$^{18}\text{F}$ -FDG is not specific for human cancers and can accumulate in granulomatous or inflammatory processes [7,15,16]. The recent report has described that the amount of  $^{18}\text{F}$ -FDG uptake in benign pulmonary lesion is also determined by the presence of glucose transporters (Glut1 and Glut3), glucose phosphorylation (hexokinase) and angiogenesis (VEGF) [16]. Especially, Glut1, Glut3 and hexokinase were highly expressed in granulomatous diseases as compared with non-granulomatous diseases. Glucose transporter and hexokinase seem to play a crucial role on the  $^{18}\text{F}$ -FDG accumulation in not only cancers but also benign lesions such as granulomatous disease.

We performed a systemic search of the MEDLINE and PUBMED databases to identify all English literatures regarding to the relationship between  $^{18}\text{F}$ -FDG PET and Glut in patients with lung cancer. The search strategy included the articles between April 1999 and May 2011 using the following key words: "PET" or "positron emission tomography"; "positron emission tomography/computer tomography" or "PET/CT"; " $^{18}\text{F}$ -FDG" or "fluorodeoxyglucose"; "lung cancer", "Glut", or "glucose transporter". We did not include preliminary sets published as abstracts or meeting's proceedings. We identified 18 studies based on our research criteria [5-7,13,17-31]. Most studies support a positive correlation between  $^{18}\text{F}$ -FDG uptake and Glut1 expression in lung cancer, especially non-small cell lung cancer (NSCLC). In all studies, the expression of Glut1 was examined by immunohistochemical staining. However, the evaluation of Glut1 immunohistochemical staining was different among the individual studies. In the analysis according to histology or tumor differentiation,  $^{18}\text{F}$ -FDG uptake and Glut1 expression were significantly higher in squamous cell carcinoma (SQC) than in adenocarcinoma (AC) and in poorly differentiated carcinoma than in other

tumor differentiation grades. A PET study for bronchioloalveolar carcinoma has shown that the relatively lower sensitivity of  $^{18}\text{F}$ -FDG PET in this clinical setting may be due to the varying level and extent of tumor Glut1 expression [26]. Song et al documented that there was a wide range of  $^{18}\text{F}$ -FDG uptake in neuroendocrine tumors of the lung and  $^{18}\text{F}$ -FDG uptake was closely correlated with Glut1 expression [28]. Kaira et al have described that  $^{18}\text{F}$ -FDG uptake in pulmonary pleomorphic carcinoma is closely associated with the presence of Glut1 and Glut3, and the level of Glut1, Glut3 and  $^{18}\text{F}$ -FDG uptake was significantly higher in pulmonary pleomorphic carcinoma than in other NSCLC [13]. These reports suggest that the presence of Glut1 expression determines the amount of  $^{18}\text{F}$ -FDG accumulation within tumor cells. Moreover, an additional modulatory factor for  $^{18}\text{F}$ -FDG uptake may be associated with the overexpression of P-glycoprotein in tumors, but it remains unknown about the exact underlying mechanism and relationship to glucose metabolism [32]. It has been observed that the lower  $^{18}\text{F}$ -FDG uptake in bronchioloalveolar carcinoma was related to an overexpression of P-glycoprotein as an in vivo marker of multidrug resistance [33]. Sasaki et al have described the relationship between P-glycoprotein uptake and alterations in tumor suppressor genes (Rb, p16, p27, p53) in patients with NSCLC [34]. The study concluded that the presence of any tumor suppressor gene abnormality is related to an expected augmentation of  $^{18}\text{F}$ -FDG uptake in lung cancer. On the other hands, Marcom et al have described that Glut1 ( $p=0.085$ ) and Glut3 ( $p=0.074$ ) expression had no statistically significant correlation with  $^{18}\text{F}$ -FDG uptake in potentially resectable NSCLC [18]. They speculated that these transporters alone do not affect the variation in  $^{18}\text{F}$ -FDG activity in NSCLC. Because their study is a small sample size ( $n=73$ ), the results may bias by the differences in the methodology of Glut immunohistochemical staining.

