3'-Deoxy-3'-[^{18}F]Fluorothymidine Uptake is Related to Thymidine Phosphorylase Expression in Various Experimental Tumor Models

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Running title: TP and [^{18}F]FLT in a range of tumor models

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ABSTRACT

Purpose: We recently reported that high thymidine phosphorylase (TP) expression is accompanied by low tumor thymidine concentration and high 3′-deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT) uptake in four untreated lung cancer xenografts. Here, we investigated whether this relationship also holds true for a broader range of tumor models.

Procedures: Lysates from *n* = 15 different tumor models originating from *n* = 6 institutions were tested for TP and thymidylate synthase (TS) expression using western blots. Results were correlated to [^{18}F]FLT accumulation in the tumors as determined by positron emission tomography (PET) measurements in the different institutions and to previously published thymidine concentrations.

Results: Expression of TP correlated positively with [^{18}F]FLT SUV_{max} ($\rho = 0.549$, $P < 0.05$). Furthermore, tumors with high TP levels possessed lower levels of thymidine ($\rho = -0.939$, $P < 0.001$).

Conclusions: In a broad range of tumors, [^{18}F]FLT uptake as measured by PET is substantially influenced by TP expression and tumor thymidine concentrations. These data strengthen the role of TP as factor confounding [^{18}F]FLT uptake.

Key words: [^{18}F]FLT, PET, thymidine phosphorylase, oncology

INTRODUCTION

Imaging of tumor metabolism is important in characterizing the viable active tumor and monitoring response to therapy. As a thymidine analog, the positron emission tomography (PET) tracer 3′-deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT) is a potential biomarker for imaging of tumor proliferation at baseline and in response to therapy. In analogy to thymidine, [^{18}F]FLT is transported into cells, primarily via the human equilibrative nucleoside transporter 1 (hENT1, [1]), where it is phosphorylated by thymidine kinase 1 (TK1). As an alternative thymidine-to-DNA pathway, phosphorylated thymidine can be generated by methylation of deoxyuridine monophosphate by thymidylate synthase (TS) (**Fig. 1**). Even though numerous studies demonstrate a good correlation of [^{18}F]FLT with cellular proliferation in tumors [2, 3], several reports show that factors like thymidine kinase 1 [4, 5] or thymidine [6] also affect uptake of this radiotracer. Recently, we demonstrated that [^{18}F]FLT uptake cannot be directly

related to proliferation, as determined by immunohistochemistry of Ki67 or 5-bromo-2′-deoxyuridine (BrdUrd) in four non-small cell lung cancer (NSCLC) xenograft models. We showed that high [^{18}F]FLT accumulation was detectable in tumors with high thymidine phosphorylase (TP) expression [7]. This was in agreement with a study, demonstrating an association of TP immunohistochemical score and [^{18}F]FLT retention in a clinical setting [8]. In our preclinical study, the presence of TP was accompanied by the corresponding enzymatic activity [7], which results in degradation of thymidine [9]. [^{18}F]FLT is resistant to the catabolic activity of TP [10, 11]. Hence, in tumors with high TP activity thymidine is degraded. Consequently, lower amounts of thymidine compete with [^{18}F]FLT for cellular uptake and retention, resulting in higher [^{18}F]FLT accumulation, as schematically depicted in **Fig. 1**. The relationship between the enzyme and [^{18}F]FLT retention has already been demonstrated by infusion of TP in a preclinical model *in vivo* [12] and by TP inhibition *in vitro* [8], whereas in the latter setting, it was shown that TP inhibition does not alter TK1 or hENT1 activity.

Here, we aimed to identify whether the relationship of TP expression, thymidine levels and [^{18}F]FLT uptake can be detected in a broad range of untreated tumors. Hence, we investigated various tumor models from different institutions with respect to their expression of thymidine metabolism proteins, and compared these data with respective [^{18}F]FLT uptake and published thymidine concentrations.

MATERIALS AND METHODS

Animal models and study design

Data were analyzed from $n = 6$ institutions. These institutions are members of the preclinical work-package of the Innovative Medicine Initiative Joint Undertaking project QuIC-ConCePT (*grant agreement* N° 115151). The institutions are: AstraZeneca, Macclesfield, UK (AZ); CRUK Cambridge Institute, Cambridge, UK (CI); Imperial College London, London, UK (IC); Radboud University Medical Centre, Nijmegen, The Netherlands (Radboudumc); Westfälische Wilhelms-Universität Münster, Münster, Germany (WWU); INSERM, Paris, France (INSERM); and Sanofi Oncology, Vitry-sur-Seine, France (Sanofi), performing the PET imaging for the INSERM tumors.

