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MINIREVIEWS

Mechanisms underlying ^{18}F-fluorodeoxyglucose accumulation in colorectal cancer

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Abstract

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) is a diagnostic tool to evaluate metabolic activity by measuring accumulation of FDG, an analogue of glucose, and has been widely used for detecting small tumors, monitoring treatment response and predicting patients' prognosis in a variety of cancers. However, the molecular mechanism of FDG accumulation into tumors remains to be investigated. It is well-known that most cancers are metabolically active with elevated glucose metabolism, a phenomenon known as the Warburg effect. The underlying mechanisms for elevated glucose metabolism in cancer tissues are complex. Recent reports have indicated the potential of FDG-PET/CT scans in predicting mutational status (*e.g.*, *KRAS* gene mutation) of colorectal cancer (CRC), which suggests that FDG-PET/CT scans may play a key role in determining therapeutic strategies by non-invasively predicting treatment response to anti-epidermal growth factor receptor (EGFR) therapy. In this review, we summarize the current findings investigating the molecular mechanism of ^{18}F-FDG accumulation in CRC.

Key words: ^{18}F-fluorodeoxyglucose-positron emission tomography; Colorectal cancer; Glucose metabolism; Mutational status; *KRAS*

Core tip: Malignant cancers are preferential to metabolize glucose by glycolysis, even in the presence of oxygen, so-called Warburg effect. This elevated glucose metabolism is responsible for ^{18}F-fluorodeoxyglucose (FDG) accumulation into cancer cells, which results in the positive signals in FDG-positron emission tomography scans. In spite of its clinical utility, the cellular and molecular mechanisms of ^{18}F-FDG accumulation have not yet been elucidated. Here we review the current literature published with respect to the mechanisms of ^{18}F-FDG accumulation into colorectal cancer tissues.

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INTRODUCTION

Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) is a imaging method used for detecting small tumors, monitoring treatment response and predicting patients' prognosis in a variety types of cancers[1,2]. This technique is based on evaluating tissue glucose metabolism by measuring accumulated FDG, a glucose analogue. FDG is incorporated into the cell through glucose transporters (GLUTs), and then phosphorylated by hexokinases (HXKs) to FDG-6-phosphate, which becomes stored within the cell. There is no standardized approach for quantitative measurement of ^{18}F-FDG accumulation yet, although the ^{18}F-FDG maximum standardized uptake value (SUVmax) is commonly considered as a barometer of tumor viability. In addition to SUVmax, there are some ^{18}F-FDG uptake-related quantitative parameters: SUVmean (average SUV within the tumor), SUVpeak (peak SUV), metabolic tumor volume (MTV), total lesion glycolysis (TLG), *etc*.

Most cancer cells are preferential to metabolize glucose by glycolysis, even in the presence of oxygen, so-called "aerobic glycolysis (Warburg effect)"[3,4]. This increased glucose metabolism accounts for ^{18}F-FDG accumulation into cancer cells, which results in the positive signals in FDG-PET/CT scans. However, the mechanisms how ^{18}F-FDG is accumulated into cancer tissues are complex[5-7]. These factors are divided into tumor-related (*e.g.*, glucose metabolism, histological differentiation, vascular factor, tumor size and hypoxia) and non-tumor-related components (*e.g.*, high serum glucose level and local inflammation). ^{18}F-FDG is not specifically accumulated into cancer; it can also be accumulated into inflammatory sites as well. In spite of its clinical usefulness, the cellular and molecular mechanisms of ^{18}F-FDG accumulation have not yet been elucidated so far.

Colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of cancer-related deaths in the world, with the majority attributable to distant metastases[8]. In spite of great advance in systemic treatment of metastatic CRC, the overall 5-year patient survival has remained lamentably low, below 10%. CRC is progressively promoted through multistep carcinogenesis of accumulated genetic changes in oncogenes and tumor suppressor genes. Most adenomas are initiated by inactivation of the *APC* gene, and then progress into adenocarcinomas through accumulation of additional alterations in the *KRAS*, *TP53* and *SMAD4* genes, *etc*[9].

In this context, this review summarizes the current literatures investigating the molecular mechanisms how ^{18}F-FDG is accumulated into CRC.