Recently, we reported the relationship between  $^{18}\text{F}$ -FDG uptake and Glut1 in metastatic pulmonary tumors as compared with primary lung cancer [24].  $^{18}\text{F}$ -FDG uptake in metastatic pulmonary tumors correlated significantly with the expression of Glut1, but it was significantly lower than primary lung cancer. However, the expression of Glut1 was significantly higher in pulmonary metastatic tumors than in primary lung cancer. Thus, the correlation between  $^{18}\text{F}$ -

FDG uptake and Glut1 expression was different between primary lung cancer ( $\gamma=0.7211$ ,  $p<0.001$ ) and metastatic pulmonary tumors ( $\gamma=0.4579$ ,  $p<0.001$ ). In the analysis according to histology,  $^{18}\text{F}$ -FDG uptake and Glut1 expression were significantly higher in AC and SQC than in sarcoma. High uptake of  $^{18}\text{F}$ -FDG was significantly associated with poor outcome after pulmonary metastasectomy in patients with metastatic pulmonary tumors.

In vitro study using cancer cell lines, the uptake of  $^{18}\text{F}$ -FDG was markedly decreased by the inhibition of Glut1 or hypoxic inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ), whereas, Glut1 upregulation by the induction of HIF-1 $\alpha$  increased the  $^{18}\text{F}$ -FDG uptake [4]. The results of this study indicated that cellular uptake of  $^{18}\text{F}$ -FDG is mediated by Glut1 and that the expression of Glut1 protein was regulated by HIF-1 $\alpha$ .

### Amino acid metabolism

Tumor cells have an increased demand for nutrients such as glucose, amino acids, fatty acids, vitamins and micronutrients. This demand is increased by availability of nutrients through vascular formation and enhanced by cellular entry of nutrients through upregulation of specific transporters. Amino acids are essential not only for protein synthesis but also as carbon and nitrogen source in the synthesis of purine and pyrimidine nucleotides, amino sugars, and glutathione. Amino acid transporter systems play an important role in the regulation of cellular proliferation, whereas the details of its function to promote tumor cell proliferation have not been clarified. Among various types of amino acid transporters, system L is a Na<sup>+</sup>-independent large and neutral amino acid transport agency [35]. L-type amino acid transporter 1 (LAT1) transports large neutral amino acids such as leucine, isoleucine, valine, phenylalanine, tyrosine, tryptophan, methionine and histidine [36]. LAT1 is widely expressed in primary human cancers and several cancer cell lines, where it has been shown to play essential roles in growth and survival [37].

We have developed L-[3- $^{18}\text{F}$ ]- $\alpha$ -methyltyrosine ( $^{18}\text{F}$ -FAMT) as an amino-acid tracer for PET imaging, and confirmed its potential usefulness in the detection of neoplasms using experimental tumor models [38].  $^{18}\text{F}$ -FAMT, an amino acid analogue, is accumulated in tumor cells solely

via an amino-acid transport system [39,40].  $^{18}\text{F}$ -FAMT is specific to neoplasm, whereas  $^{18}\text{F}$ -FDG is taken up by inflammatory cells and granulation tissue. Recent studies have demonstrated that  $^{18}\text{F}$ -FAMT is useful to differentiate between benign lesions and malignant tumors [15]. We found that the uptake of  $^{18}\text{F}$ -FAMT was closely correlated with the expression of LAT1 in patients with NSCLC [39], and both LAT1 expression and  $^{18}\text{F}$ -FAMT uptake in SQC were significantly higher than those in AC [40-48].  $^{18}\text{F}$ -FAMT uptake within primary tumor is associated with poor outcome of NSCLC, and we found that  $^{18}\text{F}$ -FAMT uptake was a stronger prognostic factor than  $^{18}\text{F}$ -FDG uptake [49]. Moreover, recent studies demonstrated that a positive LAT1 expression is correlated with the grade of neuroendocrine tumors of the lung [50] and is frequent in thymic carcinoma but is absent in thymoma [51]. These results indicate that both LAT1 expression and  $^{18}\text{F}$ -FAMT uptake have an important role on the progression and metastasis of NSCLC.