All animal experiments were carried out by the members of the consortium in accordance with the EU Directive 2010/63/EU and the NCRI Guidelines for the welfare and use of animals in cancer research [13]. The tumor models were chosen in each institute as appropriate for their future evaluation of response to specific therapies. Here, only untreated animals were used to assess [^{18}F]FLT

confounding factors at baseline. Study designs differed for the different institutions, and cohorts used for western blot analysis, [^{18}F]FLT PET scans, and thymidine analysis partly overlap, so that in total *n* = 209 animals were included in this study. All tumors were grown as subcutaneous xenografts or allografts, except for the CC531 liver metastasis model from Radboudumc. Details about the models are listed in **Table 1**.

Western blot analysis

Immediately after excision, tumors were frozen in liquid nitrogen, stored at -80 °C, and shipped to WWU on dry ice for analysis of thymidine metabolism proteins. Tumor tissue was homogenized in RIPA buffer (Cell Signaling) by a micro-dismembrator and 20 µg per sample were subjected to western blot analysis. The PVDF membrane was incubated overnight at 4 °C with specific primary antibodies. Afterwards the membrane was probed with appropriate peroxidase-coupled secondary antibodies for 1 hour at room temperature. See **Supplementary Table 1** for antibody details. Protein bands were visualized with Pierce ECL Plus Western Blotting Substrate (Pierce Biotechnology).

Band intensities were quantified by ImageJ (National Institutes of Health), using the "gel analyzer" function, and normalized to the actin loading control. To normalize for unequal exposures of different blots, all band intensities were expressed relative to a control sample (an H1975 lysate) that was loaded on all gels.

[^{18}F]FLT PET imaging of small animals

The scanning procedures of each institution are listed in **Table 2**. The animals were not fasted. For quantification, standardized uptake values (SUV_{max} and SUV_{mean}) were determined.

Statistics

Data are expressed as mean ± standard deviation. Numerical values, as well as number of samples analyzed, are depicted in **Supplementary Table 2**. Spearman correlations were calculated (SigmaPlot 13.0) and *P*-values < 0.05 were considered statistically significant.

RESULTS

Tumor lysates from untreated rodents were analyzed for TP and TS expression. The representative western blot as well as the quantification revealed large differences between tumors (**Fig. 2**). We related the TP and TS expression levels to [^{18}F]FLT uptake in the respective tumors and detected a statistically significant correlation between [^{18}F]FLT SUV_{max} and TP levels (ρ = 0.549, P < 0.05, **Fig. 3**). Also SUV_{mean} was significantly correlated with TP levels (ρ = 0.582, P < 0.05, **Supplementary Fig. 1**). No relation between TS and [^{18}F]FLT or TS and TP was observed.

When relating TP expression to respective previously published tumor thymidine concentrations [14] (confirmation of assay robustness presented in **Supplementary Fig. 2**), we observed a significant correlation (ρ = -0.939, P < 0.001, **Fig. 4A**). Moreover, tumor thymidine was inversely correlated with [^{18}F]FLT SUV_{max} (**Fig. 4B**) and [^{18}F]FLT SUV_{mean} (**Supplementary Fig. 3**).

DISCUSSION

Defining the molecular and cellular determinants of [^{18}F]FLT uptake and retention in tumors helps to determine the potential value of this tracer in clinical oncology. Here, we demonstrate that in various tumor models [^{18}F]FLT accumulation is influenced by the presence of the enzyme TP, which accounts for degradation of endogenous thymidine. We observed a statistically significant correlation of TP expression with [^{18}F]FLT uptake (**Fig. 3B** and **Supplementary Fig. 1**). Moreover, we were able to compare the TP data of ten tumor models with tumor thymidine data published previously [14]. As expected, TP expression negatively correlated with thymidine levels and these thymidine concentrations negatively correlated with [^{18}F]FLT (**Fig. 4**). The thymidine data strengthen the TP results presented here, as they provide a link between protein expression and activity. Of note, the data analyzed by Heinzmann et al. [14] only partly overlap with the data presented here, explaining slight differences in the results.