GLUCOSE TRANSPORTERS AND HEXOKINASES

A line of literatures have demonstrated that ^{18}F-FDG accumulation in cancer cells depends largely on two classes of proteins: Glucose transporters (GLUT) and Hexokinases (HXKs)[10]. ^{18}F-FDG is incorporated into the cell via a family of 14 facilitative GLUTs, and then phosphorylated by HXKs to FDG-6-phosphate, which becomes stored within the cell, because of its negative charge. The up-regulation of GLUTs is commonly occurred in most cancers and is associated with poor prognosis of patients. Although different types of tumors have distinct expressions of different GLUTs, GLUT1 up-regulation is common in most cancers and is linked to tumor stage and prognosis[11,12]. In addition, increased levels of HXK (primarily, HXK2 of the 4 types) occur in many cancers[13,14]. HXK2 binds to the mitochondria membrane and efficiently phosphorylates FDG to FDG-6-phosphate. ^{18}F-FDG accumulation depends largely on GLUT1 and the rate-limiting glycolytic enzyme, HXK2, in most types of cancers, although other GLUT proteins (*e.g.*, GLUT3) and other enzymes downstream of HXK (*e.g.*, pyruvate dehydrogenase kinase 1) may be involved[10]. While the combined expression of GLUT1 and HXK2 likely plays some role in determining ^{18}F-FDG accumulation, the presence and strength of these associations seem to vary among tumor types, and conclusive evidence for one protein playing a dominant role is lacking. Although the molecular mechanisms of ^{18}F-FDG accumulation into CRC are not as well-analyzed as in breast and lung cancers, several studies indicate that, in CRC, an increase of GLUT1 expression is more essential for ^{18}F-FDG accumulation than HXK activity[10,15].

KRAS mutations in the KRAS gene in CRCs

Oncogenic activation of *KRAS* affects several cellular functions that regulate morphology, proliferation, and motility. *KRAS* mutations occur in a variety of human malignancies, most frequently in pancreatic cancer, non-small cell lung cancer (NSCLC) and CRCs. In particular, *KRAS* mutations occur in approximately 40% of CRCs; mutations of codon 12 or 13 occur in more than 90% of the cases. The *RAS* gene family encodes membrane-bound guanosine triphosphate (GTP) proteins that interact with several metabolic pathways, such as mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K). Activating *RAS* mutations alter the activity of GTPase, inducing constitutive activation of RAS pathway. A number of clinical studies indicate that *KRAS* mutations can predict a lack of response to anti-epidermal growth factor receptor (EGFR) therapy[16,17]. The anti-EGFR antibodies (cetuximab and panitumumab) are now recommended only for CRCs with wild-type *KRAS*, although a wild-type *KRAS* gene does not guarantee a response. Therefore, mutational testing of the *KRAS* gene, using biopsied or resected tissues, is incorporated

into routine clinical practice. However, one limitation is the heterogeneity of *KRAS* mutational status, which can either be intratumoral heterogeneity within a primary CRC[18], or discordant *KRAS* status between a primary CRC and its corresponding metastatic CRC[19,20]. Another limitation is failure to judge *KRAS* status due to poor quality of extracted DNA. In addition, it is not always easy to extract the samples from metastatic CRCs due to limited access and invasive procedures. Therefore, alternative non-invasive tool to predict the mutation profile, such as ^{18}F-FDG PET scans, could help overcome these limitations.

Association between KRAS mutations and ^{18}F-FDG accumulation

There is recent preclinical evidence that *KRAS* mutations are associated with increased expression of GLUT1. Studies with isogeneic CRC cell lines indicated a significant increase in glucose uptake caused by GLUT1 up-regulation, which is prominent in CRC cells with mutant *KRAS* alleles, providing them with a growth advantage in low glucose environment[21]. In a retrospective analysis (n = 51), we previously found that SUVmax and tumor-to-liver ratio (TLR) were significantly higher in primary CRCs with mutated *KRAS* than in those with wild-type *KRAS*, and that SUVmax exhibited an odds ratio (OR) of 1.17 with an accuracy of 75% in predicting *KRAS* status when using a cutoff value of 13[22]. This was the first clinical report to show the causal relationship between *KRAS* mutations and ^{18}F-FDG accumulation in a variety of cancer.