$^{14}\text{C}$ -labeled methionine (MET) has been investigated in the imaging of various cancers [52-54].  $^{14}\text{C}$ -MET is better for imaging malignant tumors than  $^{18}\text{F}$ -FDG due to higher specificity resulting in improved differentiation between cancer and benign processes. There are several clinical studies obtained with other tyrosine derivatives such as 2- $^{18}\text{F}$ -fluoro-L-tyrosine ( $^{18}\text{F}$ -FET) and 3- $^{123}\text{I}$ -iodo- $\alpha$ -methyl-L-tyrosine ( $^{123}\text{I}$ -IMT) [55-57]. Pauleit et al investigated the diagnostic potential of  $^{18}\text{F}$ -FET for the imaging of lung cancer [56]. In their study, all SQCs were found to be  $^{18}\text{F}$ -FET-positive, whereas most ACs were found to be  $^{18}\text{F}$ -FET-negative. Compared with  $^{18}\text{F}$ -FDG,  $^{18}\text{F}$ -FET PET may allow a better distinction between tumors and inflammatory tissues in patients with SQC, however,  $^{18}\text{F}$ -FET PET seems not to be a useful method to diagnose NSCLC, because  $^{18}\text{F}$ -FET PET shows no uptake in most ACs.  $^{123}\text{I}$ -IMT SPECT has a high sensitivity for the detection of primary tumors of NSCLC (sensitivity, 94%), but it is not useful for small metastases (<2 cm in diameter) [57]. Experiments with *Xenopus* oocytes showed that the radioiodinated tyrosine derivative  $^{123}\text{I}$ -IMT was selectively transported via the human LAT1 [58]. However, several observations suggest that  $^{18}\text{F}$ -FET may be selectively transported via LAT2, which is expressed in normal cells [56]. The synthetic leucine amino acid analog anti-1-amino-3- $^{18}\text{F}$ -fluorocyclobutane-1-carboxylic acid

(anti-<sup>18</sup>F-FACBC) has been reported to be a ligand that permits the evaluation of the L-type amino acid transporter system [59]. <sup>18</sup>F-FACBC may prove useful for imaging brain and pelvic tumors because of its low uptake within the brain and the urinary bladder. However, there are no clinical studies on <sup>18</sup>F-FACBC with PET in NSCLC. Radiochemical yield of <sup>18</sup>F-FAMT is lower than <sup>18</sup>F-FET and is equivalent to FACBC [38]. However, it remains unclear whether the uptake of <sup>11</sup>C-MET, <sup>123</sup>I-FET, <sup>123</sup>I-IMT and <sup>18</sup>F-FACBC is correlated with the expression of amino acid transporters in human neoplasms. Only <sup>18</sup>F-FAMT PET has been investigated in the relationship the uptake of amino acid PET tracer and LAT1 expression using the tumor specimens.

### Hypoxic imaging

Tumor hypoxia is considered a significant impact on the biologic behavior of various malignancies, including lung cancer because it promotes resistance to radiotherapy and chemotherapy and increases tumor aggressiveness, angiogenesis, and metastatic potential, ultimately resulting worse prognosis [60,61]. Therefore, hypoxia itself could be a target for tumor imaging. During the past two decades, several hypoxia-targeting radiopharmaceuticals have been developed. <sup>18</sup>F-fluoromisonidazole (FMISO) and <sup>60</sup>Cu or <sup>64</sup>Cu-diacetyl-bis (4-(N)-methylthiosemicarbazone) (ASTM) are the principal PET tracers clinical available [62,63]. Dehdashti et al described that the usefulness of treatment monitoring (chemotherapy, radiotherapy or chemoradiotherapy) of NSCLC using PET imaging with <sup>60</sup>Cu-ASTM and <sup>18</sup>F-FDG [64]. Their preliminary results indicate that <sup>60</sup>Cu-ASTM may have great potential in identifying patients who are less likely to respond to conventional therapy. FMISO is another tracer that is selectively taken up by hypoxic cells but has a slower wash-out from normoxic cells than does <sup>60</sup>Cu-ASTM. Cherk et al reported the relationship between FMISO uptake and tumor markers of hypoxia and angiogenesis in 17 patients with NSCLC [65]. Their study demonstrated that no correlation was seen between either FMISO or <sup>18</sup>F-FDG uptake and microvessel density (MVD), HIF-1 $\alpha$ , VEGF and Glut1 expression, but there was a weakly positive correlation between both FMISO and <sup>18</sup>F-FDG uptake and the proliferative marker Ki-67. However, previous studies have documented that <sup>18</sup>F-FDG uptake is closely cor-