For some tumor models, plasma thymidine levels were available. This parameter would be more easily accessible in the clinical setting. Although these plasma thymidine values weakly correlated with tumor thymidine values in this subset of models, no direct relation of this parameter with TP expression or [^{18}F]FLT uptake could be detected (**Supplementary Fig. 4**). However, as the sample size for some of the models is low, these data should be treated with caution.

In our setup, immunohistochemistry, [^{18}F]FLT PET measurements and the thymidine assay were only partly performed using the same animals. When looking at overlapping datasets on a per-tumor-basis, available from a total of $n = 54$ tumors, a significant correlation of [^{18}F]FLT with TP and thymidine, as well as TP with thymidine can also be detected (**Supplementary Fig. 5**), strengthening the conclusion, that these factors are related.

In addition to the single institution studies published so far, covering only a limited spectrum of models [7, 8, 12], our data provide evidence that the relationship of [^{18}F]FLT, thymidine and TP can be detected in a wider range of tumors in a multi-center setting. This reinforces the role of TP as a factor affecting [^{18}F]FLT uptake. This is of importance for the implementation of this tracer as imaging biomarker for tumor therapy follow up, potentially improving therapy in clinical cancer research.

Ex vivo analysis of TP expression might potentially help in determining the utility of [^{18}F]FLT PET for a specific tumor model. Some high proliferating tumors might have low [^{18}F]FLT uptake at baseline due to low TP expression and are not good candidates for [^{18}F]FLT response studies. Accordingly, some of the tumors analyzed here, showing high TP expression and high [^{18}F]FLT uptake, could be successfully utilized for preclinical monitoring of tumor therapies [15, 16].

As the moderate correlation coefficient between TP and [^{18}F]FLT SUV_{max} suggests ($\rho = 0.549$, $P < 0.05$), other factors also influence [^{18}F]FLT uptake. It is well recognized that nucleoside transporters and TK1 are involved in [^{18}F]FLT accumulation. Consequently, care must be taken when employing therapies targeting [^{18}F]FLT modulating factors, as shown already for TS-inhibitors [3]. Our study provides evidence that the same might hold true for agents modulating TP or thymidine concentrations. For instance, taxol and oxaliplatin can increase TP levels [17, 18]. Hence, TP and thymidine should be considered when employing [^{18}F]FLT PET in combination with a novel treatment approach. If a treatment does not affect an [^{18}F]FLT confounding component, changes in [^{18}F]FLT uptake can still reflect treatment response, as described in a range of systematic reviews [3, 19].

In our study, [^{18}F]FLT uptake was determined in different institutions with different scanners and in different rodent models. Therefore, it is even more striking that a statistically significant correlation of [^{18}F]FLT uptake with TP could be observed. These variables also differ in the clinical situation. Hence, we speculate that this relation could also be detected in clinical specimens. Lee et al. have demonstrated an association of [^{18}F]FLT and TP immunohistochemistry score in a cohort of 58 non-small cell lung cancer patients. However, no thymidine analysis was performed [8]. It is known that plasma thymidine levels in humans are much lower than in rodents [6, 20] and that TP levels vary

between clinical tumor specimens [21]. Whether this variation is related to thymidine and [^{18}F]FLT in the respective tumors remains to be determined.

One limitation of the present study is the fact that protein expression, as determined here, is not necessarily directly related to enzymatic activity. Furthermore, quantification of expression levels via western blot densitometry is only semi-quantitative [22]. Of note, TP western blot results are in line with TP levels determined by immunohistochemistry, as we reported previously [7]. This is of importance, as immunohistochemistry is a more clinically accessible method.

CONCLUSION

[^{18}F]FLT accumulation in tumors can be influenced by competition with endogenous thymidine, which might be controlled by TP. Hence, our data provide further evidence that TP is a major factor influencing [^{18}F]FLT uptake, which should be taken into account when employing this radiotracer in tumor therapy follow up studies.

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CONCFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

All applicable institutional and national guidelines for the care and use of animals were followed.