Following this report, some other groups have also shown that ^{18}F-FDG accumulation can reflect *KRAS* mutational status in CRC and NSCLC (Table 1). Using a larger size of sample (n = 121), Chen *et al*[23] investigated the association between ^{18}F-FDG uptake-related parameters and *KRAS* mutational status, and found that SUVmax and TW40% (a 40% threshold level of SUVmax for tumor width (TW) were 2 predictors for *KRAS* mutations of CRC. Receiver operating characteristics analysis revealed that the accuracy of SUVmax was highest (70%) with a cutoff value of 11, and that the TW40% method could achieve higher accuracy (71.4%) when focusing on rectal cancer. Miles *et al*[24] reported that multifunctional imaging with PET/CT and recursive decision-tree analysis to combine measurements of tumor ^{18}F-FDG uptake (SUVmax), CT texture (expressed as mean of positive pixels) and blood perfusion (measured by dynamic contrast-enhanced CT) enabled to identify CRCs with *KRAS* mutations showing hypoxic or proliferative phenotypes. This exploratory study with 33 CRC patients indicated that the true-positive rate, false-positive rate and accuracy of the decision tree were 82.4% (63.9%-93.9%), 0% (0%-10.4%) and 90.1% (79.2%-96.0%), respectively. The accuracy of SUVmax could be improved when combined with other imaging features: SUVmax, CT texture and perfusion. Lee *et al*[25] investigated the relationship between ^{18}F-FDG uptake-related parameters (*e.g.*, SUVmax, SUVpeak, MTV and TLG), *KRAS* mutations and C-reactive protein (CRP) with 179 CRC cases. Multivariate analysis demonstrated that SUVmax and SUVpeak are significantly associated with *KRAS* mutational status (OR, 3.3, P = 0.005 and OR, 3.9, P = 0.004, respectively) together with histological findings and lymph node metastasis. ^{18}F-FDG accumulation was significantly higher in CRCs with mutated *KRAS* and normal CRP levels. CRCs with high CRP levels (> 6.0 mg/L; n = 47) was correlated to larger tumor size, higher SUVmax, higher SUVpeak, higher MTV and higher TLG, compared to those with low CRP levels (< 6.0 mg/L; n = 132), which indicates that local inflammation with high CRP levels could affect ^{18}F-FDG quantification in CRC tumors.

However, the clinical benefit of above findings was limited, because endoscopic biopsy for *KRAS* mutational testing is easy in primary CRC. Importantly, we have recently examined whether a similar relationship can exist in metastatic CRC[26]. In a retrospective analysis with 55 metastatic CRC tumors, we found that SUVmax was not associated with *KRAS* mutational status. However, when focusing on tumors larger than 10 mm in order to remove the partial volume effect, SUVmax was significantly higher in CRCs with mutated *KRAS* than in those with wild-type *KRAS* (8.3 ± 4.1 and 5.7 ± 2.4, respectively; P = 0.03). *KRAS* status of metastatic CRC was predicted with an accuracy of 71.4% when using a SUVmax cutoff value of 6.0. This is the first clinical study showing a causal relationship between ^{18}F-FDG accumulation and *KRAS* mutations in metastatic CRC, which indicates that FDG-PET/CT scans might determine therapeutic strategies by predicting treatment response to anti-EGFR therapy. Meanwhile, Krikelis *et al*[27] reported a lack of association between ^{18}F-FDG accumulation and *KRAS* mutational status of metastatic CRC. Although sample size and ethnic differences might be sources of the bias, we suppose that the lack of association may be due to improper patient selection. In other clinical studies, patients with high serum glucose levels, small-sized tumors or high CRP levels were excluded, because these variables interfere with ^{18}F-FDG accumulation.

In genetically engineered mouse models (GEMM)-derived orthotopic transplant models of CRC, subcutaneous tumors from *KRAS*-mutant *APC*$^{-/-}$ *TP53*$^{-/-}$ CRC cells produced a significantly higher ^{18}F-FDG PET signal compared to *KRAS*-wild-type APC$^{-/-}$ *TP53*$^{-/-}$ CRC cells[28]. Oncogenic *KRAS* promotes an increase in cellular glucose uptake and lactate production *in vitro* and *in vivo*.

Regarding NSCLC (n = 102), Caicedo *et al*[29] found that NSCLC tumors harboring *KRAS* mutations exhibited significantly higher ^{18}F-FDG accumulation than those with wild-type *KRAS*, although no associations between different EGFR mutation types and ^{18}F-FDG uptake were found. The sensitivity and specificity of *KRAS* mutational status were 78.6% and 62.2%, respectively, with a diagnostic accuracy of 66.7%. A multivariate model with stage, gender, age and SUVmean could predict *KRAS* mutational status in stage Ⅲ or Ⅳ. A recent study using GEMM of lung cancer reported that mice harboring lung tumors with *KRAS* and *LKB1* or *TP53* mutations showed

Table 1 Clinical reports investigating the relationship between ^{18}F-fluorodeoxyglucose accumulation and *KRAS* mutations