related with the expression of Glut1, HIF-1 $\alpha$ , MVD and VEGF in resectable NSCLC [24,27], and these studies were a sample size of more than one hundred patients with NSCLC. As their study is a small sample size of 17 patients with NSCLC, the sample size may bias the correlation between FMISO uptake and tumor biomarkers. Therefore, larger studies are needed to evaluate the relationship between hypoxia PET imaging and tumor markers such as HIF-1 $\alpha$ , MVD, VEGF and Glut1.

### DNA synthesis

3'-deoxy-3'-[<sup>18</sup>F] fluorothymidine (<sup>18</sup>F-FLT) is a thymidine analog used to assess cell proliferation [66]. <sup>18</sup>F-FLT is phosphorylated by thymidine kinase and enters the salvage pathway without incorporation into DNA molecule. Recent study revealed that <sup>18</sup>F-FLT uptake correlated with the proliferation of cancer cells, as indicated by immunohistochemical analysis with Ki-67 [67]. <sup>18</sup>F-FLT is described to be more tumor-specific than <sup>18</sup>F-FDG, and it is thought to be useful for identifying malignant cells and for monitoring tumor response in human cancers [68]. Since <sup>18</sup>F-FLT accumulates in the bone marrow and the liver, tumors in these organs are not studied for PET diagnosis with <sup>18</sup>F-FLT. Recently, Yamamoto et al described the correlation of <sup>18</sup>F-FLT and <sup>18</sup>F-FDG uptake on PET with Ki-67 immunohistochemistry in 18 patients with NSCLC [67]. The sensitivity of <sup>18</sup>F-FLT and <sup>18</sup>F-FDG PET for the detection of lung cancer was 72% and 89%, respectively. A statistically significant correlation was observed between <sup>18</sup>F-FLT uptake and Ki-67 index ( $\gamma=0.77$ ;  $p<0.0002$ ) and for <sup>18</sup>F-FDG uptake ( $\gamma=0.81$ ;  $p<0.0001$ ). Their preliminary study demonstrated that <sup>18</sup>F-FLT may be less sensitive for primary staging of NSCLC patients as compared with <sup>18</sup>F-FDG, and the correlation of <sup>18</sup>F-FLT uptake and proliferative activity was not better than that of <sup>18</sup>F-FDG uptake. In some studies, <sup>18</sup>F-FLT correlated significantly better with the proliferative activity than did <sup>18</sup>F-FDG [69,70], but pulmonary metastases and benign lesions were included. Thus, the differences in patients selection may bias the relationship between <sup>18</sup>F-FLT uptake and Ki-67. As only a small number of NSCLC patients have been examined in the previous studies, larger studies are needed to assess the biologic correlation of <sup>18</sup>F-FLT PET in patients with NSCLC.

## Discussion and conclusion

This review described the relationship between the underlying molecular biology and the uptake of the PET tracer targeting glucose metabolism, amino acid metabolism, hypoxia and DNA synthesis. The level of  $^{18}\text{F}$ -FDG uptake in lung cancer is modulated by many histologic and molecular factors. Higher  $^{18}\text{F}$ -FDG accumulation is recognized by the overexpression of Glut, hexokinase and HIF-1 $\alpha$ . Moreover, a positive correlation was also found between  $^{18}\text{F}$ -FDG uptake and Ki-67 proliferation index and angiogenesis (VEGF and MVD) [24,44]. The analysis according to histology demonstrated that higher  $^{18}\text{F}$ -FDG uptake is generally noted in SQC than in AC and in poorly differentiated carcinoma than in other tumor grades. These phenotypes are generally secondary to Glut1 overexpression and to some extent Glut3. The Glut1-mediated increased  $^{18}\text{F}$ -FDG uptake within tumor cells is modulated by hypoxic markers including HIF-1 $\alpha$  and hexokinase, alternations in tumor suppresser genes, and P-glycoprotein activity.