ELECTRONIC SUPPLEMENTARY MATERIAL

Supplementary Fig. 1 TP expression correlated to [^{18}F]FLT uptake in the tumor models investigated

Supplementary Fig. 2 Inter-experiment reproducibility of the thymidine assay

Supplementary Fig. 3 Relation of [^{18}F]FLT SUV_{mean} to tumor thymidine levels

Supplementary Fig. 4 Plasma thymidine concentrations are not correlated with TP expression or [^{18}F]FLT uptake in tumors

Supplementary Fig. 5 When analyzing data on a per-tumor-basis, the relation of [^{18}F]FLT, TP and thymidine can also be detected

Supplementary Table 1 Antibodies used for western blot analysis

Supplementary Table 2 Numerical values of data presented in this manuscript, as well as number of samples analyzed (in brackets)

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FIGURES LEGENDS

Fig. 1 Schematic illustration of the competition between uptake of [^{18}F]FLT and thymidine and the influence of TP. When thymidine is degraded by TP, as indicated by dotted lines, less of this nucleoside competes with [^{18}F]FLT for uptake into cells, or the phosphorylation (indicated by a black dot) via TK1. hENT1, as the major transporter, and TS, as the key enzyme of the alternative thymidine-to-DNA pathway, are also shown.

Fig. 2 Western blot analysis revealed varying amounts of thymidine metabolism proteins in different tumor models. Actin was used as loading control (a). Quantification of TP (b) and TS (c) expression was performed via densitometric analysis. The TS band of the rodent K8484 and CC351 tumors is slightly shifted, which can probably be attributed to species-specific differences in the protein

sequence. The TP antibody used is not optimized for rodent samples. Hence, these samples were excluded from any correlations.

Fig. 3 TP expression was significantly correlated to [^{18}F]FLT uptake in the tumor models investigated. [^{18}F]FLT SUV_{max} was determined by PET measurements in the different institutions (a). Correlation was assessed by the Spearman method (b).

Fig 4 Correlation of TP, thymidine and [^{18}F]FLT. We related our findings of western blot and PET analyses to tumor thymidine levels. Thymidine contents were inversely correlated to TP levels (a) and [^{18}F]FLT uptake was inversely correlated with thymidine concentrations (b).

TABLES

Table 1. Information on investigated tumor models.

Institution	Cell line	Tumor origin	Model type	Host (supplier)
AZ	A431	human epidermis	Xenograft	AP ONU mouse (AZ)
	PC9	human lung	Xenograft	AP CB17 SCID mouse (AZ)
	H1975	human lung	Xenograft	AP ONU mouse (AZ)
CI	AsPC-1	human pancreas	Xenograft	CB17 SCID mouse (CR)
	K8484	murine pancreas	Syngeneic allograft	PC mouse (p53R172H; Pdx1-Cre) (CRUK CI)
	MiaPaCa-2	human pancreas	Xenograft	CB17 SCID mouse (CR)
IC	HCT116	human colorectum	Xenograft	BALB/c nu mouse (CR)
Radboudumc	CC531	rat colorectum	Syngeneic liver metastasis	Wag/Rij rats (CR)
WWU	A549	human lung	Xenograft	NMRI nu (Janvier)
	HTB56	human lung	Xenograft	NMRI nu (Janvier)
	EBC1	human lung	Xenograft	NMRI nu (Janvier)
	H1975	human lung	Xenograft	NMRI nu (Janvier)
INSERM / Sanofi	HCT116	human colorectum	Xenograft	CB17 SCID (CR)
	CR-IC-O13M-Cetux1	human colon – hepatic metastasis	Xenograft	CB17 SCID (CR)
	CR-IC-O13M	human colon	Xenograft	CB17 SCID (CR)

CR = Charles River

Table 2. PET imaging and analysis parameters

Institution	PET scanner	imaging time (min)	injected dose (MBq)	ROIs defined on	reconstruction method	voxel size (mm)	matrix size (pixel)
AZ	Inveon (Siemens)	50-60	~10	PET	2D-FBP	0.77 x 0.77 x 0.80	128 x 128 x 159
CI	NanoPET/CT (Mediso)	60-90	~ 8.3	CT	3D OSEM	0.4 x 0.4 x 0.4	255 x 255 x 236
IC	Inveon (Siemens)	50-60	~3.7	CT	3D-OSEM/MAP	0.8 x 0.8 x 0.8	128 x 128 x 159
Radboudumc	Inveon (Siemens)	60-75	10 - 12	PET	3D-OSEM	0.43 x 0.43 x 0.8	256 x 256 x 159
WWU	quadHIDAC (Oxford Positron Systems)	70-90	~10	CT	3D-OPL-EM	0.4 x 0.4 x 0.4	150 x 150 x 300
Sanofi/ INSERM	Inveon (Siemens)	75-90	~7	PET	3D-OSEM	0.30 x 0.30 x 0.796	256 x 256 x 97