Ref.	Cancer type	Sample size	Parameters related to *KRAS* mutations	Sensitivity (%)	Specificity (%)	Accuracy (%)
Kawada *et al*[22]	CRC	51	SUVmax	74.0	75.0	75.0
			TLR	70.0	71.0	71.0
Chen *et al*[23]	CRC	121	SUVmax	52.4	71.7	70.0
	CRC	121	TW40%	53.2	67.6	62.0
	RC	49	TW40%	80.0	79.1	71.4
Miles *et al*[24]	CRC	33	Dicision tree with SUVmax, MPP and BF	82.4	100.0	90.1
Lee *et al*[25]	CRC	132	SUVmax	60.0	50.3	54.0
			SUVpeak	73.3	60.5	67.8
Caicedo *et al*[29]	NSCLC	102	SUVmean	78.6	62.2	66.7
Kawada *et al*[26]	mCRC	42	SUVmax	68.0	74.0	71.4

SUV: Standardized uptake value; TLR: Tumor-to-liver SUV ratio; TW40%: A 40% threshold level of SUVmax for tumor width; MPP: Mean of positive pixels; BF: Blood flow; CRC: Colorectal cancer; RC: Rectal cancer; NSCLC: Non-small-cell lung cancer; mCRC: Metastatic CRC.

significantly higher ^{18}F-FDG accumulation than those with only *KRAS* mutations[30]. Taken together, FDG-PET/CT scans could predict *KRAS* mutational status in a variety of human *KRAS*-related cancers (CRC, NSCLC, pancreatic cancer, *etc.*).

HYPOXIA

The relationship between glucose metabolism and tumor growth can be explained by adaptation to hypoxia through up-regulation of GLUTs as well as the translocation and increased enzymatic activity of HXK[31]. Hypoxia-inducible factor-1α (HIF-1α) mediates cellular response to hypoxia, such as glucose metabolism and angiogenesis. Under hypoxic conditions, HIF-1α accelerates glycolysis by up-regulation of inducing glucose transporters and some enzymes[32]. Some researchers have reported that there is a synergistic interaction between hypoxia, mutated *KRAS* and GLUT1 expression[33-36]. When CRC cells were cultured *in vitro* under hypoxia, mutated *KRAS* increased the translation of HIF-1α by the PI3K pathway[33]. In addition, hypoxia or HIF-1α could also increase mutated *KRAS* activity, which indicate that there is a positive feedback between KRAS pathway and hypoxia[36]. Hypoxia can boost expression levels of GLUT1 through HIF-1α[35]. We have recently reported that mutated *KRAS* causes higher ^{18}F-FDG accumulation by up-regulation of GLUT1 and at least partially by induction of HIF-1α under hypoxia[37]. We also examined 51 clinical CRC samples, and found that *KRAS* mutational status was significantly associated with SUVmax and with GLUT1 expression, but not with HXK2 expression[21,35]. These data suggest that ^{18}F-FDG accumulation observed in FDG-PET scans could reflect elevated glucose metabolism by mutated *KRAS* and hypoxia.

Goh *et al*[38] investigated the *in vivo* flow-metabolic phenotype by integrated ^{18}F-FDG PET/perfusion CT and its relationship to histopathological findings with 45 primary CRCs. The flow-metabolic ratio was significantly lower for CRCs with high expressions of VEGF or HIF-1α compared to CRCs with lower expression, which indicated that CRCs with a low-flow-high-metabolism phenotype reflected a more angiogenic phenotype. With breast cancer cell lines, Smith *et al*[39] reported that hypoxia up-regulated GLUT1 and 6-phosphofructo-2-kinase (PFK) involved in glucose transport and glycolysis, and that these changes were induced by HIF-1α up-regulation and AMP-activated protein kinase (AMPK) activation. Preclinical studies have reported a correlation between ^{18}F-FDG accumulation and tumor hypoxia detected by pimonidazole[40] or ^{18}F-fluoromisonidazole (FMISO)[41], a PET tracer designed to identify hypoxic cells. Similarly, some studies noted a correlation between ^{18}F-FDG and ^{18}F-FMISO retention in a clinical setting[42,43].

ONCOGENE PATHWAY ACTIVATION

Using GEMM, Alvarez *et al*[44] investigated ^{18}F-FDG accumulation in tumors driven by c-Myc, HER2/neu, Akt1, Wnt1 or H-RAS oncogenes, and found that ^{18}F-FDG accumulation was correlated positively with HXK2 and HIF-1α, and negatively with PFK2b and p-AMPK. The correlation between HXK2 and ^{18}F-FDG accumulation was not dependent on all variables tested, indicating that HXK2 could independently predict ^{18}F-FDG accumulation in this model. In contrast, GLUT1 expression was associated with ^{18}F-FDG accumulation only in tumors driven by Akt1 or HER2/neu. These above results demonstrated that the oncogenic pathway was a determinant of ^{18}F-FDG accumulation mediated by glycolytic enzymes. Moreover, certain oncogenes such as Src and c-Myc, as well as elements of the PI3K/Akt pathway, can be associated with activated glycolysis[45-47].