However,  $^{18}\text{F}$ -FDG accumulation is not tumor-specific, therefore several other radiotracers have been developed for the imaging of human cancers. Most of these PET tracers are more tumor-specific than  $^{18}\text{F}$ -FDG. Nowadays, PET is considered to be one of the standard means of molecular imaging using these tracers as probes for cellular metabolism, proliferation, angiogenesis, hypoxia, receptor and apoptosis.  $^{18}\text{F}$ -FAMT, an amino acid analogue, is accumulated in tumor cells solely via L-type amino acid transporter, and is specific to neoplasms. However,  $^{18}\text{F}$ -FAMT PET has a low sensitivity for the detection of primary lung cancer (sensitivity, 90%) as compared with  $^{18}\text{F}$ -FDG PET (sensitivity, 94%), demonstrating no significant difference ( $p=0.35$ ) [39]. Biologically, the uptake of  $^{18}\text{F}$ -FAMT was closely correlated with the expression of not only LAT1 but also VEGF, MVD and Ki-67 [37,40-45].  $^{18}\text{F}$ -FAMT PET is a promising PET tracer for monitoring response to chemoradiotherapy and for predicting the prognosis of patients with lung cancer [49,71]. Recently, we reported the antitumor activity of inhibiting LAT1 in lung cancer cell lines, and found that inhibition of LAT1 reduced the level of phosphorylation of mammalian target of rapamycin (mTOR), p70S6K and 4EBP1 [37]. Considering a close correlation of  $^{18}\text{F}$ -FAMT uptake and LAT1 expression,  $^{18}\text{F}$ -FAMT accumulation within tumor

cells may be also associated with the activation of mTOR signal pathway. As it has not been yet examined whether the uptake of the other amino acid PET tracers is correlated with the expression of amino acid transporter in human neoplasms, further investigation is warranted.

The recent small-scale study demonstrated a negative correlation between FMISO uptake and the expression of hypoxic markers [65]. This result concluded that hypoxic cell fraction of NSCLC measured by FMISO is consistently low, and there is no significant correlation between hypoxia and glucose metabolism in NSCLC assessed by  $^{18}\text{F}$ -FDG. Therefore, it remains unknown whether hypoxic PET tracer could be useful molecular imaging for representing the hypoxic condition with tumor cells.

$^{18}\text{F}$ -FLT PET is a cell proliferation tracer and has more-specific potential than  $^{18}\text{F}$ -FDG PET. Therefore,  $^{18}\text{F}$ -FLT PET may be more useful in determining therapeutic response than measurements of glucose metabolism. However, it remains unclear whether the uptake of  $^{18}\text{F}$ -FLT is correlated with the expression of Glut1, LAT1, hexokinase, HIF-1 $\alpha$ , VEGF and MVD. As cell metabolism, hypoxia and angiogenesis are associated with tumor cell proliferation,  $^{18}\text{F}$ -FLT PET may have an alternative role on the imaging of these molecular markers.

$^{18}\text{F}$ -FDG PET is accepted as a diagnostic imaging tool for the assessment of various human cancers, but the potential uses of PET in oncology extend beyond the imaging of glucose metabolism, including hypoxia, cell metabolism synthesis and DNA synthesis. These PET tracers could be an alternative imaging tool for representing the underlying molecular biology in lung cancer. The role of these more targeted radiopharmaceuticals will most certainly continue to evolve as the utility of molecular biology in future.

## Conflicts of interest statement

We, all authors, have no financial or personal relationships with other people or organizations that could inappropriately influence our work.

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