Tian *et al*[48] investigated the correlations between SUVmax and expressions of GLUT1, hepatocyte growth factor (HGF) and vascular endothelial growth factor-C (VEGF-C) in 33 CRC patients, and found that there was a significant differences in SUVmax among CRCs expressing GLUT1, HGF, c-Met and VEGF-1. Choi *et al*[49] investigated the correlations between SUVmax and EGFR expression with 132 CRC patients, and found that SUVmax was significantly lower in EGFR-non-expressing tumors than in EGFR-expressing tumors (10.0 ± 4.2 *vs* 12.1 ± 2.1; P = 0.012). At the SUVmax threshold of 7.5, the sensitivity and specificity for predicting EGFR expression were 84.9% and 40.4%, which indicated SUVmax had a limited role in

predicting EGFR expression. In preclinical murine models with tumor xenografts, Ma *et al*[50] reported that ^{18}F-FDG PET accumulation was correlated with activated Akt and cellular membrane-bound GLUT1, and that the FDG-PET response did not correlate with the tumor growth response during mammalian target of rapamycin (mTOR) inhibitor therapy.

HUMAN CYTOMEGALOVIRUS AND EPSTEIN-BARR VIRUS

It has been debated whether human cytomegalovirus (HCMV) and Epstein-Barr virus (EBV) are involved in rectal cancer. Sole *et al*[51] reported that patients with HCMV/EBV co-infection had a significantly higher SUVmax than patients without viral co-infection, when analyzing 37 rectal cancer patients (P = 0.02). *KRAS* wild-type status was significantly more frequently observed in patients with EBV and HCMV/EBCV co-infection.

F-BOX AND WD REPEAT DOMAIN-CONTAINING 7

F-box and WD repeat domain-containing 7 (FBW7) is a E3 ubiquitin ligase and a tumor suppressor frequently mutated in CRC. In CRC, it was recently reported that FBW7 targets CDX2 (caudal-related homeobox transcription factor 2) for degradation *via* two cdc42-phosphoclegron motifs in a GSK3beta-dependent manner[52]. Ji *et al*[53] have recently reported that *KRAS* mutations inhibit the tumor suppressor FBW7, which negatively regulates glucose metabolism by targeting the c-Myc/TXNIP (thioredoxin binding protein) axis in pancreatic cancer. The expression level of FBW7 was negatively associated with PET/CT SUVmax in 60 pancreatic cancer patients, indicating that FBW7 is an important KRAS downstream effector and might reverse KRAS-driven metabolic change.

LACTATE DEHYDROGENASE A

Lactate dehydrogenase A (LDHA) converts pyruvate to lactate and is overexpressed in many cancers[54]. Up-regulation of LDHA ensures efficient glycolytic metabolism for tumor cells and reduces oxygen dependency[55]. In a retrospective analysis of 51 lung adenocarcinomas, Zhou *et al*[56] reported that SUVmax was significantly higher in the LDHA high-expression group than the LDHA low-expression group (P = 0.018). GLUT1 expression in lung adenocarcinomas was significantly associated with ^{18}F-FDG accumulation and LDHA expression, whereas HXK2 expression was not. In CRC, it was recently reported that LDHA negatively regulated by miRNAs promotes aerobic glycolysis[57].

PROLIFERATION-ASSOCIATED ANTIGEN KI-67

According to a meta-analysis (81 studies, 3242 patients), Deng *et al*[58] reported that the relationship between ^{18}F-FDG accumulation and Ki-67 expression was significant in thymic epithelial tumors, gastrointestinal stromal tumors (GISTs), moderate in breast, lung and pancreatic cancers, and average in CRCs, and poor in thyroid and gastric cancers.

CONCLUSION

For prediction of *KRAS* mutations in CRC, the overall accuracy of SUVmax alone has only been found to be modest, ranging from 60% to 75%, although the accuracy could be improved when combined with other clinicopathologic or imaging parameters. New targeted therapies are being developed for tumors that selectively express *KRAS* mutations[59]. Hence, the availability of non-invasive methods, such as molecular imaging, for predicting *KRAS* mutational status could have considerable clinical relevance, because of their potential to improve the assessment of other molecular alterations in the future. Future advances in PET radiotracers may increase the sensitivity and specificity of this technique to provide full molecular assessment of CRC.

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